National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Hematopoietic Growth Factors

Version 2.2020 — January 27, 2020

NCCN.org

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NCCN Guidelines Version 2.2020
Hematopoietic Growth Factors

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NCCN Guidelines Panel Disclosures

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Clinical Trials: NCCN believes that the best management for any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

To find clinical trials online at NCCN Member Institutions, click here: nccn.org/clinical_trials/member_institutions.aspx.

NCCN Categories of Evidence and Consensus: All recommendations are category 2A unless otherwise indicated.

See NCCN Categories of Evidence and Consensus.

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Updates in Version 2.2020 of the NCCN Guidelines for Hematopoietic Growth Factors from Version 1.2020 include:

MS-1

The Discussion section has been updated to reflect the changes in the algorithm.

Updates in Version 1.2020 of the NCCN Guidelines for Hematopoietic Growth Factors from Version 2.2019 include:

General

The following footnotes haves been included throughout the guideline where individual biosimilars were previously listed (ie. filgrastim-aafi, filgrastim-sndz, pegfilgrastim-jmdb, pegfilgrastim-cbqv, epoetin alfa-epbx):

- **An FDA-approved biosimilar is an appropriate substitute for filgrastim and pegfilgrastim.**
- **An FDA-approved biosimilar is an appropriate substitute for epoetin alfa.**

MGF-1

- **Footnote h modified here and on subsequent pages: ~~G-CSF refers to the following approved agents: filgrastim, filgrastimsndz, filgrastim-aafi, tbo-filgrastim, pegfilgrastim, pegfilgrastim-jmdb and pegfilgrastim-cbqv.~~ See G-CSFs for Prophylaxis of Febrile Neutropenia and Maintenance of Scheduled Dose Delivery (MGF-B).**
- **Footnote removed: There is category 1 evidence for G-CSF for a reduction of: risk of febrile neutropenia, hospitalization, and intravenous antibiotics during the course of therapy. There is category 2A evidence for G-CSF for a reduction in infection-related mortality during the course of treatment (see Discussion for details).**

MGF-4

- **Radiation-induced myelosuppression description modified: Patients ~~presents~~ with ~~acute exposure to~~ radiation-induced ~~myelosuppressive doses of RT~~ myelosuppression following a radiologic/nuclear incident (hematopoietic acute radiation syndrome [H-ARS])**
- **Footnote n added: Farese AM, MacVittie TJ. Filgrastim for the treatment of hematopoietic acute radiation syndrome. Drugs Today (Barc) 2015;51:537-48.**

MGF-A (1 of 5)

- **Bone cancer regimens added:**
  - **Cisplatin/doxorubicin**
  - **VDC (cyclophosphamide, vincristine, doxorubicin or dactinomycin)**
- **Breast cancer regimen modified: Dose-dense AC followed by *dose-dense* ~~+~~ *paclitaxel* (doxorubicin, cyclophosphamide, paclitaxel)**
- **Colorectal cancer regimen added: FOLFOXIRI (fluorouracil, leucovorin, oxaliplatin, irinotecan)**
- **Pancreatic cancer regimen added: FOLFIRINOX (fluorouracil, leucovorin, irinotecan, oxaliplatin)**

MGF-A (2 of 5)

- **Non-Hodgkin's Lymphoma regimens added:**
  - **CHP (cyclophosphamide, doxorubicin, prednisone) + brentuximab vedotin**
  - **Bendamustine**
- **Footnote e added: There is variable risk with FOLFOX regimens. Please refer to the risk level of the specified FOLFOX regimen being used for therapy.**
- **Footnote removed: A small retrospective trial had a 17% risk of febrile neutropenia in the neoadjuvant setting and a randomized trial had a 5.4% risk in the metastatic setting (G-CSF was administered to 42.5% of patients who received FOLFIRINOX). While G-CSF was not recommended as primary prophylaxis, it may be considered in patients with high-risk clinical features.**

MGF-B

- **Third primary bullet removed: Prophylactic use of G-CSF in patients given concurrent chemotherapy and radiation is not recommended**

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Updates in Version 1.2020 of the NCCN Guidelines for Hematopoietic Growth Factors from Version 2.2019 include:

MGF-D
- Footnote e added: G-CSFs are not recommended for use within 14 days after receipt of chimeric antigen receptor (CAR)-modified T cells due to concern for exacerbation of cytokine release syndrome. Use after that time period can be considered for treatment of neutropenia.
- Footnote h added: Available data support use of naproxen and other NSAIDs or loratadine. See Discussion for more details.

ANEM-1
- Ninth sub-bullet added: Anemia of chronic inflammation (ie, C-reactive protein [CRP] and erythrocyte sedimentation rate [ESR])
- Footnote c added: Consideration of gender in evaluation of anemia is relevant since women have a lower baseline Hb than men. See Discussion for more details.

The information on 2.2019 ANEM-3 was moved to the Discussion section.

ANEM-3
- Footnote j modified: A few studies suggest that patients with small cell lung cancer on myelosuppressive chemotherapy may not have an increase in mortality when receiving ESAs. ~~Oncologic Drugs Advisory Committee March 2008; Pirker et al. J Clin Oncol 2008;26:2342-3249; Grote et al. J Clin Oncol 2005;23:9377- 9386.~~ (Nagel S, Kellner O, Engel-Riedel W, et al. Addition of darbepoetin alfa to dose-dense chemotherapy: results from a randomized phase II trial in small-cell lung cancer patients receiving carboplatin plus etoposide. Clin Lung Cancer 2011;12:62-69.)

ANEM-A (4 of 5)
- Information on seizures as an adverse effect of erythropoietic therapy has been removed.

ANEM-B (1 of 2)
- Low-Molecular-Weight Iron Dextran test dose modified: Test dose required: 25 mg slow IV push *over 1–2 min. If tolerated, follow with 75 mg IV bolus for total dose of 100 mg*
- Iron Sucrose dosage modified: 200 mg IV over 2–5 min*, 5 times within 14 days* ~~(repeated every 1–4 wks)~~

- Footnote removed: Ferric carboxymaltose has not been prospectively evaluated in patients with cancer- or chemotherapy-induced anemia and therefore should only be considered when other parenteral iron preparations fail.
- Footnote c modified: Ferumoxytol is indicated for the treatment of iron deficiency anemia in adult patients who have intolerance to oral iron or have had unsatisfactory response to oral iron, or those with chronic kidney disease. ~~There are no data to show the efficacy of ferumoxytol in patients with cancer.~~ Ferumoxytol has not been prospectively evaluated in patients with cancer- or chemotherapy-induced anemia. Ferumoxytol may cause interference with MRI scans causing potential false interpretation of organ iron overload.

ANEM-B (2 of 2)
- Reference removed: Chertow GM, Mason PD, Vaage-Nilsen O, Ahlmen J. Update on adverse drug events associated with parenteral iron. Nephrol Dial Transplant 2006;21:378-382.
- Reference removed: Auerbach M, Ballard H, Glaspy J. Clinical update: intravenous iron for anaemia. Lancet 2007;369:1502-1504.
- Reference modified: Kim YW, Bae JM, Park YK, et al. Effect of intravenous ferric carboxymaltose on hemoglobin response among patients with acute isovolemic anemia following gastrectomy: the FAIRY randomized clinical trial. JAMA 2017;317:2097-2104. Keeler BD, Simpson JA, Ng O, et al. Randomized clinical trial of preoperative oral versus intravenous iron in anaemic patients with colorectal cancer. Br J Surg 2017;104:214-221.

ANEM-C (1 of 2)
- Bullet removed: Patients receiving myelosuppressive chemotherapy with curative intent

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Management of Neutropenia

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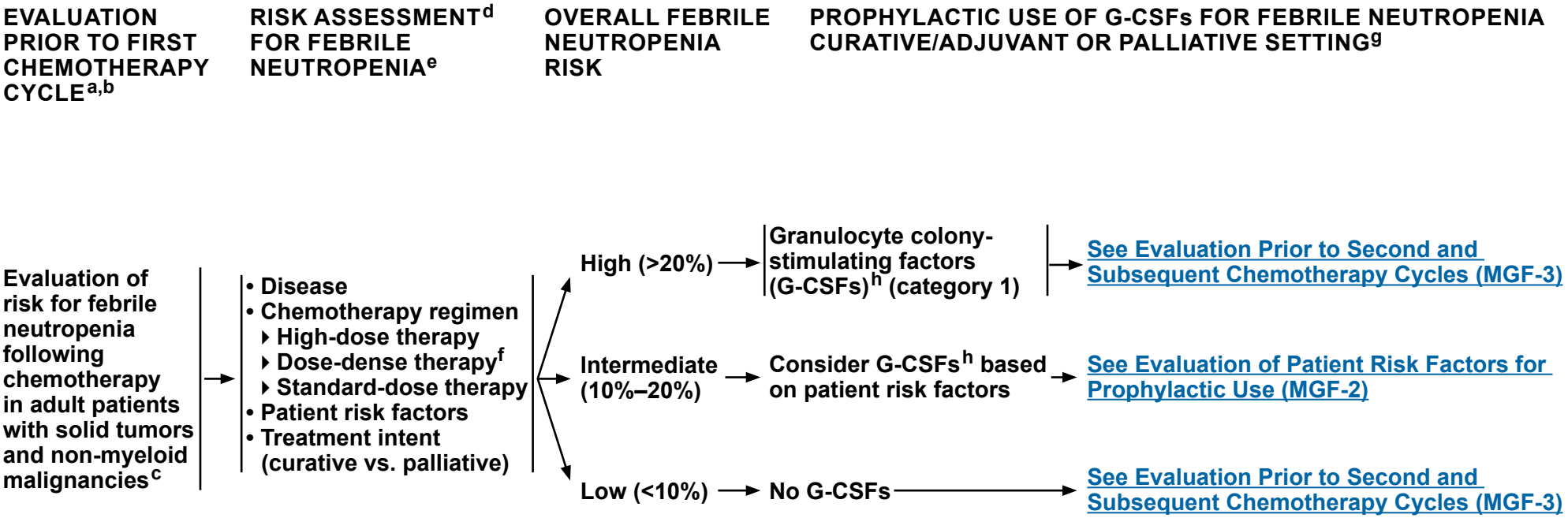

[a]The NCCN Guidelines for Hematopoietic Growth Factors were formulated in reference to adult patients.
[b]Patients receiving cytotoxic chemotherapy as part of a clinical trial may be evaluated for prophylaxis with myeloid growth factor (MGF) as clinically indicated, unless precluded by trial specifications.
[c]For use of growth factors in myelodysplastic syndromes (MDS), see the NCCN Guidelines for Myelodysplastic Syndromes; in acute myeloid leukemia (AML), see the NCCN Guidelines for Acute Myeloid Leukemia; and in chronic myeloid leukemia (CML), see the NCCN Guidelines for Chronic Myeloid Leukemia.
[d]There are many factors that need to be evaluated to determine a patient's risk categorization; these include type of chemotherapy regimen (See MGF-A) and patient risk factors (See MGF-2).
[e]Febrile neutropenia is defined as single temperature: ≥38.3 °C orally or ≥38.0 °C over 1 h; neutropenia: <500 neutrophils/mcL or <1,000 neutrophils/mcL and a predicted decline to ≤500 neutrophils/mcL over the next 48 h. See NCCN Guidelines for Prevention and Treatment of Cancer-Related Infections.
[f]In general, dose-dense regimens require MGF support to maintain dose intensity and schedule.
[g]See Toxicity Risks with Myeloid Growth Factors (MGF-D).
[h]See G-CSFs for Prophylaxis of Febrile Neutropenia and Maintenance of Scheduled Dose Delivery (MGF-B).

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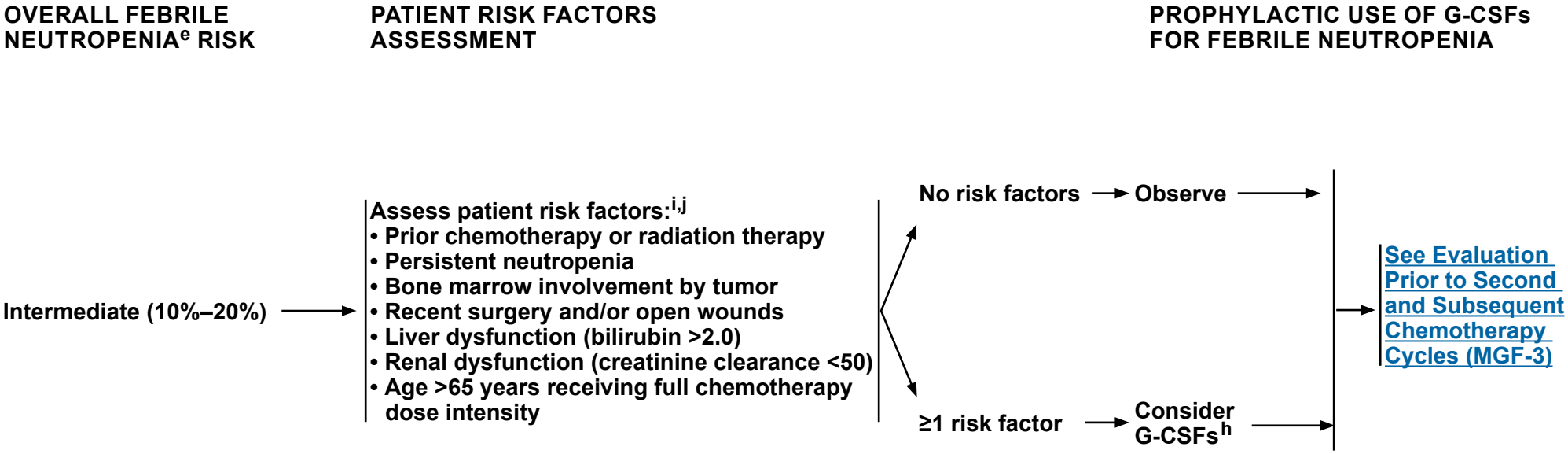

[e]Febrile neutropenia is defined as single temperature: ≥38.3 °C orally or ≥38.0 °C over 1 h; neutropenia: <500 neutrophils/mcL or <1,000 neutrophils/mcL and a predicted decline to ≤500 neutrophils/mcL over the next 48 h. See NCCN Guidelines for Prevention and Treatment of Cancer-Related Infections.

[h]See G-CSFs for Prophylaxis of Febrile Neutropenia and Maintenance of Scheduled Dose Delivery (MGF-B).

[i]Other possible patient risk factors for febrile neutropenia may include poor performance status or HIV infection (in particular, patients with low CD4 counts). The listed patient risk factors are based on a multivariable risk model using a prospective cohort study of several thousand ambulatory cancer patients receiving chemotherapy. This cohort did not include patients with HIV, acute leukemia, or hematopoetic cell transplant. (Lyman GH, Abella E, Pettengell R. Risk factors for febrile neutropenia among patients with cancer receiving chemotherapy: A systematic review. Crit Rev Oncol Hematol 2014;90:190-199.)

[j]Other factors may warrant the use of G-CSFs (eg, chronic immunosuppression in the post-transplant setting, including organ transplant).

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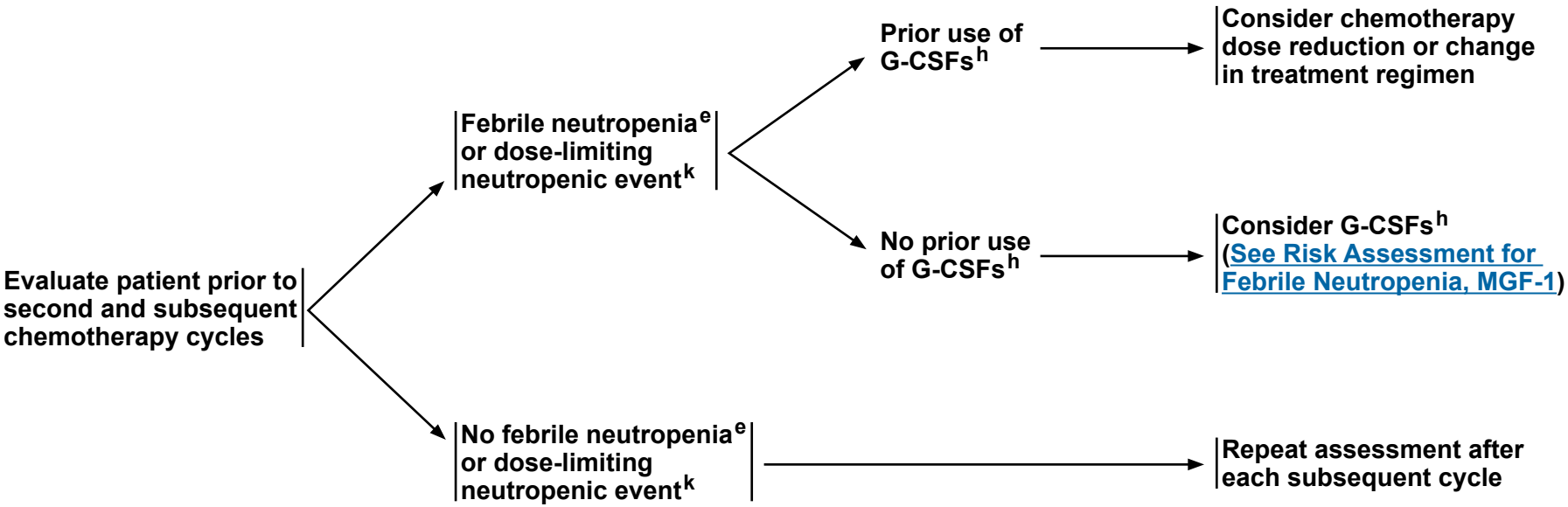
EVALUATION PRIOR TO SECOND AND SUBSEQUENT CHEMOTHERAPY CYCLES

SECONDARY PROPHYLAXIS



[e]Febrile neutropenia is defined as single temperature: ≥38.3 °C orally or ≥38.0 °C over 1 h; neutropenia: <500 neutrophils/mcL or <1,000 neutrophils/mcL and a predicted decline to ≤500 neutrophils/mcL over the next 48 h. See NCCN Guidelines for Prevention and Treatment of Cancer-Related Infections.

[h]See G-CSFs for Prophylaxis of Febrile Neutropenia and Maintenance of Scheduled Dose Delivery (MGF-B).

[k]Dose-limiting neutropenic event could be a nadir count or day of treatment count that could otherwise impact planned dose of chemotherapy.

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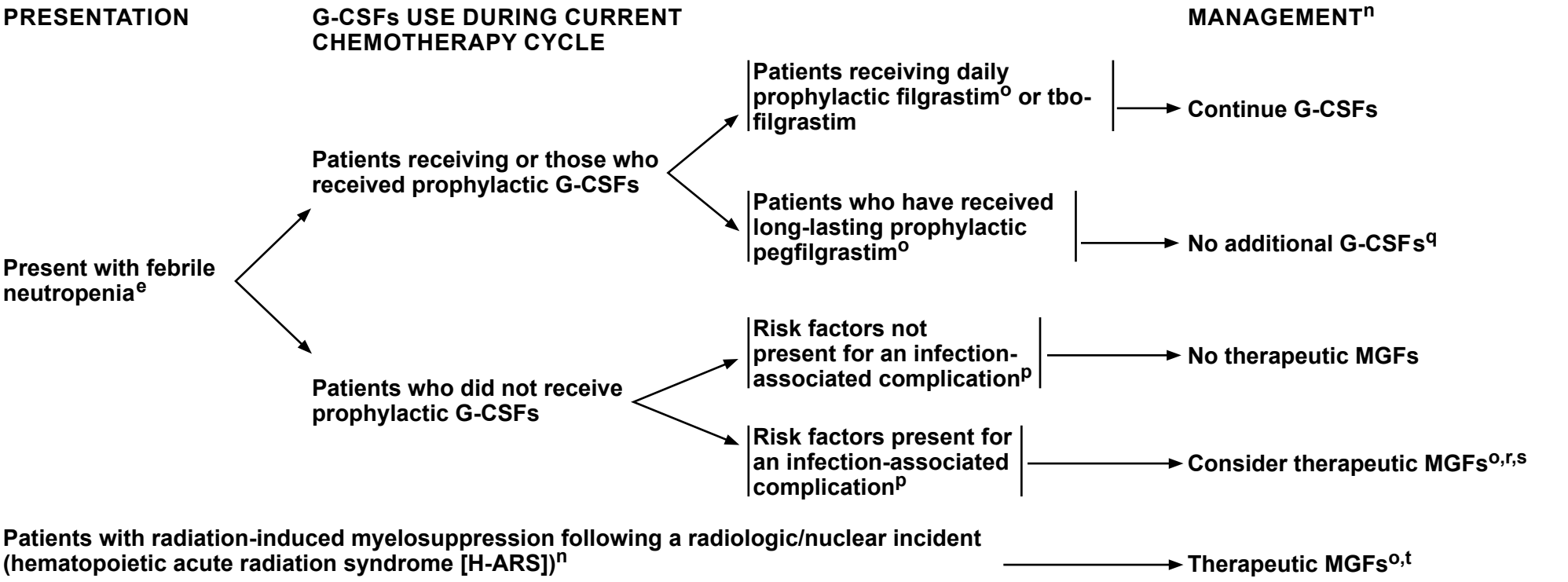
THERAPEUTIC USE OF MYELOID GROWTH FACTORS (MGFs)[e,l,m]



Patients with radiation-induced myelosuppression following a radiologic/nuclear incident (hematopoietic acute radiation syndrome [H-ARS])[n] → **Therapeutic MGFs[o,t]**

[e]Febrile neutropenia is defined as single temperature: ≥38.3 °C orally or ≥38.0 °C over 1 h; neutropenia: <500 neutrophils/mcL or <1,000 neutrophils/mcL and a predicted decline to ≤500 neutrophils/mcL over the next 48 h. See NCCN Guidelines for Prevention and Treatment of Cancer-Related Infections.

[l]For antibiotic therapy recommendations for fever and neutropenia, see the NCCN Guidelines for Prevention and Treatment of Cancer-Related Infections.

[m]The decision to use MGFs in the therapeutic setting is controversial. See Discussion for further details.

[n]Farese AM, MacVittie TJ. Filgrastim for the treatment of hematopoietic acute radiation syndrome. Drugs Today (Barc) 2015;51:537-48.

[o]An FDA-approved biosimilar is an appropriate substitute for filgrastim and pegfilgrastim.

[p]Risk factors/possible indications for therapeutic MGFs include sepsis syndrome, age >65 years, absolute neutrophil count [ANC] <100/mcL, neutropenia expected to be >10 days in duration, pneumonia or other clinically documented infections, invasive fungal infection, hospitalization at the time of fever, and prior episode of febrile neutropenia.

[q]There are no studies that have addressed therapeutic use of filgrastim for febrile neutropenia in patients who have already received prophylactic pegfilgrastim. However, pharmacokinetic data of pegfilgrastim demonstrated high levels during neutropenia and suggest that additional G-CSFs may not be beneficial; however, in patients with prolonged neutropenia additional G-CSFs may be considered.

[r]See Discussion for further details. Pegfilgrastim (or biosimilars) have only been studied for prophylactic use. Filgrastim (or biosimilars), tbo-filgrastim, or sargramostim may be used therapeutically with initial dosing and discontinued at time of neutrophil recovery.

[s]Filgrastim (or biosimilars) or tbo-filgrastim: daily dose of 5 mcg/kg; Sargramostim: used in clinical trials at a dose of 250 mcg/m^2 per day. Continue therapeutic MGFs until post-nadir ANC recovery to normal or near-normal levels by laboratory standards.

[t]Therapeutic options include filgrastim (or biosimilars), tbo-filgrastim, pegfilgrastim (or biosimilars), and sargramostim.

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EXAMPLES OF DISEASE SETTINGS AND CHEMOTHERAPY REGIMENS WITH A HIGH RISK FOR FEBRILE NEUTROPENIA (>20%)[a]

- ***This list is not comprehensive***; there are other agents/regimens that have a high risk for the development of febrile neutropenia. Regimens recommended in the NCCN Guidelines for Treatment of Cancer by Site are considered when updating this list of examples.
- The type of chemotherapy regimen is only one component of the Risk Assessment. (See Patient Risk Factors for Developing Febrile Neutropenia, MGF-2)
- The exact risk includes agent, dose, and the treatment setting (ie, treatment naive vs. heavily pretreated patients). (See MGF-1)
- In general, dose-dense regimens require MGF support to maintain dose intensity and schedule.

Acute Lymphoblastic Leukemia (ALL)
- Select ALL regimens as directed by treatment protocol (See NCCN Guidelines for ALL)

Bladder Cancer
- Dose-dense MVAC (methotrexate, vinblastine, doxorubicin, cisplatin)[1]

Bone Cancer
- VAI (vincristine, doxorubicin or dactinomycin, ifosfamide)[2]
- VDC-IE (vincristine, doxorubicin or dactinomycin, and cyclophosphamide alternating with ifosfamide and etoposide)[3]
- Cisplatin/doxorubicin[4]
- VDC (cyclophosphamide, vincristine, doxorubicin or dactinomycin)[5]
- VIDE (vincristine, ifosfamide, doxorubicin or dactinomycin, etoposide)[6]

Breast Cancer
- Dose-dense AC followed by dose-dense paclitaxel (doxorubicin, cyclophosphamide, paclitaxel)[7]
- TAC (docetaxel, doxorubicin, cyclophosphamide)[8]
- TC[a,b] (docetaxel, cyclophosphamide)[9]
- TCH[a] (docetaxel, carboplatin, trastuzumab)[10]

Colorectal Cancer
FOLFOXIRI (fluorouracil, leucovorin, oxaliplatin, irinotecan)[11]

Head and Neck Squamous Cell Carcinoma
- TPF (docetaxel, cisplatin, 5-fluorouracil)[12-14]

Hodgkin Lymphoma
- Brentuximab vedotin + AVD (doxorubicin, vinblastine, dacarbazine)[15]
- Escalated BEACOPP[c] (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone)[16]

Kidney Cancer
- Doxorubicin/gemcitabine[17]

Non-Hodgkin's Lymphomas
- Dose-adjusted EPOCH[a] (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin)[18]
- ICE (ifosfamide, carboplatin, etoposide)[a,19,20]
- Dose-dense CHOP-14[a] (cyclophosphamide, doxorubicin, vincristine, prednisone)[21,22]
- MINE[a] (mesna, ifosfamide, mitoxantrone, etoposide)[23]
- DHAP[a] (dexamethasone, cisplatin, cytarabine)[24]
- ESHAP[a] (etoposide, methylprednisolone, cisplatin, cytarabine)[25]
- HyperCVAD[a] (cyclophosphamide, vincristine, doxorubicin, dexamethasone)[26,27]

Melanoma
- Dacarbazine-based combination with IL-2, interferon alfa (dacarbazine, cisplatin, vinblastine, IL-2, interferon alfa)[28]

Multiple Myeloma
- DT-PACE (dexamethasone/thalidomide/cisplatin/doxorubicin/cyclophosphamide/etoposide)[29] ± bortezomib (VTD-PACE)[30]

Ovarian Cancer
- Topotecan[a,31]
- Docetaxel[32]

Pancreatic Cancer
FOLFIRINOX[d] (fluorouracil, leucovorin, irinotecan, oxaliplatin)

Soft Tissue Sarcoma
- MAID (mesna, doxorubicin, ifosfamide, dacarbazine)[33]
- Doxorubicin[a,34]
- Ifosfamide/doxorubicin[35]

Small Cell Lung Cancer
- Topotecan[36]

Testicular Cancer
- VeIP (vinblastine, ifosfamide, cisplatin)[37]
- VIP (etoposide, ifosfamide, cisplatin)
- TIP (paclitaxel, ifosfamide, cisplatin)[38]

See Disease Settings and Chemotherapy Regimens with an Intermediate Risk for Febrile Neutropenia, MGF-A (2 of 5)

[a]Guidelines apply to chemotherapy regimens with or without monoclonal antibodies (eg, trastuzumab, rituximab). There is the potential for increased neutropenia risk with the addition of monoclonal antibodies. Rituximab has been associated with prolonged neutropenia with or without chemotherapy. For details on when monoclonal antibodies are recommended with the regimens listed above in clinical practice, see NCCN Guidelines for Treatment of Cancer by Site.

[b]Risk for febrile neutropenia has been reported variably as intermediate risk or high risk depending on the study.

[c]Risk of bleomycin-induced pulmonary toxicity may be increased in patients treated with G-CSFs. See Toxicity Risks with Myeloid Growth Factors (MGF-D).

[d]A small retrospective trial had a 17% risk of febrile neutropenia in the neoadjuvant setting[39] and a randomized trial had a 5.4% risk in the metastatic setting (G-CSFs were administered to 42.5% of patients who received FOLFIRINOX).[40] While G-CSFs was not recommended as primary prophylaxis, it may be considered in patients with high-risk clinical features.

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Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

References

EXAMPLES OF DISEASE SETTINGS AND CHEMOTHERAPY REGIMENS WITH AN INTERMEDIATE RISK FOR FEBRILE NEUTROPENIA (10%–20%)[a]

- ***This list is not comprehensive***; **there are other agents/regimens that have an intermediate risk for the development of febrile neutropenia. Regimens recommended in the NCCN Guidelines for Treatment of Cancer by Site are considered when updating this list of examples.**
- **The type of chemotherapy regimen is only one component of the Risk Assessment. See Patient Risk Factors for Developing Febrile Neutropenia (MGF-2).**
- **The exact risk includes agent, dose, and the treatment setting (ie, treatment naive vs. heavily pretreated patients). (See MGF-1)**
- **In general, dose-dense regimens require myeloid growth factor support to maintain dose intensity and schedule.**

Occult Primary- Adenocarcinoma
- Gemcitabine/docetaxel[41]

Breast Cancer
- Docetaxel[a,42,43]
- AC (doxorubicin, cyclophosphamide) + sequential docetaxel (taxane portion only)[a,44]
- Paclitaxel every 21 days[a,45]

Cervical Cancer
- Cisplatin/topotecan[46-48]
- Paclitaxel/cisplatin[a,48]
- Topotecan[49]
- Irinotecan[50]

Colorectal Cancer
- FOLFOX[a] (fluorouracil, leucovorin, oxaliplatin)[e,51]

Esophageal and Gastric Cancers
- Irinotecan/cisplatin[a,52]
- Epirubicin/cisplatin/5-fluorouracil[53]
- Epirubicin/cisplatin/capecitabine[53]

Non-Hodgkin's Lymphomas
- GDP (gemcitabine, dexamethasone, cisplatin/carboplatin)[a,54]
- CHOP[a] (cyclophosphamide, doxorubicin, vincristine, prednisone)[55,56] including regimens with pegylated liposomal doxorubicin[57,58]
- CHP (cyclophosphamide, doxorubicin, prednisone) + brentuximab vedotin
- Bendamustine[a]

Non-Small Cell Lung Cancer
- Cisplatin/paclitaxel[59]
- Cisplatin/vinorelbine[60]
- Cisplatin/docetaxel[59,61]
- Cisplatin/etoposide[62]
- Carboplatin/paclitaxel[a,f,63]
- Docetaxel[61]

Ovarian Cancer
- Carboplatin/docetaxel[64]

Prostate Cancer
- Cabazitaxel[g,65]

Small Cell Lung Cancer
- Etoposide/carboplatin[66]

Testicular Cancer
- BEP[h] (bleomycin, etoposide, cisplatin)[67-69]
- Etoposide/cisplatin[70]

Uterine Sarcoma
- Docetaxel[71]

[a]Guidelines apply to chemotherapy regimens with or without monoclonal antibodies (eg, trastuzumab, rituximab). There is the potential for increased neutropenia risk with the addition of monoclonal antibodies. Rituximab has been associated with prolonged neutropenia with or without chemotherapy. For details on when monoclonal antibodies are recommended with the regimens listed above in clinical practice, see NCCN Guidelines for Treatment of Cancer by Site.

[e]There is variable risk with FOLFOX regimens. Please refer to the risk level of the specified FOLFOX regimen being used for therapy.

[f]If carboplatin dose is AUC >6 and/or patient is of Japanese ancestry.

[g]The published results for cabazitaxel have an 8% rate of febrile neutropenia but neutropenic deaths were reported. Primary prophylaxis with G-CSFs should be considered in patients with high-risk clinical features.

[h]Risk of bleomycin-induced pulmonary toxicity may be increased in patients treated with G-CSFs. See Toxicity Risks with Myeloid Growth Factors (MGF-D).

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Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

References

CHEMOTHERAPY REGIMEN REFERENCES

Note: The references listed for each regimen are limited by the specific populations studied, methods, and collection of data for febrile neutropenia in the clinical trial.

[1]Sternberg CN, de Mulder PH, Schornagel JH, et al. Randomized phase III trial of high-dose-intensity methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) chemotherapy and recombinant human granulocyte colony stimulating factor versus classic MVAC in advanced urothelial tract tumors: European Organization for Research and Treatment of Cancer Protocol no. 30924. J Clin Oncol 2001;19:2638-2646.

[2]Paulussen M, Craft AW, Lewis I, et al. Results of the EICESS-92 Study: two randomized trials of Ewing's sarcoma treatment--cyclophosphamide compared with ifosfamide in standard-risk patients and assessment of benefit of etoposide added to standard treatment in high-risk patients. J Clin Oncol 2008;26(27):4385-4393.

[3]Grier HE, Krailo MD, Tarbell NJ, et al. Addition of ifosfamide and etoposide to standard chemotherapy for Ewing's sarcoma and primitive neuroectodermal tumor of bone. N Engl J Med 2003;348(8):694-701.

[4]Lewis IJ, Nooij MA, Whelan J, et al. Improvement in histologic response but not survival in osteosarcoma patients treated with intensified chemotherapy: a randomized phase III trial of the European Osteosarcoma Intergroup. J Natl Cancer Inst 2007;99(2):112-128.

[5]Miser JS, Krailo MD, Tarbell NJ, et al. Treatment of metastatic Ewing's sarcoma or primitive neuroectodermal tumor of bone: evaluation of combination ifosfamide and etoposide--a Children's Cancer Group and Pediatric Oncology Group study. J Clin Oncol 2004;22(14):2873-2876.

[6]Juergens C, Weston C, Lewis I, et al. Safety assessment of intensive induction with vincristine, ifosfamide, doxorubicin, and etoposide (VIDE) in the treatment of Ewing tumors in the EURO-E.W.I.N.G. 99 clinical trial. Pediatr Blood Cancer 2006;47(1):22-29.

[7]Citron ML, Berry DA, Cirrincione C, et al. Randomized trial of dose-dense versus conventionally scheduled and sequential versus concurrent combination chemotherapy as postoperative adjuvant treatment of node positive primary breast cancer: first report of Intergroup Trial C9741/Cancer and Leukemia Group B Trial 9741. J Clin Oncol 2003;21:1431-1439.

[8]Martin M, Lluch A, Segui MA, et al. Prophylactic growth factor (GF) support with adjuvant docetaxel, doxorubicin, and cyclophosphamide (TAC) for node-negative breast cancer (BC): An interim safety analysis of the GEICAM 9805 study [abstract]. Proc Amer Soc Clin Oncol 2004;23:Abstract 620.

[9]Kosaka Y, Rai Y, Masuda N, et al. Phase III placebo-controlled, double-blind, randomized trial of pegfilgrastim to reduce the risk of febrile neutropenia in breast cancer patients receiving docetaxel/cyclophosphamide chemotherapy. Support Care Cancer 2015;23(4):1137-1143.

[10]Gilbar P, McPherson I, Sorour N, Sanmugarajah J. High incidence of febrile neutropenia following adjuvant breast chemotherapy with docetaxel, carboplatin and trastuzumab. Breast Cancer Manag 2014;3:327-333.

[11]Falcone, A et al. Phase III trial of infusional fluorouracil, leucovorin, oxaliplatin, and irinotecan (FOLFOXIRI) compared with infusional fluorouracil, leucovorin, and irinotecan (FOLFIRI) as first-line treatment for metastatic colorectal cancer: the Gruppo Oncologico Nord Ovest. J Clin Oncol. 2007 May 1;25(13):1670-6

[12]Posner MR, Hershock DM, Blajman CR, et al. Cisplatin and fluorouracil alone or with docetaxel in head and neck cancer. N Engl J Med 2007;357:1705-1715.

[13]Pointreau Y, Garaud P, Chapet S, et al. Randomized trial of induction chemotherapy with cisplatin and 5-fluorouracil with or without docetaxel for larynx preservation. J Natl Cancer Inst 2009;101:498-506.

[14]Vermorken JB, Remenar E, van Herpen C, et al. Cisplatin, fluorouracil, and docetaxel in unresectable head and neck cancer. N Engl J Med 2007;357:1695-1704.

[15]Connors JM, Jurczak W, Straus DJ, et al. Brentuximab vedotin with chemotherapy for stage III or IV Hodgkin's lymphoma. N Engl J Med 2018;378:331-344.

[16]Diehl V, Franklin J, Pfreundschuh M, et al. Standard and increased-dose BEACOPP chemotherapy compared with COPP-ABVD for advanced Hodgkin's disease. N Engl J Med 2003;348:2386-2395.

[17]Nanus DM, Garino A, Milowsky MI, et al. Active chemotherapy for sarcomatoid and rapidly progressing renal cell carcinoma. Cancer 2004;101:1545-1551.

[18]Gutierrez M, Chabner B, Pearson D, et al. Role of a doxorubicin-containing regimen in relapsed and resistant lymphomas: An 8-year follow-up study of EPOCH. J Clin Oncol 2000;18:3633-3642.

[19]Hertzberg MS, Crombie C, Benson W, et al. Outpatient fractionated ifosfamide, carboplatin and etoposide as salvage therapy in relapsed and refractory non-Hodgkin's and Hodgkin's lymphoma. Ann Oncol 2006;Suppl 4:iv25-30.

[20]Kewalramani T, Zelenetz AD, Nimer SD, et al. Rituximab and ICE as second-line therapy before autologous stem cell transplantation for relapsed or primary refractory diffuse large B-cell lymphoma. Blood 2004;103:3684-3688.

[21]Blayney DW, LeBlanc ML, Grogan T, et al. Dose-intense chemotherapy every 2 weeks with dose-intense cyclophosphamide, doxorubicin, vincristine, and prednisone may improve survival in intermediate- and high-grade lymphoma: a phase II study of the Southwest Oncology Group (SWOG 9349). J Clin Oncol 2003;21:2466-2473.

[22]Watanabe T, Tobinai K, Shibata T, et al. Phase II/III study of R-CHOP-21 versus R-CHOP-14 for untreated indolent B-cell non-Hodgkin's lymphoma: JCOG 0203 trial. J Clin Oncol 2011;29:3990-3998.

[23]Rodriguez MA, Cabanillas FC, Hagemeister FB, et al. A phase II trial of mesna/ifosfamide, mitoxantrone and etoposide for refractory lymphomas. Ann Oncol 1995;6:609-611.

[24]Velasquez WS, Cabanillas F, Salvador P, et al. Effective salvage therapy for lymphoma with cisplatin in combination with high-dose Ara-C and dexamethasone (DHAP). Blood 1988;71:117-122.

[25]Velasquez WS, McLaughlin P, Tucker S, et al. ESHAP--an effective chemotherapy regimen in refractory and relapsing lymphoma: A 4-year follow-up study. J Clin Oncol 1994;12:1169-1176.

Continued

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CHEMOTHERAPY REGIMEN REFERENCES

Note: The references listed for each regimen are limited by the specific populations studied, methods, and collection of data for febrile neutropenia in the clinical trial.

[26]Thomas DA, Faderl S, O'Brien S, et al. Chemoimmunotherapy with hyper-CVAD plus rituximab for the treatment of adult Burkitt and Burkitt-type lymphoma or acute lymphoblastic leukemia. Cancer 2006;106:1569-1580.
[27]Romaguera JE, Fayad L, Rodriguez MA, et al. High rate of durable remissions after treatment of newly diagnosed aggressive mantle-cell lymphoma with rituximab plus hyper-CVAD alternating with rituximab plus high-dose methotrexate and cytarabine. J Clin Oncol 2005;23:7013-7023.
[28]Eton O, Legha S, Bedikian A, et al. Sequential biochemotherapy versus chemotherapy for metastatic melanoma: Results from a phase III randomized trial. J Clin Oncol 2002;20:2045-2052.
[29]Lee CK, Barlogie B, Munshi N, DTPACE: An effective, novel combination chemotherapy with thalidomide for previously treated patients with myeloma. J Clin Oncol 2003;21:2732-2739.
[30]Barlogie B, Anaissie E, van Rhee F, et al. Incorporating bortezomib into upfront treatment for multiple myeloma: early results of total therapy 3. Br J Haematol 2007;138:176-185.
[31]Swisher EM, Mutch DG, Rader JS, et al. Topotecan in platinum- and paclitaxel-resistant ovarian cancer. Gynecol Oncol 1997;66:480-486.
[32]Verschraegen CF, Sittisomwong T, Kudelka AP, et al. Docetaxel for patients with paclitaxel-resistant Mullerian carcinoma. J Clin Oncol 2000;18:2733-2739.
[33]Antman K, Crowley J, Balcerzak SP, et al. A Southwest Oncology Group and Cancer and Leukemia Group B phase II study of doxorubicin, dacarbazine, ifosfamide, and mesna in adults with advanced osteosarcoma, Ewing's sarcoma, and rhabdomyosarcoma. Cancer 1998;82:1288-1295.
[34]Nielsen OS, Dombernowsky P, Mouridsen H, et al. High-dose epirubicin is not an alternative to standard-dose doxorubicin in the treatment of advanced soft tissue sarcomas. A study of the EORTC soft tissue and bone sarcoma group. Br J Cancer 1998;78:1634-1639.
[35]Patel SR, Vadhan-Raj S, Burgess MA, et al. Results of two consecutive trials of dose-intensive chemotherapy with doxorubicin and ifosfamide in patients with sarcomas. Am J Clin Oncol 1998;21:317-321.
[36]Von Pawel J, Schiller JH, Shepherd FA, et al. Topotecan versus cyclophosphamide, doxorubicin, and vincristine for the treatment of recurrent small-cell lung cancer. J Clin Oncol 1999;17:658-667.
[37]Miller KD, Loehrer PJ, Gonin R, Einhorn LH. Salvage chemotherapy with vinblastine, ifosfamide, and cisplatin in recurrent seminoma. J Clin Oncol 1997;15:1427-1431.
[38]Kondagunta GV, Bacik J, Donadio A, et al. Combination of paclitaxel, ifosfamide, and cisplatin is an effective second-line therapy for patients with relapsed testicular germ cell tumors. J Clin Oncol 2005;23:6549-6555.
[39] Hosein PJ, Macintyre J, Kawamura C, et al. A retrospective study of neoadjuvant FOLFIRINOX in unresectable or borderline-resectable locally advanced pancreatic adenocarcinoma. BMC Cancer 2012;12:199.
[40]Conroy T, Desseigne F, Ychou M et al. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. N Engl J Med 2011;364:1817-1825.
[41]Pouessel D, Culine S, Becht C, et al. Gemcitabine and docetaxel as front line chemotherapy in patients with carcinoma of an unknown primary site. Cancer 2004;10:1257-1261.
[42]Marty M, Cognetti F, Maraninchi D, et al. Randomized phase II trial of the efficacy and safety of trastuzumab combined with docetaxel in patients with human epidermal growth factor receptor 2–positive metastatic breast cancer administered as first-line treatment: the M77001 study group. J Clin Oncol 2005;23:4265-4274.
[43]Burris HA 3rd. Single-agent docetaxel (Taxotere) in randomized phase III trials. Seminars in Oncol 1999;26:1-6.
[44]Sparano JA, Wang M, Martino S, et al. Phase III study of doxorubicin-cyclophosphamide followed by paclitaxel or docetaxel given every 3 weeks or weekly in patients with axillary node-positive or high-risk node-negative breast cancer: Results of North American Breast Cancer Intergroup Trial E1199. SABCS 2005 #48.
[45]AD, Tiersten A, Hudis C, et al. Phase II trial of paclitaxel by 3-hour infusion as initial and salvage chemotherapy for metastatic breast cancer. J Clin Oncol 1995;13:2575-2581.
[46]Long III HJ, Bundy BN, Grendys Jr EC, et al. Randomized phase III trial of cisplatin with or without topotecan in carcinoma of the uterine cervix: A Gynecologic Oncology Group Study. J Clin Oncol 2005;23:4626-4633.
[47]Monk B, Sill MW, McMeekin DS, et al. Phase III trial of four cisplatin-containing doublet combinations in stage IVB, recurrent, or persistent cervical carcinoma: a Gynecologic Oncology Group study. J Clin Oncol 2009;7:4649-4655.
[48]Long, HJ 3rd, Bundy BN, Grendys EC Jr, . et al. Randomized phase III trial of cisplatin with or without topotecan in carcinoma of the uterine cervix: a Gynecologic Oncology Group Study. J Clin Oncol 2005;23:4626-4633.
[49]Muderspach LI, Blessing JA, Levenback C, et al. A phase II study of topotecan in patients with squamous cell carcinoma of the cervix: a gynecologic oncology group study. Gynecol Oncol 2001;81:213-215.
[50]Verschraegen CF, Levy T, Kudelka AP, et al. Phase II study of irinotecan in prior chemotherapy-treated squamous cell carcinoma of the cervix. J Clin Oncol 1997;15:625-631.
[51]Goldberg RM, Sargent DJ, Morton RF, et al. Randomized controlled trial of reduced-bolus fluorouracil plus leucovorin and irinotecan or infused fluorouracil plus leucovorin and oxaliplatin in patients with previously untreated metastatic colorectal cancer: A North American Intergroup Trial. J Clin Oncol 2006;24:3347-3353.
[52]Ilson DH. Phase II trial of weekly irinotecan/cisplatin in advanced esophageal cancer. Oncology (Williston Park) 2004;18(14 Suppl 14):22-25.
[53]Cunningham D, Starling N, Rao S, et al. Capecitabine and oxaliplatin for advanced esophagogastric cancer. N Eng J Med 2008;358:36-46.

Continued

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CHEMOTHERAPY REGIMEN REFERENCES

Note: The references listed for each regimen are limited by the specific populations studied, methods, and collection of data for febrile neutropenia in the clinical trial.

[54]Crump M, Baetz T, Couban S, et al. Gemcitabine, dexamethasone, and cisplatin in patients with recurrent or refractory aggressive histology B-cell non-hodgkin lymphoma: a Phase II study by the National Cancer Institute of Canada Clinical Trials Group (NCIC-CTG). Cancer 2004;101:1835-1842.
[55]Coiffier B, Lepage E, Briere J, et al. CHOP chemotherapy plus rituximab compared with CHOP alone in elderly patients with diffuse large-B-cell lymphoma. N Engl J Med 2002;346:235-242.
[56]Lyman G, Delgado DJ. Risk of febrile neutropenia among patients with intermediate-grade non-Hodgkin's lymphoma receiving CHOP chemotherapy. Leuk Lymphoma 2003;44:2069-2076.
[57]Martino R, Perea G, Caballero MD, et al. Cyclophosphamide, pegylated liposomal doxorubicin (Caelyx), vincristine and prednisone (CCOP) in elderly patients with diffuse large B-cell lymphoma: results from a prospective phase II study. Haematologica 2002;87:822-827.
[58]Zaja F, Tomadini V, Zaccaria A, et al. CHOP-rituximab with pegylated liposomal doxorubicin for the treatment of elderly patients with diffuse large B-cell lymphoma. Leuk Lymphoma 2006;47:2174-2180.
[59]Schiller JH, Harrington D, Belani CP, et al. Comparison of four chemotherapy regimens for advanced non-small cell lung cancer. N Engl J Med 2002;346:92-98.
[60]Pujol J-L, Breton J-L, Gervais R, et al. Gemcitabine-docetaxel versus cisplatin-vinorelbine in advanced or metastatic non-small-cell lung cancer: a phase III study addressing the case for cisplatin. Ann Oncol 2005;16:602-610.
[61]Fossella F, Pereira JR, von Pawel J, et al. Randomized, multinational, phase III study of docetaxel plus platinum combinations versus vinorelbine plus cisplatin for advanced non-small-cell lung cancer: The TAX 326 study group. J Clin Oncol 2003;21:3016-3024.
[62]Cardenal F, Lopez-Cabrerizo P, Anton A, et al. Randomized phase III study of gemcitabine-cisplatin versus etoposide-cisplatin in the treatment of locally advanced or metastatic non-small-cell lung cancer. J Clin Oncol 1999;17:12-18.
[63]Ohe Y, Ohashi Y, Kubota K, et al. Randomized phase III study of cisplatin plus irinotecan versus carboplatin plus paclitaxel, cisplatin plus gemcitabine, and cisplatin plus vinorelbine for advanced non-small-cell lung cancer: Four-Arm Cooperative Study in Japan. Ann Oncol 2007;18:317-323.
[64]Vasey, PA, Jayson GC, Gordon, A, et al. Phase III randomized trial of docetaxel-carboplatin versus paclitaxel-carboplatin as first line chemotherapy for ovarian carcinoma. J Nat Can Inst 2004;96:1682-1691.
[65]de Bono JS, Oudard S, Ozguroglu M, et al. Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: a randomised open-label trial. Lancet 2010;376:1147-1154.
[66]Kosmidis PA, Samantas E, Fountzilas G, et al. Cisplatin/etoposide versus carboplatin/etoposide chemotherapy and irradiation in small cell lung cancer randomized phase II study. Hellenic Cooperative Oncology Group for Lung Cancer Trials. Semin Oncol 1994;21(3 Suppl 6):23-30.
[67]Garcia del Muro X, Maroto P, Guma J, et al. Chemotherapy as an alternative to radiotherapy in the treatment of stage IIA and IIB testicular seminoma: a Spanish Germ Cell Cancer Group Study. J Clin Oncol 2008;26:5416-5421.
[68]Fizazi K, Pagliaro L, Laplanche A, et al. Personalised chemotherapy based on tumour marker decline in poor prognosis germ-cell tumours (GETUG 13): a phase 3, multicentre, randomised trial. Lancet Oncol 2014;15:1442-1450.
[69]de Wit R, Skoneczna I, Daugaard G, et al. Randomized phase III study comparing paclitaxel-bleomycin, etoposide, and cisplatin (BEP) to standard BEP in intermediate-prognosis germ-cell cancer: intergroup study EORTC 30983. J Clin Oncol 2012;30:792-799.
[70]Motzer RJ, Sheinfeld J, Mazumdar M, et al. Etoposide and cisplatin adjuvant therapy for patients with pathologic stage II germ cell tumors. J Clin Oncol 1995;13:2700-2704.
[71]van Hoesel Q, Verweij J, Catimel G, et al. Phase II study with docetaxel (Toxotere) in advanced soft tissue sarcomas of the adult. Ann Oncol 1994;5:539-542.

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G-CSFs FOR PROPHYLAXIS OF FEBRILE NEUTROPENIA AND MAINTENANCE OF SCHEDULED DOSE DELIVERY

- **Filgrastim[b] (category 1) or tbo-filgrastim[a] (category 1)**
  - **Daily dose of 5 mcg/kg (rounding to the nearest vial size by institution-defined weight limits) until post-nadir ANC recovery to normal or near-normal levels by laboratory standards.**
  - **Start the next day or up to 3–4 days after completion of myelosuppressive chemotherapy and treat through post-nadir recovery.[c,d]**
- **Pegfilgrastim[b] (category 1)**
  - **One dose of 6 mg**
    - ◊ **Based on clinical trial data, pegfilgrastim[b] should be administered the day after myelosuppressive chemotherapy (category 1).[e]**
    - ◊ **There should be at least 12 days between the dose of pegfilgrastim[b] and the next cycle of chemotherapy.**
    - ◊ **If the treatment cycle includes chemotherapy administration on days 1 and 15, pegfilgrastim[b] may be given after each chemotherapy treatment.**
    - ◊ **For patients who cannot return to the clinic for next-day administration, there is an FDA-approved delivery device available that can be applied the same day as chemotherapy in order to deliver the full dose of pegfilgrastim the following day (approximately 27 hours after application).[f,g]**
    - ◊ **Administration of pegfilgrastim[b] up to 3–4 days after chemotherapy is also reasonable based on trials with filgrastim.**
  - **There is evidence to support use for chemotherapy regimens given every 3 weeks (category 1).**
  - **There are phase II studies that demonstrate efficacy for chemotherapy regimens given every 2 weeks.**
  - **There are insufficient data to support use for cytotoxic chemotherapy regimens administered every week; therefore, pegfilgrastim should not be used.**
- **Subcutaneous route is preferred for all G-CSFs listed above.**
- **For information regarding prophylactic anti-infectives (ie, viral, fungal, bacterial), see NCCN Guidelines for Prevention and Treatment of Cancer-Related Infections.**

See Toxicity Risks with Myeloid Growth Factors (MGF-D)

[a] Tbo-filgrastim is a human G-CSF approved by the FDA through an original biologic license application. All of these G-CSFs are indicated for reducing the duration of severe neutropenia in patients with nonmyeloid malignancies receiving myelosuppressive chemotherapy associated with a clinically significant incidence of febrile neutropenia.

[b] An FDA-approved biosimilar is an appropriate substitute for filgrastim and pegfilgrastim. See Discussion for more details.

[c] Studies suggest that shorter durations of G-CSFs may be less efficacious. (Weycker D, Li X, Tzivelekis S, et al. Burden of chemotherapy-induced febrile neutropenia hospitalizations in US clinical practice, by use and patterns of prophylaxis with colony-stimulating factor. Support Care Cancer 2017;25:439-447.)

[d] Neutrophil counts should be monitored, as indicated, appropriate to the setting.

[e] Lyman GH, Allcott K, Garcia J, et al. The effectiveness and safety of same-day versus next-day administration of long-acting granulocyte colony-stimulating factors for the prophylaxis of chemotherapy-induced neutropenia: a systematic review. Support Cancer Care 2017;25:2619-2629.

[f] Rarely, there is a failure to inject that requires further medical attention.

[g] Yang BB, Morrow PK, Wu X, et al. Comparison of pharmacokinetics and safety of pegfilgrastim administered by two delivery methods: on-body injector and manual injection with a prefilled syringe. Cancer Chemother Pharmacol 2015;75:1199-1206.

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MYELOID GROWTH FACTORS IN MOBILIZATION AND POST HEMATOPOIETIC CELL TRANSPLANT

Effective mobilization regimens include growth factor alone, chemotherapy and growth factor combined, and incorporation of plerixafor with either approach.

Mobilization of Hematopoietic Progenitor Cells in Autologous Setting

- **Single-agent growth factor:[1-3]**
  - **Filgrastim[a] or tbo-filgrastim**
    - ◊ **Dose: 10–32 mcg/kg per day by subcutaneous injection, in daily or twice-daily dosing. Begin apheresis on day 4 or 5 and continue until leukapheresis.**
- **Combination chemotherapy followed by filgrastim[a] or tbo-filgrastim with the goal of mobilization during count recovery[4-6] that may result in higher collection yields with fewer days of apheresis but increased rate of hospitalizations for neutropenic fever.[7] This approach may also reduce burden of residual tumor.**
  - **Filgrastim[a] or tbo-filgrastim is started about 24 hours after completion of chemotherapy.**
- **Concurrent filgrastim[a] + sargramostim (category 2B)**
  - **Filgrastim[a] 7.5 mcg/kg each morning, sargramostim 7.5 mcg/kg each evening, and leukapheresis beginning on day 5.[8]**
- **Filgrastim[a] or tbo-filgrastim + plerixafor[9-14]**
  - **Plerixafor is FDA approved in combination with G-CSFs for the purpose of mobilizing autologous hematopoietic stem cells to the peripheral blood in patients with non-Hodgkin's lymphoma and multiple myeloma.**
  - **Existing literature suggests that a preemptive "just in time" strategy of adding plerixafor for patients who do not mount a sufficient CD34+ cell count is highly successful.[15-17]**
  - **There are limited data on parameters for predicting poor mobilization and which patients may benefit from upfront use of plerixafor. Risk factors that have been associated with poor mobilization include older age, extensive prior therapy, prior radiation to marrow-containing regions, or multiple cycles of certain agents such as fludarabine or lenalidomide. See Discussion.**
  - **Dosing for MGF and plerixafor: See MGF-C (2 of 4)**

See Toxicity Risks with Myeloid Growth Factors (MGF-D)

[a]An FDA-approved biosimilar is an appropriate substitute for filgrastim. See Discussion for more details.

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References

MYELOID GROWTH FACTORS IN MOBILIZATION AND POST HEMATOPOIETIC CELL TRANSPLANT

- **Dosing for MGF and plerixafor:**
  - ◊ **Filgrastim or tbo-filgrastim dose: 10 mcg/kg per day x 4 days.**
  - ◊ **On the evening of day 4 of growth factors, start plerixafor by subcutaneous injection 11 hours prior to initiation of apheresis (day 5 collection the next morning).**
  - ◊ **Repeat plerixafor dose up to 4 consecutive days.**
  - ◊ **Recommended plerixafor dose:[d]**

Estimated Creatinine Clearance	Dose	
	Body weight ≤83 kg	Body weight >83 kg and <160 kg
>50 (mL/min)	20 mg or 0.24 mg/kg once daily	0.24 mg/kg once daily (not to exceed 40 mg/day)
≤50 (mL/min)	13 mg or 0.16 mg/kg once daily	0.16 mg/kg once daily (not to exceed 27 mg/day)

Mobilization of Allogeneic Donors

- **Allogeneic hematopoietic cell donors:[18-21]**
  - **Filgrastim[a] or tbo-filgrastim (category 2B)**
    - ◊ **Dose: 10–16 mcg/kg per day by subcutaneous injection, start collection on day 4 or 5.[22-24]**
  - **Plerixafor (category 2B): Use in normal donors is under study.[25-27]**
- **For granulocyte transfusion:**
  - **Filgrastim[a] or tbo-filgrastim (category 2B)**
    - ◊ **Single dose: 5 mcg/kg subcutaneously with dexamethasone 10 mg PO 8–24 hours prior to collection.[28]**

Supportive Care Options

- **Filgrastim[a,b,29] or tbo-filgrastim**
  - **Post-autologous hematopoietic cell transplant, haploidentical transplant, or cord blood transplant**
  - **5 mcg/kg per day. Begin day 5–7 post transplant until recovery of ANC (eg, >1.5 x 10^9/L x 2 days).[c]**
- **Pegfilgrastim[a,30-36]- Post-autologous hematopoietic cell transplant**

See Toxicity Risks with Myeloid Growth Factors (MGF-D)

[a]An FDA-approved biosimilar is an appropriate substitute for filgrastim and pegfilgrastim. See Discussion for more details.
[b]Filgrastim accelerates neutrophil recovery but has not impacted survival. See Discussion for details.
[c]For additional dosing information refer to the package insert.
[d]U.S. Food and Drug Administration. Plerixafor label information. 2017. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/022311s018lbl.pdf. Accessed March 7, 2019.

References

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MYELOID GROWTH FACTORS IN MOBILIZATION AND POST HEMATOPOIETIC CELL TRANSPLANT
REFERENCES

[1]Kroger N, Zeller W, Fehse N, et al. Mobilizing peripheral blood stem cells with high-dose G-CSF alone is as effective as with Dexa-BEAM plus G-CSF in lymphoma patients. Br J Haematol 1998;102:1101-1106.
[2]Elayan MM, Horowitz JG, Magraner JM, et al. Tbo-filgrastim versus filgrastim during mobilization and neutrophil engraftment for autologous stem cell transplantation. Biol Blood Marrow Transplant 2015;21:1921-1925.
[3]Trifilio S, Zhou Z, Galvin J, et al. Filgrastim versus tbo-filgrastim to reduce the duration of neutropenia after autologous hematopoietic stem cell transplantation: TBO, or not TBO, that is the question. Clin Transplant 2015;29:1128-1132.
[4]Haynes A, Hunter A, McQuaker G, et al. Engraftment characteristics of peripheral-blood stem-cells mobilized with cyclophosphamide and the delayed addition of G-CSF. Bone Marrow Transplant 1995;16:359-363.
[5]Matasar MJ, Czuczman MS, Rodriguez MA, et al. Ofatumumab in combination with ICE or DHAP chemotherapy in relapsed or refractory intermediate grade B-cell lymphoma. Blood 2013;122:499-506.
[6]Barlogie B, Anaissie E, van Rhee F, et al. Incorporating bortezomib into upfront treatment for multiple myeloma: early results of total therapy 3. Br J Haematol 2007;138:176-185.
[7]Chao N, Grima D, Carrum G, et al. Chemo-mobilization provides superior mobilization and collection in autologous stem cell transplants but with less predictability and at a higher cost [abstract] Blood 2011;118: Abstract 4048.
[8]Lonial S, Akhtari M, Kaufman J, et al. Mobilization of hematopoietic progenitors from normal donors using the combination of granulocyte-macrophage colony-stimulating factor and granulocyte colony-stimulating factor results in fewer plasmacytoid dendritic cells in the graft and enhanced donor T cell engraftment with Th1 polarization: results from a randomized clinical trial. Biol Blood Marrow Transplant 2013;19:460-467.
[9]Becker PS. Optimizing stem cell mobilization: lessons learned. J Natl Compr Canc Netw 2014;12:1443-1449.
[10]DiPersio JF, Micallef IN, Stiff PJ, et al. Phase III prospective randomized double-blind placebo-controlled trial of plerixafor plus granulocyte colony-stimulating factor compared with placebo plus granulocyte colony-stimulating factor for autologous stem-cell mobilization and transplantation for patients with non-Hodgkin's lymphoma. J Clin Oncol 2009;27:4767-4773.
[11]DiPersio JF, Stadtmauer EA, Nademanee A, et al. Plerixafor and G-CSF versus placebo and G-CSF to mobilize hematopoietic stem cells for autologous stem cell transplantation in patients with multiple myeloma. Blood 2009;113:5720-5726.
[12]Giralt S, Costa L, Schriber J, et al. Optimizing autologous stem cell mobilization strategies to improve patient outcomes: consensus guidelines and recommendations. Biol Blood Marrow Transplant 2014;20(3):295-308.
[13]Duong HK, Savani BN, Copelan E, et al. Peripheral blood progenitor cell mobilization for autologous and allogeneic hematopoietic cell transplantation: guidelines from the American Society for Blood and Marrow Transplantation. Biol Blood Marrow Transplant 2014;20(9):1262-1273.
[14]Dugan MJ, Maziarz RT, Bensinger WI, et al. Safety and preliminary efficacy of plerixafor (Mozobil) in combination with chemotherapy and G-CSF: an open label, multicenter, exploratory trial in patients with multiple myeloma and non-Hodgkin's lymphoma undergoing stem cell mobilization. Bone Marrow Transplant 2010;45:39-47.
[15]Gopal AK, Karami M, Mayor J, et al. The effective use of plerixafor as a real-time rescue strategy for patients poorly mobilizing autologous CD34(+) cells. J Clin Apher 2012;27:81-87.
[16]Milone G, Tripepi G, Martino M, et al. Early measurement of CD34+ cells in peripheral blood after cyclophosphamide and granulocyte colony-stimulating factor treatment predicts later CD34+ mobilisation failure and is a possible criterion for guiding "on demand" use of plerixafor. Blood Transfus 2013;11:94-101.
[17]Micallef IN, Stiff PJ, DiPersio JF, et al. Successful stem cell remobilization using plerixafor (mozobil) plus granulocyte colony-stimulating factor in patients with non-hodgkin lymphoma: Results from the plerixafor NHL phase 3 study rescue protocol. Biol Blood Marrow Transplant 2009;15:1578-1586.
[18]Antelo ML, Zabalza A, Sanchez Anton MP, et al. Mobilization of hematopoietic progenitor cells from allogeneic healthy donors using a new biosimilar G-CSF (Zarzio®). J Clin Apher ~~2015~~ 2016;31:48-52.
[19]Schmitt M, Xu X, Hilgendorf I, et al. Mobilization of PBSC for allogeneic transplantation by the use of the G-CSF biosimilar XM02 in healthy donors. Bone Marrow Transplant 2013;48:922-925.

Continued

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

MYELOID GROWTH FACTORS IN MOBILIZATION AND POST HEMATOPOIETIC CELL TRANSPLANT
REFERENCES

[20]Sivgin S, Karakus E, Keklik M, et al. Evaluation of the efficacy and safety of original filgrastim (Neupogen(R)), biosimilar filgrastim (Leucostim®) and Lenograstim (Granocyte(R)) in CD34(+) peripheral hematopoietic stem cell mobilization procedures for allogeneic hematopoietic stem cell transplant donors. Transfus Apher Sci 2016;54:410-415.

[21]Danylesko I, Sareli R, Bloom-Varda N, et al. Biosimilar filgrastim (tevagrastim, XM02) for allogeneic hematopoietic stem cell mobilization and transplantation in patients with acute myelogenous leukemia/myelodysplastic syndromes. Biol Blood Marrow Transplant 2016;22:277-283.

[22]Bensinger WI, Weaver CH, Appelbaum FR, et al. Transplantation of allogeneic peripheral blood stem cells mobilized by recombinant human granulocyte colony-stimulating factor. Blood 1995;85:1655-1658.

[23]Cavallaro AM, Lilleby K, Majolino I, et al. Three to six year follow-up of normal donors who received recombinant human granulocyte colony-stimulating factor. Bone Marrow Transplant 2000;25:85-89.

[24]Rinaldi C, Savignano C, Pasca S, et al. Efficacy and safety of peripheral blood stem cell mobilization and collection: a single-center experience in 190 allogeneic donors. Transfusion 2012;52:2387-2394.

[25]Gattillo S, Marktel S, Rizzo L, et al. Plerixafor on demand in ten healthy family donors as a rescue strategy to achieve an adequate graft for stem cell transplantation. Transfusion 2015;55:1993-2000.

[26]Schriber J, Fauble V, Sproat LO, Briggs A. Plerixafor 'just in time' for stem cell mobilization in a normal donor. Bone Marrow Transplant 2011;46:1026-1027.

[27]Schroeder MA, Rettig MP, Lopez S, et al. Mobilization of allogeneic peripheral blood stem cell donors with intravenous plerixafor mobilizes a unique graft. Blood 2017;129:2680-2692.

[28]Stroncek DF, Matthews CL, Follmann D, Leitman SF. Kinetics of G-CSF-induced granulocyte mobilization in healthy subjects: effects of route of administration and addition of dexamethasone. Transfusion 2002;42:597-602.

[29]Trivedi M, Martinez S, Corringham S, et al. Review and revision of clinical practice of using G-CSF after autologous and allogeneic hematopoietic stem cell transplantation at UCSD. J Oncol Pharm Pract 2011;17:85-90.

[30]Castagna L, Bramanti S, Levis A, et al. Pegfilgrastim versus filgrastim after high-dose chemotherapy and autologous peripheral blood stem cell support. Ann Oncol 2010;21:1482-1485.

[31]Sebban C, Lefranc A, Perrier L, et al. A randomized phase II study of the efficacy, safety, and cost-effectiveness of pegfilgrastim and filgrastim after autologous stem cell transplant for lymphoma and myeloma (PALM study). Eur J Cancer 2012;48:713-720.

[32]Wannesson L, Luthi F, Zucca E, et al. Pegfilgrastim to accelerate neutrophil engraftment following peripheral blood stem cell transplant and reduce the duration of neutropenia, hospitalization, and use of intravenous antibiotics: a phase II study in multiple myeloma and lymphoma and comparison with filgrastim-treated matched controls. Leuk Lymphoma 2011;52:436-443.

[33]Samaras P, Buset EM, Siciliano RD, et al. Equivalence of pegfilgrastim and filgrastim in lymphoma patients treated with BEAM followed by autologous stem cell transplantation. Oncology 2010;79:93-97.

[34]Samaras P, Blickenstorfer M, Siciliano RD, et al. Pegfilgrastim reduces the length of hospitalization and the time to engraftment in multiple myeloma patients treated with melphalan 200 and auto-SCT compared with filgrastim. Ann Hematol 2011;90:89-94.

[35]Rifkin R, Spitzer G, Orloff G, et al. Pegfilgrastim appears equivalent to daily dosing of filgrastim to treat neutropenia after autologous peripheral blood stem cell transplantation in patients with non-Hodgkin lymphoma. Clin Lymphoma Myeloma Leuk 2010;10:186-191.

[36]Gerds A, Fox-Geiman M, Dawravoo K, et al. Randomized phase III trial of pegfilgrastim versus filgrastim after autologous peripheral blood stem cell transplantation. Biol Blood Marrow Transplant 2010;16:678-685.

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TOXICITY RISKS WITH MYELOID GROWTH FACTORS

Filgrastim,[a] Pegfilgrastim,[a] and Tbo-filgrastim[b,c,d,e]

- **Warnings**
  - **Allergic reactions**
    - ◊ **Skin: rash, urticaria, facial edema**
    - ◊ **Respiratory: wheezing, dyspnea**
    - ◊ **Cardiovascular: hypotension, tachycardia, anaphylaxis**
  - **Bleomycin-containing regimens: pulmonary toxicity[d]**
  - **Splenic rupture[f]**
  - **Acute respiratory distress syndrome**
  - **Alveolar hemorrhage and hemoptysis**
  - **Sickle cell crises (only in patients with sickle cell disease)**
  - **MDS and AML[g]**
- **Precautions**
  - **Cutaneous vasculitis**
  - **Immunogenicity**
- **Adverse reactions**
  - **Bone pain[f,h]**

Sargramostim[b,d]

- **Warnings**
  - **Fluid retention**
  - **Respiratory symptoms**
  - **Cardiovascular symptoms: Use with caution in patients with preexisting cardiac disease.**
  - **Renal and hepatic dysfunction: Monitor patients who display renal or hepatic dysfunction prior to initiation of treatment.**
- **Adverse events occurring in >10% of patients receiving sargramostim**
  - **AML - fever, skin reactions, metabolic disturbances, nausea, vomiting, weight loss, edema, anorexia**
  - **Autologous hematopoietic cell transplant or peripheral blood progenitor cell transplant - asthenia, malaise, diarrhea, rash, peripheral edema, urinary tract disorder**
  - **Allogeneic hematopoietic cell transplant or peripheral blood progenitor cell transplant - abdominal pain, chills, chest pain, diarrhea, nausea, vomiting, hematemesis, dysphagia, GI hemorrhage, pruritus, bone pain, arthralgia, eye hemorrhage, hypertension, tachycardia, bilirubinemia, hyperglycemia, increased creatinine, hypomagnesemia, edema, pharyngitis, epistaxis, dyspnea, insomnia, anxiety, high blood urea nitrogen (BUN), and high cholesterol**

[a] An FDA-approved biosimilar is an appropriate substitute for filgrastim and pegfilgrastim.
[b] Full prescribing information for specific product information.
[c] Not all of the toxicities listed have been seen with each preparation, but similar toxicities are expected with filgrastim, tbo-filgrastim, pegfilgrastim, and biosimilars.
[d] The toxicities listed are from the prescribing information and are based on studies from different patient populations. For filgrastim, tbo-filgrastim, and biosimilars, the toxicities are based on non-myeloid malignancies. For sargramostim, the toxicities are based primarily on studies from leukemia and transplant patients, and the listed toxicities may reflect intravenous route of administration and may differ from those of subcutaneous administration.
[e] G-CSFs are not recommended for use within 14 days after receipt of chimeric antigen receptor (CAR)-modified T cells due to concern for exacerbation of cytokine release syndrome. Use after that time period can be considered for treatment of neutropenia.
[f] See Discussion for details.
[g] Lyman et al reported an increase in absolute and relative risk of AML/MDS of 0.41% and 1.92, respectively, related to G-CSFs. Overall mortality was decreased. See Discussion for details and reference.
[h] Available data support use of naproxen and other NSAIDs or loratadine. See Discussion for more details.

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HEMOGLOBIN CONCENTRATION TO PROMPT AN EVALUATION OF ANEMIA

EVALUATION OF ANEMIA[a,b]

Hemoglobin (Hb) ≤11 g/dL or ≥2 g/dL below baseline[c] →

- **CBC with indices**
- **Blood smear morphology** →

Evaluate anemia for possible cause as indicated[b] (see Discussion):

- **First check**
  - **Reticulocyte count[d] and mean corpuscular volume (MCV)**
- **Then consider**
  - **Hemorrhage (stool guaiac, endoscopy)**
  - **Hemolysis (ie, direct antiglobulin test [DAT], disseminated intravascular coagulation [DIC] panel, haptoglobin, indirect bilirubin, lactate dehydrogenase [LDH])**
  - **Nutritional (ie, iron, total iron-binding capacity, ferritin, B_{12}, folate)[e]**
  - **Inherited (ie, prior history, family history)**
  - **Renal dysfunction (Glomerular filtration rate [GFR] <60 mL/min/1.73 m^2)**
  - **Radiation-induced myelosuppression**
  - **Hormone dysfunction (ie, hypogonadism, adrenal dysfunction, hyper/hypothyroidism)**
  - **Anemia of chronic inflammation (ie, C-reactive protein [CRP] and erythrocyte sedimentation rate [ESR])**
- **See Evaluation of Iron Deficiency (ANEM-4)**

→ **Treat as indicated**

→ **No cause identified** → **See Risk Assessment and Indications for Transfusion (ANEM-2)**

Myelodysplastic syndromes → **See NCCN Guidelines for Myelodysplastic Syndromes**

Myeloid malignancies or Acute lymphoblastic leukemia → **Treat underlying disease per NCCN Guideline**
See NCCN Guidelines Table of Contents

[a]The NCCN Guidelines for Hematopoietic Growth Factors were formulated in reference to adult patients.
[b]This is a basic evaluation for possible causes of anemia.
[c]Consideration of gender in evaluation of anemia is relevant since women have a lower baseline Hb than men. See Discussion for more details.
[d]Correct reticulocyte count for degree of anemia. See Discussion.
[e]The ferritin value indicating iron deficiency is laboratory-specific. In general, the lower the level of ferritin, the higher the probability that the patient has true iron deficiency anemia. However, in the cancer setting, be aware of a chronic inflammatory state, which may falsely elevate the serum ferritin. Additionally, if serum iron studies are not performed while the patient is fasting or if the patient has taken a recent oral iron tablet, serum iron levels may be falsely elevated, and thus also falsely elevate the percent transferrin saturation. Fasting is preferred when testing for serum iron and total iron-binding capacity.

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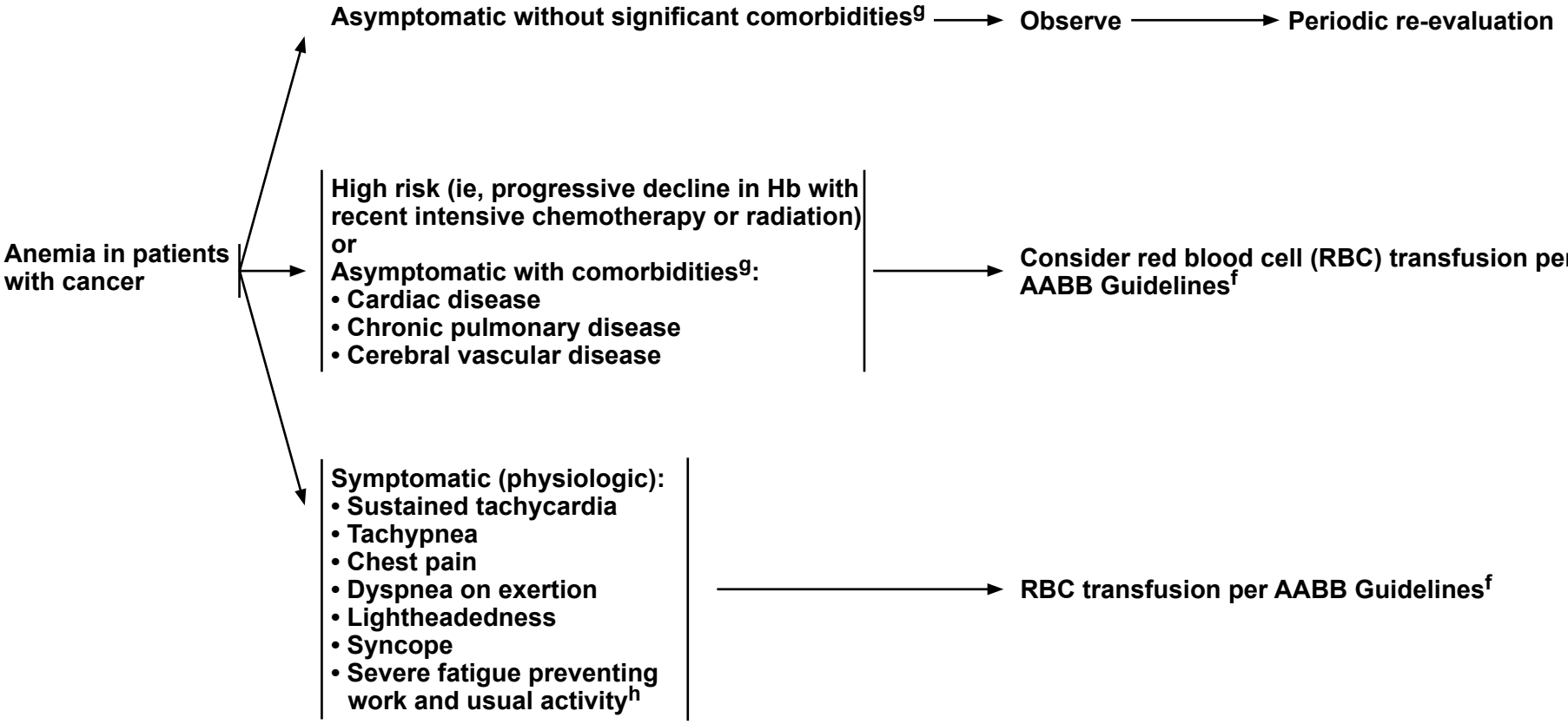
RISK ASSESSMENT AND INDICATIONS FOR INITIAL TRANSFUSION IN ACUTE SETTING[f]



See Discussion for Comparison of Risks and Goals of ESA Use Versus RBC Transfusion

See Special Categories in Considering ESA Use (ANEM-3)

[f]The AABB has made recommendations regarding appropriate indications for RBC transfusion. See Discussion for details.
[g]Degree of severity of comorbidities in combination with the degree of severity of anemia should be taken into consideration when initiating RBC transfusion.
[h]Fatigue (FACT-F) and Anemia (FACT-An) subscales of the Functional Assessment of Cancer Therapy (FACT) and Brief Fatigue Inventory (BFI) are examples of standardized measures for assessing patient-reported fatigue.

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SPECIAL CATEGORIES IN CONSIDERING ESA USE

Cancer and chronic kidney disease (moderate to severe) → **Consider Erythropoiesis-stimulating agents (ESAs) by FDA dosing/dosing adjustments[k,l,m]** →

Patient undergoing palliative treatment[i] →

Remainder of patients with anemia on myelosuppressive chemotherapy without other identifiable cause of anemia[i] →

Consider based on patient preferences:
- **ESAs by FDA dosing/dosing adjustments[k,l]** →
  or
- **RBC transfusion per AABB Guidelines**
  or
- **Clinical trial**

→ **See Evaluation of Iron Deficiency (ANEM-4)**

Select patients who refuse blood transfusions → **Consider ESAs by FDA dosing/dosing adjustments[k,l]**
See Management of Patients Who Refuse Blood Transfusions (ANEM-C) →

- **Patients with cancer not receiving therapy**
- **Patients receiving non-myelosuppressive therapy**
- **Patients receiving myelosuppressive chemotherapy with curative intent[j]**
  (Examples of cancers for which there is therapy with curative intent: Early-stage breast cancer, Hodgkin lymphoma, non-Hodgkin's lymphomas, testicular cancer, early-stage non-small cell lung cancer, and small cell lung cancer)

→ **There is not enough evidence to support ESA use in these patient populations; therefore, ESAs are not recommended at this time**

[i]For Comparison of Risks and Goals of ESA Use Versus RBC Transfusion See Discussion.

[j]A few studies suggest that patients with small cell lung cancer on myelosuppressive chemotherapy may not have an increase in mortality when receiving ESAs. (Nagel S, Kellner O, Engel-Riedel W, et al. Addition of darbepoetin alfa to dose-dense chemotherapy: results from a randomized phase II trial in small-cell lung cancer patients receiving carboplatin plus etoposide. Clin Lung Cancer 2011;12:62-69.)

[k]See Erythropoietic Therapy - Dosing, Titration, and Adverse Effects (ANEM-A).

[l]Patients with previous risk factors for thrombosis are at higher risk for thrombosis with the use of ESAs. If considering use of ESAs, evaluate the risk factors for thrombosis: history of thromboembolism, known heritable mutation, hypercoagulability, elevated pre-chemotherapy platelet counts, hypertension, steroids, prolonged immobilization, recent surgery, certain therapies for multiple myeloma, hormonal agents, etc. (See NCCN Guidelines for Cancer-Associated Venous Thromboembolic Disease).

[m]The Hb threshold for treatment and dosing with ESAs is different for chemotherapy-induced anemia and chronic kidney disease. For more details on the use of ESAs in patients with cancer and chronic kidney disease, see Discussion.

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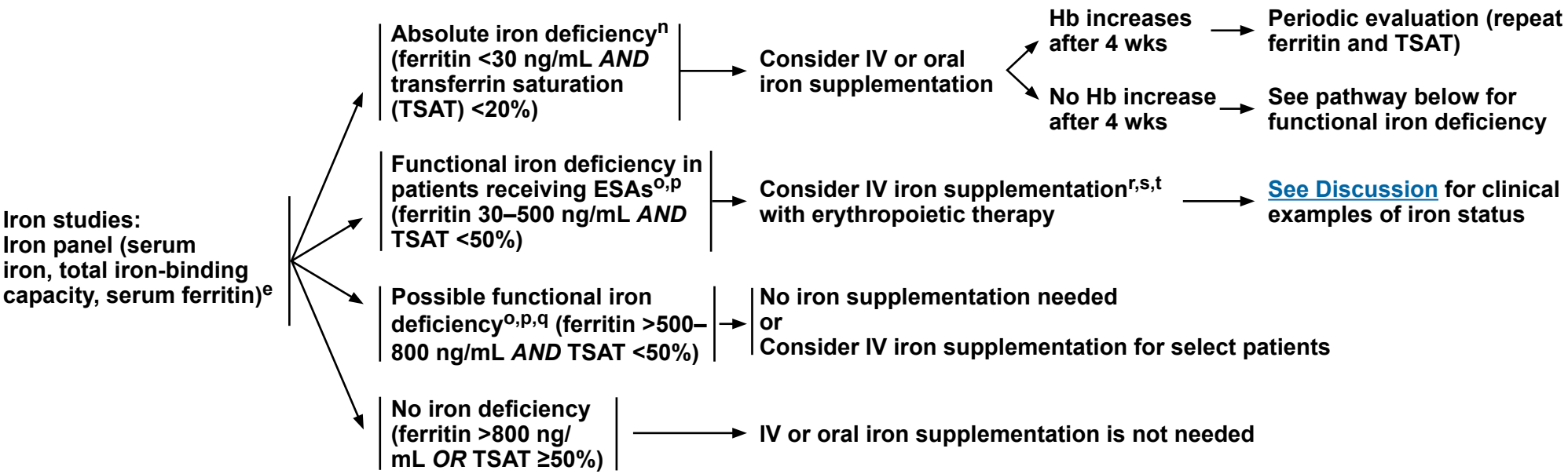

See Parenteral Iron Preparations (ANEM-B)

[e]The ferritin value indicating iron deficiency is laboratory-specific. In general, the lower the level of ferritin, the higher the probability that the patient has true iron deficiency anemia. However, in the cancer setting, be aware of a chronic inflammatory state, which may falsely elevate the serum ferritin. Additionally, if serum iron studies are not performed while the patient is fasting or if the patient has taken a recent oral iron tablet, serum iron levels may be falsely elevated, and thus also falsely elevate the percent transferrin saturation. Fasting is preferred when testing for serum iron and total iron-binding capacity.

[n]If the ferritin and TSAT are discordant, the low ferritin value should take precedence in determining whether IV iron will be of benefit.

[o]In clinical trials using IV iron plus an ESA, a higher response rate is seen when iron is used for patients with a TSAT <20%. For patients who received IV iron that had baseline TSATs >20%, the response rate to IV iron is both diminished and prolonged as the TSAT increased from 20% to 50%. Therefore, the decision to offer IV iron to this subset of patients should be reserved for those in whom benefits are likely to outweigh risks.

[p]Only one of six studies (Henry DH, et al. Oncologist 2007;12:231-242) of IV iron therapy in patients with cancer provided a TSAT guideline for monitoring.

[q]Although patients with ferritin levels of >500–800 ng/mL may have functional iron deficiency, as evidenced by clinical trials in patients with cancer, there are insufficient data to support the routine use of IV iron in this setting. Administration of IV iron to such patients should be individualized with the goal of avoiding allogeneic transfusion.

[r]IV iron has superior efficacy and should be considered for supplementation. Oral iron has been more commonly used but is less effective. See Parenteral Iron Preparations (ANEM-B).

[s]Although all combinations of serum ferritin and TSAT could be found in at least one of six randomized controlled trials evaluating the use of IV iron with an ESA, eligibility criteria testing for serum ferritin and TSAT generally ranged from >10 to <900 ng/mL and >15% to <60%, respectively.

[t]There are insufficient data to routinely recommend IV iron as monotherapy without an ESA for the treatment of functional iron deficiency anemia.

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ERYTHROPOIETIC THERAPY - DOSING AND TITRATION (1 of 5)[a,b,c,d,e]

INITIAL DOSING	TITRATION FOR NO RESPONSE**
PACKAGE INSERT DOSING SCHEDULE	
Epoetin alfa[f] 150 units/kg 3 times per wk by subcutaneous injection	→ Increase dose of epoetin alfa[f] to 300 units/kg 3 times per wk by subcutaneous injection
or	
Epoetin alfa[f] 40,000 units every wk by subcutaneous injection	→ Increase dose of epoetin alfa[f] to 60,000 units every wk by subcutaneous injection
or	
Darbepoetin alfa 2.25 mcg/kg every wk by subcutaneous injection	→ Increase darbepoetin alfa to up to 4.5 mcg/kg every wk by subcutaneous injection
or	
Darbepoetin alfa 500 mcg* every 3 wks by subcutaneous injection	
ALTERNATIVE REGIMENS[g]	
Darbepoetin alfa 100 mcg fixed dose every wk by subcutaneous injection	→ Increase darbepoetin alfa to up to 150–200 mcg fixed dose every wk by subcutaneous injection[2]
or	
Darbepoetin alfa 200 mcg fixed dose every 2 wks by subcutaneous injection[3]	→ Increase darbepoetin alfa to up to 300 mcg fixed dose every 2 wks by subcutaneous injection[3]
or	
Darbepoetin alfa 300 mcg* fixed dose every 3 wks by subcutaneous injection[7]	→ Increase darbepoetin alfa to up to 500 mcg fixed dose every 3 wks by subcutaneous injection[4]
or	
Epoetin alfa[f] 80,000 units every 2 wks by subcutaneous injection[5]	
or	
Epoetin alfa[f] 120,000 units every 3 wks by subcutaneous injection[6]	

TITRATION FOR RESPONSE

- The dose should be adjusted for each patient to maintain the lowest Hb level sufficient to avoid RBC transfusion.
- If Hb reaches a level needed to avoid transfusion or increases >1 g/dL in any 2-week period, reduce dose by 25% for epoetin alfa or epoetin alfa-epbx[c,1] and by 40% for darbepoetin alfa.

See Footnotes and References (ANEM-A 2 of 5)

See Erythropoietic Therapy - Adverse Effects (ANEM-A 3 of 5)

*Data indicate that darbepoetin alfa 300 mcg is equivalent in terms of efficacy to darbepoetin alfa 500 mcg for initial dosing.[7]

**No response is defined as Hb increase less than 1 g/dL and remains below 10 g/dL after the initial 4 weeks of epoetin, or 6 weeks of darbepoetin. Discontinue therapy after 8 weeks if no response.

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ERYTHROPOIETIC THERAPY - DOSING AND TITRATION (2 of 5)

FOOTNOTES AND REFERENCES FOR ANEM-A (1 of 5)

Footnotes

[a]The head-to-head comparisons of epoetin alfa versus darbepoetin alfa are inconclusive with regard to superiority of one drug over another. Schwartzberg LS, Yee LK, Senecal, FM, et al. A randomized comparison of every-2-week darbepoetin alfa and weekly epoetin alfa for the treatment of chemotherapy-induced anemia in patients with breast, lung, or gynecologic cancer. Oncologist 2004;9:696-707. Waltzman R, Croot C, Justice G, et al. Randomized comparison of epoetin alfa (40,000 U weekly) and darbepoetin alfa (200 mcg every 2 weeks) in anemic patients with cancer receiving chemotherapy. Oncologist 2005;10:642-650. Grant MD, Piper M, Bohlius J, et al. AHRQ Comparative Effectiveness Reviews. Epoetin and Darbepoetin for Managing Anemia in Patients Undergoing Cancer Treatment: Comparative Effectiveness Update. Rockville (MD): Agency for Healthcare Research and Quality (US); 2013.

[b]Less-frequent dosing regimens of darbepoetin or epoetin alfa could be considered as an alternative to dose reduction.

[c]The epoetin alfa and darbepoetin alfa dosages and regimens included in this table have been evaluated in patients with cancer receiving chemotherapy. Epoetin alfa-epbx has been studied in patients with chronic kidney disease; there are limited data in patients with cancer.

[d]IV iron has superior efficacy and should be considered for supplementation. Oral iron has been more commonly used but is less effective. (See Discussion for details.) See Parenteral Iron Preparations (ANEM-B).

[e]See prescribing information for perioperative deep vein thrombosis (DVT) prophylaxis.

[f]An FDA-approved biosimilar is an appropriate substitute for epoetin alfa.

[g]There are no data on alternative dosing schedules for epoetin alfa-epbx.

References

[1]Losem C, Koenigsmann M, Rudolph C. Biosimilar Retacrit((R)) (epoetin zeta) in the treatment of chemotherapy-induced symptomatic anemia in hematology and oncology in Germany (ORHEO) - non-interventional study. Onco Targets Ther 2017;10:1295-1305.

[2]Vansteenkiste J, Pirker R, Massuti B, et al. Double-blind, placebo-controlled, randomized phase III trial of darbepoetin alfa in lung cancer patients receiving chemotherapy. J Natl Cancer Inst 2002;94:1211-1220.

[3]Thames WA, Smith SL, Scheifele AC, et al. Evaluation of the US Oncology Network's recommended guidelines for therapeutic substitution with darbepoetin alfa 200 microg every 2 weeks in both naïve patients and patients switched from epoetin alfa. Pharmacotherapy 2004;24:313-323.

[4]Canon JL, Vansteenkiste J, Bodoky G, et al. Randomized, double-blind, active-controlled trial of every 3-week darbepoetin alfa for the treatment of chemotherapy-induced anemia. J Natl Cancer Inst 2006;98:273-284.

[5]Henry DH, Gordan LN, Charu V, et al. Randomized, open-label comparison of epoetin alfa extended dosing (80 000 U Q2W) vs weekly dosing (40 000 U QW) in patients with chemotherapy-induced anemia. Curr Med Res Opin 2006;22:1403-1413.

[6]Steensma DP, Molina R, Sloan JA, et al. Phase III study of two different dosing schedules of erythropoietin in anemic patients with cancer. J Clin Oncol 2006;24:1079-1089.

[7]Auerbach M, Silberstein PT, Webb RT, et al. Darbepoetin alfa 300 or 500 mcg once every 3 weeks with or without intravenous iron in patients with chemotherapy-induced anemia. Am J Hematol 2010;85:655-663.

See Erythropoietic Therapy - Dosing and Titration (ANEM-A 1 of 5)

See Erythropoietic Therapy- Adverse Effects (ANEM-A 3 of 5)

Note: All recommendations are category 2A unless otherwise indicated.
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ERYTHROPOIETIC THERAPY - ADVERSE EFFECTS (3 of 5)

Survival of Patients with Cancer

- Studies have reported possible decreased survival in patients with cancer receiving erythropoietic drugs for correction of anemia. Analyses of eight studies in patients with cancer found decreased survival in patients receiving erythropoietic drugs for correction of anemia and target Hb levels of >12 g/dL.[1-8] One analysis in patients with cancer not receiving active therapy found decreased survival in patients treated with ESAs.[6] Please refer to the FDA website for additional information: https://www.fda.gov/drugs/drug-safety-and-availability/postmarket-drug-safety-information-patients-and-providers. Unless new evidence demonstrates a change in benefit:risk estimates, physicians should be advised not to administer ESAs (darbepoetin alfa, epoetin alfa, or epoetin alfa-epbx) to patients outside of the treatment period of cancer-related chemotherapy. A treatment period is defined as anemia following initiation of therapy and continuing approximately 6 weeks after the completion of treatment.
- While three meta-analysis updates on survival have indicated an increased mortality risk with the use of ESAs,[9,10-12] two meta-analyses have indicated that ESA use did not significantly affect mortality or disease progression.[13,14]
- Recent pharmacovigilance trials have reported no adverse effects on survival in patients with cancer with chemotherapy-induced anemia receiving ESAs.[15-17]
- The risks of shortened survival and tumor progression have not been excluded when ESAs have been dosed to a target Hb of <12 g/dL.
- Additional prospective clinical trials designed and powered to measure survival of patients with cancer are ongoing to provide clinicians with data to guide optimal use of erythropoietic agents.
- Because of the above issues, providers should inform patients of risks and benefits of ESA therapy versus RBC transfusion. (See Discussion for Comparison of Risks and Goals of ESA Use Versus RBC Transfusion).
- Recent studies suggest that use of ESAs may be deleterious when used in patients with metastatic breast cancer. See Discussion.

Erythropoietic Therapy - Adverse Effects continued (ANEM-A 4 of 5)

See References (ANEM-A 5 of 5)

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ERYTHROPOIETIC THERAPY - ADVERSE EFFECTS (4 of 5)

Thrombosis

- Early trials of recombinant human erythropoietin reported that a high-target hematocrit (42 ± 3%) was found to have an increased number of vascular events (arterial and venous).
- Erythropoietin has a thrombogenic potential independent of Hb levels.[18] Patients with previous risk factors for thrombosis may be at higher risk for thrombosis with the use of ESAs. If considering use of ESAs, evaluate the risk factors for thrombosis: history of thromboembolism, heritable mutation, hypercoagulability, elevated pre-chemotherapy platelet counts, hypertension, steroids, prolonged immobilization, recent surgery, certain therapies for multiple myeloma, hormonal agents, etc.
  (See NCCN Guidelines for Cancer-Associated Venous Thromboembolic Disease)
- Five meta-analyses reported an increase in relative risk of thrombotic events ranging from 48% to 69% with ESA use.[9,12-14,19]
  The absolute risk of venous thromboembolism was 7.5% in patients treated with ESAs compared to 4.9% in control patients.[9]
- A clinical trial in chronic kidney disease demonstrated a 92% increase in the relative risk of stroke (absolute risk 5.0% vs. 2.6%) with darbepoetin alfa.[20]

Hypertension

- Blood pressure should be controlled in all patients prior to initiating therapy with erythropoietic drugs and must be monitored regularly in treated patients.
- Hb level should be monitored to decrease the risk of hypertension. (See Titration for Response ANEM-A 1 of 5)

ESA-Neutralizing Antibodies (pure red cell aplasia, PRCA)

- Between 1998–2004, 197 cases of PRCA were reported in patients treated with erythropoietin.[21] Greater than 90% of these cases occurred with Eprex, an epoetin alfa product used outside of the United States. Patients who develop a loss of response to erythropoietic drugs should be evaluated for possible PRCA, and if present, all erythropoietic drugs should be discontinued.[22]
- In 2005, the FDA's interpretation of anemia associated with neutralizing antibodies evolved to include both PRCA and severe anemia. Since 2005, FDA safety databases have included information on 30 new cases of antibody-associated PRCA, primarily associated with subcutaneous administration of epoetin alfa and darbepoetin alfa.[23] This interpretation resulted in a class label change for all ESAs. The toxicity has been reported predominantly in patients with chronic renal failure receiving ESAs by subcutaneous administration. Any patient who develops a sudden loss of response to an ESA, accompanied by severe anemia and a low reticulocyte count, should be evaluated for the etiology of loss of effect, including the presence of neutralizing antibodies to erythropoietin. If anti-erythropoietin antibody-associated anemia is suspected, ESAs should be withheld and plasma should be sent for evaluation of assays for binding and neutralizing antibodies. ESAs should be discontinued in patients with antibody-mediated anemia. Patients should not be immediately switched to other ESA products as antibodies may cross-react.

See References (ANEM-A 5 of 5)

Note: All recommendations are category 2A unless otherwise indicated.
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ERYTHROPOIETIC THERAPY - ADVERSE EFFECTS (5 of 5)

ADVERSE EFFECTS REFERENCES

[1]Leyland-Jones B, BEST Investigators and Study Group. Breast cancer trial with erythropoietin terminated unexpectedly. Lancet Oncol 2003;4:459-460.
[2]Henke M, Laszig R, Rube C, et al. Erythropoietin to treat head and neck cancer patients with anaemia undergoing radiotherapy: Randomised, double-blind, placebo-controlled trial. Lancet 2003;362:1255-1260.
[3]Wright JR, Ung YC, Julian JA, et al. Randomized, double-blind, placebo-controlled trial of erythropoietin in non-small-cell lung cancer with disease-related anemia. J Clin Oncol 2007;25:1027-1032.
[4]Hedenus M, Adriansson M, San Miguel J, et al. Efficacy and safety of darbepoetin alfa in anaemic patients with lymphoproliferative malignancies: A randomized, double-blind, placebo-controlled study. Br J Haematol 2003;122:394-403.
[5]Overgaard J, Hoff C, Sand Hansen H, et al. Randomized study of the importance of novel erythropoiesis stimulating protein (Aranesp) for the effect of radiotherapy in patients with primary squamous cell carcinoma of head and neck (HNCSS): The Danish Head and Neck Cancer Group DAHANCA 10 rand [abstract] Eur J Cancer Suppl 2007;5:7.
[6]Smith R, Aapro MS, Ludwig H, et al. Darbepoetin alpha for the treatment of anemia in patients with active cancer not receiving chemotherapy or radiotherapy: results of a phase III, multicenter, randomized, double-blind, placebo-controlled study. J Clin Oncol 2008;26:1040-1050.
[7]Thomas G, Ali S, Hoebers FJ, Darcy KM, et al. Phase III trial to evaluate the efficacy of maintaining hemoglobin levels above 12.0 g/dL with erythropoietin vs above 10.0 g/dL without erythropoietin in anemic patients receiving concurrent radiation and cisplatin for cervical cancer. Gynecol Oncol 2008;108:317-325.
[8]Untch M, Fasching PA, Bauerfeind I, et al. PREPARE trial. A randomized phase III trial comparing preoperative, dose-dense, dose-intensified chemotherapy with epirubicin, paclitaxel and CMF with a standard dosed epirubicin/cyclophosphamide followed by paclitaxel ± darbepoetin alfa in primary breast cancer: A preplanned interim analysis of efficacy at surgery. J Clin Oncol 26:2008 (May 20 suppl; abstr 517).
[9]Bennett CL, Silver SM, Djulbegovic B, et al. Venous thromboembolism and mortality associated with recombinant erythropoietin and darbepoetin administration for the treatment of cancer-associated anemia. JAMA 2008;299:914-924.
[10]Bennett CL, Henke M, Lai SY. Erythropoiesis-stimulating agents in the treatment of cancer-associated anemia reply. JAMA 2008;300:2855-2857.
[11]Bohlius J, Schmidlin K, Brillant C, et al. Recombinant human erythropoiesis-stimulating agents and mortality in patients with cancer: A meta-analysis of randomised trials. Lancet 2009;373:1532-1542.
[12]Tonelli M, Hemmelgarn B, Reiman T, et al. Benefits and harms of erythropoiesis-stimulating agents for anemia related to cancer: A meta-analysis. CMAJ 2009;180(11):E62-71.
[13]Glaspy J, Crawford J, Vansteenkiste J, et al. Erythropoiesis-stimulating agents in oncology: A study-level meta-analysis of survival and other safety outcomes. Br J Cancer 2010;102:301-315.
[14]Ludwig H, Crawford J, Osterborg A et al. Pooled analysis of individual patient-level data from all randomized, double-blind, placebo-controlled trials of darbepoetin alfa in the treatment of patients with chemotherapy-induced anemia. J Clin Oncol 2009; 27:2838-2847.
[15]Engert A, Josting A, Haverkamp H, et al. Epoetin alfa in patients with advanced-stage Hodgkin's lymphoma: results of the randomized placebo-controlled GHSG HD15EPO trial. J Clin Oncol 2010;28:2239-2245.
[16]Moebus V, Jackisch C, Lueck H, et al. Intense dose-dense sequential chemotherapy with epirubicin, paclitaxel, and cyclophosphamide compared with conventionally scheduled chemotherapy in high-risk primary breast cancer: Mature results of an AGO phase III study. J Clin Oncol 2010;28:2874-2880.
[17]Untch M, von Minckwitz G, Konecny GE, et al. PREPARE trial: A randomized phase III trial comparing preoperative, dose-dense, dose-intensified chemotherapy with epirubicin, paclitaxel, and CMF versus a standard-dosed epirubicin– cyclophosphamide followed by paclitaxel with or without darbepoetin alfa in primary breast cancer—outcome on prognosis. Ann Oncol 2011;22:1999-2006.
[18]Singh A, Szczech L, Tang K, et al. Correction of anemia with epoetin alfa in chronic kidney disease. N Engl J Med 2006;355:2085-2098.
[19]Tonia T, Mettler A, Robert N, et al. Erythropoietin or darbepoetin for patients with cancer. Cochrane Database Syst Rev 2012;12:CD003407.
[20]Pfeffer MA, Burdmann EA, Chen C, et al. A trial of darbepoetin alfa in type 2 diabetes and chronic kidney disease. N Engl J Med 2009;361:2019-2032.
[21]Bennett CL, Luminari S, Nissenson AR, et al. Pure red-cell aplasia and epoetin therapy. N Eng J Med 2004;351:1403-1408.
[22]Bennett CL, Cournoyer D, Carson KR, et al. Long-term outcome of individuals with pure red cell aplasia and aniterythropoietin antibodies in patients treated with recombinant epoetin: A follow-up report from the Research on Adverse Drug Events and Reports (RADAR) Project. Blood 2005;106:3343-3347.
[23]McKoy J, Stonecash R, Cournoyer D, et al. Epoetin-associated pure red cell aplasia: past, present, and future considerations. Transfusion 2008;48:1754-1762.

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PARENTERAL IRON PREPARATIONS[1-6,a]

RECOMMENDATIONS FOR ADMINISTERING PARENTERAL IRON PRODUCTS

	Low-Molecular-Weight Iron Dextran[8,b]	Ferric Gluconate[11,b]	Iron Sucrose[14,b]	Ferric Carboxymaltose[16,17,18,b] (in select cases)	Ferumoxytol[19,20,21,b,c] (in select cases)
Test dose[d]	Test dose required: 25 mg slow IV push over 1–2 min. If tolerated, follow with 75 mg IV bolus for total dose of 100 mg.	Test dose at MD discretion based on risk for reaction	Test dose at MD discretion based on risk for reaction	Test dose at MD discretion based on risk for reaction	Test dose at MD discretion based on risk for reaction
Dosage[7,e]	100 mg IV over 5 min[3] • Repeated dosing once weekly for 10 doses to total of 1000 mg or • Total dose infusion given over several hours[9,f] ▸ Calculated total iron dextran dose in 500 mL of 0.9% NaCl solution administered at 175 mL/h[10]	125 mg IV over 60 min[2,4,5,12] • Repeated dosing given once weekly for 8 doses • Individual doses above 125 mg are not recommended based on published trial results[12] • Total treatment course = 1000 mg	200 mg IV over 60 min[6] (repeated every 2–3 wks) or 200 mg IV over 2–5 min, 5 times within 14 days • Individual doses over 300 mg are not recommended[15] • Total treatment course = 1000 mg	750 mg IV for patients weighing ≥50 kg (110 lbs) • Repeat dose once at least 7 days later • Total treatment course = 1500 mg or 15 mg/kg body weight IV for patients <50 kg (110 lbs) • Repeat dose once at least 7 days later • Total treatment course not to exceed 1500 mg	510 mg IV dose over 15 min • Repeat 510 mg dose 3–8 days later • Total treatment course = 1020 mg
Routes	IV; IM (not recommended)	IV	IV	IV	IV

[a]Five[2-6] of six[12] studies suggest that parenteral iron products improve Hb response rates in treating absolute or functional iron deficiency in patients with cancer who are receiving ESAs.

[b]Examples of adverse events associated with FDA-approved doses of parenteral iron preparations include: hypotension, hypertension, nausea, vomiting, diarrhea, pain, fever, dyspnea, pruritus, headaches, and dizziness. Adverse effects associated with low-molecular-weight iron dextran may be delayed 24–48 hours. Ferric carboxymaltose has been associated with severe phosphate deficiency.

[c]Ferumoxytol is indicated for the treatment of iron deficiency anemia in adult patients who have intolerance to oral iron or have had unsatisfactory response to oral iron, or those with chronic kidney disease. Ferumoxytol has not been prospectively evaluated in patients with cancer- or chemotherapy-induced anemia. Ferumoxytol may cause interference with MRI scans causing potential false interpretation of organ iron overload.[13]

[d]Premedications should be given prior to the IV iron test dose as reactions to the test dose may be severe.

[e]For additional details about iron dosing, see prescribing information.

[f]Dose (mL) = 0.0442 (Desired Hgb - Observed Hgb) x LBW + (0.26 X LBW); Dose (mg) = Dose (mL) x 50 mg/mL. LBW = Lean Body Weight (kg); Hgb = Hemoglobin (g/dL). If dose exceeds 1000 mg, remaining dose may be given after 4 weeks if inadequate Hb response.

References

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PARENTERAL IRON PREPARATIONS[1-6]

REFERENCES

1Silverstein SB, Rodgers GM. Parenteral iron therapy options. Am J Hematol 2004;76:74-78.

2Henry DH, Dahl NV, Auerbach M, et al. Intravenous ferric gluconate significantly improves response to epoetin alfa versus oral iron or no iron in anemic patients with cancer receiving chemotherapy. Oncologist 2007;12:231-242.

3Auerbach M, Ballard H, Trout JR, et al. Intravenous iron optimizes the response to recombinant human erythropoietin in cancer patients with chemotherapy-related anemia: A multicenter, open-label, randomized trial. J Clin Oncol 2004;22:1301-1307.

4Pedrazzoli P, Farris A, Del Prete S, et al. Randomized trial of intravenous iron supplementation in patients with chemotherapy-related anemia without iron deficiency treated with darbepoetin alpha. J Clin Oncol 2008;26:1619-1625.

5Hedenus M, Birgegård G, Näsman P, et al. Addition of intravenous iron to epoetin beta increases hemoglobin response and decreases epoetin dose requirement in anemic patients with lymphoproliferative malignancies: a randomized multicenter study. Leukemia 2007;21:627-632.

6Bastit L, Vandebroek A, Altintas S, et al. Randomized, multicenter, controlled trial comparing the efficacy and safety of darbepoetin alpha administered every 3 weeks with or without intravenous iron in patients with chemotherapy-induced anemia. J Clin Oncol 2008;26:1611-1618.

7Gilreath JA, Sageser DS, Jorgenson JA, Rodgers GM. Establishing an anemia clinic for optimal erythropoietic-stimulating agent use in hematology-oncology patients. J Natl Compr Canc Netw 2008;6:577-584.

8National Institutes of Health. Iron dextran package insert. Available at: http://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=abacb7fa-2fc2-471e-9200-944eeac8ca2a Accessed March 8, 2019.

9Gilreath JA, Stenehjem DD, Rodgers GM. Total dose iron dextran infusion in cancer patients: is it SaFe2+? J Natl Compr Canc Netw 2012;10:669-676.

10Auerbach M, Ballard H, Trout JR, et al. Intravenous iron optimizes the response to recombinant human erythropoietin in cancer patients with chemotherapy-related anemia: A multicenter, open-label, randomized trial. J Clin Oncol 2004;22:1301-1307.

11National Institutes of Health. Ferric gluconate package insert. Available at: http://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=1fe028ff-42ac-4329-b1a5-a9dadfcb79f6 Accessed March 8, 2019.

12Steensma DP, Sloan JA, Dakhil SR, et al. Phase III, randomized study of the effects of parenteral iron, oral iron, or no iron supplementation on the erythropoietic response to darbepoetin alfa for patients with chemotherapy-associated anemia. J Clin Oncol 2011;29:97-105.

13Schieda N. Parenteral ferumoxytol interaction with magnetic resonance imaging: a case report, review of the literature and advisory warning. Insights Imaging 2013;4:509-512.

14National Institutes of Health. Iron sucrose package insert. Available at: http://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=626dc9e5-c6b4-4f9c-9bf4-774fd3ae619a Accessed March 8, 2019.

15Chandler G, Harchowal J, Macdougall IC. Intravenous iron sucrose: Establishing a safe dose. Am J Kidney Dis 2001;38:988-991.

16National Institutes of Health. Ferric carboxymaltose package insert. Available at: http://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=517b4a19-45b3-4286-9f6a-ced4e10447de Accessed March 8, 2019.

17Toledano A, Luporsi E, Morere JF, et al. Clinical use of ferric carboxymaltose in patients with solid tumours or haematological malignancies in France. Support Care Cancer 2016;24:67-75.

18Keeler BD, Simpson JA, Ng O, et al. Randomized clinical trial of preoperative oral versus intravenous iron in anaemic patients with colorectal cancer. Br J Surg 2017;104:214-221.

19Vadhan-Raj S, Dahl NV, Bernard K, et al. Efficacy and safety of IV ferumoxytol for iron deficiency anemia in patients with cancer. J Blood Med 2017;8:199-209.

20Vadhan-Raj S, Strauss W, Ford D, et al. Efficacy and safety of IV ferumoxytol for adults with iron deficiency anemia previously unresponsive to or unable to tolerate oral iron. Am J Hematol 2014;89:7-12.

21U.S. Food & Drug Administration. Ferumoxytol package insert. Available at https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm Accessed November 15, 2019.

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MANAGEMENT OF CANCER- AND CHEMOTHERAPY-INDUCED ANEMIA FOR PATIENTS WHO REFUSE BLOOD TRANSFUSIONS[1-8]

- There are limited available data on the best management of cancer- and chemotherapy-induced anemia for patients who refuse blood transfusions.
- In extreme cases of severe, life-threatening anemia, pure oxygen (400 mm Hg, SaO2 = 1.0) by mechanical ventilation has been used to increase blood oxygenation.
- To reduce blood loss, minimize phlebotomy, use pediatric tubes, return discard in closed system, and batch test.
- Prior to initiation of myelosuppressive chemotherapy:
  - Consider anemia risk when making treatment decisions
  - Consider daily folic acid and B_{12} supplementation
  - Evaluate and correct baseline coagulation abnormalities
  - In patients with high clinical suspicion of folate and vitamin B_{12} deficiency, nutritional deficiency should be ruled out and iron deficiency should be corrected using intravenous (IV) iron.
- Consider use of ESAs for select patients by FDA dosing/dosing adjustments, given there is no option for transfusion.
  - ESAs are NOT recommended for:
    - ◊ Patients with cancer not receiving chemotherapy
    - ◊ Patients receiving non-myelosuppressive therapy
  - Therefore, if ESAs are prescribed off-label for the indications listed immediately above, patients should be made aware of the potential increased risks of thrombosis and tumor progression, and should know that under these circumstances the ESAs are being used off-label.
- Blood substitutes
  - A clinician may obtain access to investigational blood substitute products for a single patient by submitting an Expanded Access - Investigational New Drug Application (IND) through the FDA.[4]

References

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MANAGEMENT OF CANCER- AND CHEMOTHERAPY-INDUCED ANEMIA FOR PATIENTS WHO REFUSE BLOOD TRANSFUSIONS

References

[1]Heh-Foster AM, Naber M, Pai MP, Lesar TS. Epoetin in the 'untransfusable' anaemic patient: a retrospective case series and systematic analysis of literature case reports. Transfus Med 2014;24:204-208.
[2]Resar LM, Frank SM. Bloodless medicine: what to do when you can't transfuse. Hematology Am Soc Hematol Educ Program 2014;2014:553-558.
[3]Resar LM, Wick EC, Almasri TN, et al. Bloodless medicine: current strategies and emerging treatment paradigms. Transfusion 2016;56:2637-2647.
[4]Panico ML, Jenq GY, Brewster UC. When a patient refuses life-saving care: issues raised when treating a Jehovah's Witness. Am J Kidney Dis 2011;58:647-653.
[5]Scharman CD, Burger D, Shatzel JJ, et al. Treatment of individuals who cannot receive blood products for religious or other reasons. Am J Hematol 2017;92:1370-1381.
[6]McConachie SM, Almadrahi Z, Wahby KA, Wilhelm SM. Pharmacotherapy in acutely anemic Jehovah's Witnesses: an evidence-based review. Ann Pharmacother 2018;52:910-919.
[7]McConachie S, Wahby K, Almadrahi Z, Wilhelm S. Early experiences with PEGylated carboxyhemoglobin bovine in anemic Jehovah’s Witnesses: A case series and review of the literature. J Pharm Pract 2018 Dec 5. [Epub ahead of print]
[8]Joseph NS, Kaufman JL, Boise LH, et al. Safety and survival outcomes for bloodless transplanation in patients with myeloma. Cancer 2019 Jan 15;125(2):185-193.

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NCCN Categories of Evidence and Consensus	
Category 1	Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
Category 2A	Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
Category 2B	Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.
Category 3	Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise indicated.

NCCN Categories of Preference	
Preferred intervention	Interventions that are based on superior efficacy, safety, and evidence; and, when appropriate, affordability.
Other recommended intervention	Other interventions that may be somewhat less efficacious, more toxic, or based on less mature data; or significantly less affordable for similar outcomes.
Useful in certain circumstances	Other interventions that may be used for selected patient populations (defined with recommendation).

All recommendations are considered appropriate.

NCCN Guidelines Version 2.2020
Hematopoietic Growth Factors

Discussion

This discussion corresponds to the NCCN Guidelines for Hematopoietic Growth Factors. Last updated on 01/27/20.

Table of Contents

Overview

Hematopoietic growth factors are defined by their ability to promote proliferation and differentiation of hematopoietic progenitors into mature blood cells.[1] Colony-stimulating factors are hematopoietic growth factors that regulate the growth and differentiation of cells in the myeloid and erythroid lineages. Myeloid growth factors (MGFs), such as granulocyte colony-stimulating factors (G-CSF), are primarily used to reduce the incidence of febrile neutropenia (FN) in patients with non-myeloid malignancies receiving myelosuppressive chemotherapy. Erythropoiesis-stimulating agents (ESAs), including epoetin alfa and darbepoetin alfa, are primarily used to manage cancer- and chemotherapy-induced anemia (CIA). Management and prevention of FN and CIA are integral parts of the supportive care approach for many patients undergoing cancer treatment.

FN is defined as an absolute neutrophil count (ANC) of <500 neutrophils/mcL, or an anticipated decline to ≤500 within the next 48 hours, accompanied by a single oral temperature of ≥38.3°C or a temperature ≥38.0°C for a duration of over 1 hour.[2] FN is a major dose-limiting toxicity of many chemotherapy regimens. Patients who develop FN often require prolonged hospitalizations and treatment with broad-spectrum antibiotics.[3] Development of FN increases treatment costs and can prompt dose reductions or treatment delays, which may compromise clinical outcome.[4] Additionally, correlations between changes in neutrophil counts and quality of life, as measured by physical functioning, vitality, and mental health, have been reported.[5]

These guidelines focus on the two MGFs that have shown the most promise for clinical use: G-CSF and granulocyte-macrophage colony-stimulating factor (GM-CSF). For simplicity, the term “MGF” will be utilized when the data are supported by studies for both G-CSF and GM-CSF. Filgrastim, filgrastim-sndz, tbo-filgrastim, filgrastim-aafi, pegfilgrastim, pegfilgrastim-jmdb, pegfilgrastim-cbqv, and pegfilgrastim-bmez are pharmacologic G-CSFs currently approved by the U.S. Food and Drug Administration (FDA) to decrease the incidence of FN in patients with non-myeloid malignancies receiving myelosuppressive chemotherapy.[6-13] Filgrastim-sndz, filgrastim-aafi, pegfilgrastim-jmdb, pegfilgrastim-cbqv, and pegfilgrastim-bmez were approved as biosimilars allowing their use for the broader indications of the originator products (see *Biosimilars* below for more information). Tbo-filgrastim was approved by the FDA in an original biologic license application[14] and therefore has a more restricted indication.[8] The only GM-CSF that is FDA-approved is sargramostim, although some clinical trials have used the GM-CSF molgramostim. Molgramostim is not recommended by the panel due to increased adverse events compared to sargramostim[15] as well as the lack of FDA approval. Sargramostim is primarily used for treatment of FN; prophylactic use is not recommended. MGFs are also indicated for patients with radiation-induced myelosuppression following a radiologic/nuclear incident (hematopoietic acute radiation syndrome [H-ARS]),[16,17] severe chronic neutropenia, and in the HCT setting for mobilization and supportive care.

CIA is prevalent, occurring in 30% to 90% of cancer patients.[18,19] Improvement of CIA can be achieved by transfusion with packed red blood cells (PRBCs) or administration of ESAs, with or without iron supplementation, in select patients being treated with myelosuppressive chemotherapy. The first ESA approved by the FDA for the treatment of anemia in patients receiving myelosuppressive chemotherapy was epoetin alfa, a recombinant human erythropoietin (rhEpo).[20] A second-generation rhEpo, darbepoetin alfa, with a longer half-life than epoetin alfa, has also been FDA-approved for this indication.[21] In 2018, the FDA approved epoetin alfa-epbx as the first epoetin alfa biosimilar, allowing its use for the same indications as the originator product.[22,23]

Anemia is characterized by a decrease in hemoglobin (Hb) concentration, red blood cell (RBC) count, and/or hematocrit (Hct) to subnormal levels. The pathophysiologic origins of anemia can be grouped into three

categories: 1) decreased production of functional RBCs; 2) increased destruction of RBCs; and 3) blood loss. The degree of anemia can be graded according to the anemia scale provided by the National Cancer Institute (Table 1).

Table 1. National Cancer Institute Anemia Scale

Grade	**Scale** (hemoglobin level in g/dL)
1 (mild)	10 – <lower limit of normal
2 (moderate)	8 – <10
3 (severe)	<8
4 (life-threatening)	Life-threatening consequences; urgent intervention indicated
5 (death)	Death

Source: Adapted from the Common Terminology Criteria for Adverse Events.

The NCCN Guidelines for Hematopoietic Growth Factors are divided into two sections outlining the evaluation, prevention, and management of FN and CIA, respectively. The purpose of these guidelines is two-fold: 1) to operationalize the evaluation, prevention, and treatment of FN and CIA in adult patients with cancer, especially those who are receiving chemotherapy; and 2) to enable the patient and clinician to assess management options for FN and CIA in the context of an individual patient's condition.

These guidelines focus on adult patients with solid tumors and lymphoid malignancies. Use of hematopoietic growth factors in the treatment of myeloid disorders or leukemias is discussed in the NCCN Guidelines for Myelodysplastic Syndromes, the NCCN Guidelines for Chronic Myeloid Leukemia, the NCCN Guidelines for Acute Myeloid Leukemia, and the NCCN Guidelines for Hairy Cell Leukemia.

Literature Search Criteria and Guidelines Update Methodology

Prior to this update of the NCCN Guidelines for Hematopoietic Growth Factors, an electronic search of the PubMed database was performed to obtain key literature using the following search terms: myeloid growth factors and cancer; colony stimulating factors and cancer; filgrastim and cancer; filgrastim biosimilar and cancer; pegfilgrastim and cancer; pegfilgrastim biosimilar and cancer; anemia and cancer; anemia and chemotherapy; erythropoiesis stimulating agents and cancer. The PubMed database was chosen as it remains the most widely used resource for medical literature and indexes peer-reviewed biomedical literature.[24]

The search results were narrowed by selecting studies in humans published in English. Results were confined to the following types: Clinical Trial, Phase II; Clinical Trial, Phase III; Clinical Trial, Phase IV; Guideline; Meta-Analysis; Randomized Controlled Trial; Systematic Reviews; and Validation Studies.

The data from key PubMed articles selected by the panel for review during the Guidelines update meeting as well as articles from additional sources deemed as relevant to these Guidelines and discussed by the panel have been included in this version of the Discussion section (eg, e-publications ahead of print, meeting abstracts). Recommendations for which high-level evidence is lacking are based on the panel's review of lower-level evidence and expert opinion.

The complete details of the Development and Update of the NCCN Guidelines are available at www.NCCN.org.

Biosimilars

Biologics such as filgrastim, pegfilgrastim, and epoetin alfa are costly, which has limited their accessibility for many patients. In 2009, the Biologics Price Competition and Innovation Act established an

abbreviated licensure pathway for biosimilars with the goal of reducing expenditure for costly biologic drugs.[25,26] The first drug granted FDA approval on the biosimilar pathway was filgrastim-sndz in 2015.[27] The increased need for cost-effective hematopoietic growth factors has recently led to the rapid approval of additional biosimilars.

A biosimilar is a biological product that is highly similar to the FDA-approved originator product with the exception of minor differences in clinically inactive components and no clinically meaningful differences in efficacy, safety, and purity.[28] FDA-approved biosimilars have the same amino acid sequence as the originator product; however, differences may be seen in the three-dimensional structure, glycosylation sites, isoform profiles, and the level of protein aggregation.[28] Therefore, pharmacokinetic and pharmacodynamic studies are essential in evaluating biological activity, efficacy, and safety.[26,29] Since biosimilars are supported by limited clinical data at the time of approval, data must be extrapolated in order to support the use of biosimilars for additional indications of the originator product. Scientific justification is required for extrapolation, including mechanism-of-action studies in each indication as well as pharmacokinetic, immunogenicity and toxicity assessments in different patient populations.[14] If overall safety and efficacy are equivalent, biosimilars may be approved for the same indications and can be substituted for the originator product.

Switching between the biosimilar and the originator product without the intervention of a health care provider is permitted if a biosimilar is designated as interchangeable.[28] Concerns regarding interchangeability include enhanced immunogenicity, compromised safety, and diminished efficacy. Although there are no biosimilars designated as interchangeable by the FDA, limited data suggest that patients can alternate between the biosimilar and the originator biologic without any clinically meaningful differences regarding efficacy or safety.[30] Another concern is the potential for product drift that may arise during the manufacturing process of biologics and biosimilars that could result in differences in efficacy and safety over time. Continued postmarketing surveillance of all biologic products is necessary for long-term monitoring of these agents. Health care providers should be aware of the FDA's nomenclature for biosimilars (originator biologic name followed by a random 4-letter suffix), which is important for the pharmacovigilance of specific products.

It should be noted that tbo-filgrastim was approved as an original biologic in the United States, and therefore has a more restricted indication than filgrastim biosimilars.[8] Several studies have demonstrated similar outcomes with the use of tbo-filgrastim compared to filgrastim for the prevention of FN. One trial randomized 348 patients with breast cancer receiving docetaxel/doxorubicin therapy to tbo-filgrastim, filgrastim, or placebo.[31] Tbo-filgrastim was equivalent to filgrastim and superior to placebo in reducing the duration of severe neutropenia and incidence of FN. Two other randomized studies in patients with lung cancer and non-Hodgkin lymphoma (NHL) receiving chemotherapy also report similar efficacy and toxicity for tbo-filgrastim and filgrastim.[32,33] A meta-analysis of these 3 trials concluded tbo-filgrastim to be non-inferior to filgrastim in reducing the incidence of FN.[34] Studies in healthy subjects demonstrated similar pharmacokinetic and pharmacodynamic profiles.[35,36] Tbo-filgrastim has demonstrated low immunogenicity in cancer patients receiving chemotherapy with no evidence for the development of neutralizing antibodies or immunogenic adverse events.[37]

Based on recent FDA approvals and review of the data, filgrastim-sndz, filgrastim-aafi, pegfilgrastim-jmdb, pegfilgrastim-cbqv, pegfilgrastim-bmez, and epoetin alfa-epbx have been included in the NCCN Guidelines as appropriate substitutions for originator filgrastim, pegfilgrastim, and epoetin alfa, respectively. The FDA's approval of these biosimilars was based on review of evidence including structural and functional characterization, animal study data, human pharmacokinetic and

pharmacodynamic data, clinical immunogenicity data, and other clinical safety and effectiveness data, which are discussed further below.

Filgrastim Biosimilars

In March 2015, the FDA approved the first biosimilar, filgrastim-sndz, for all indications of the originator filgrastim.[7,27] The approval of filgrastim-sndz was based on review of data demonstrating highly similar protein structure to filgrastim with near-identical pharmacokinetics, pharmacodynamics, and immunogenicity in healthy volunteers and cancer patients.[7,38-40] Data have shown filgrastim-sndz to have identical mass, size, charge, and hydrophobicity to the originator product.[38] Pharmacokinetic and pharmacodynamic modeling have further confirmed that the mechanism of action is the same and occurs through binding of the G-CSF receptor.[39] Clinical data leading to the approval of filgrastim-sndz were predominately based on data from healthy volunteers and data in patients with cancer in the context of the prevention of chemotherapy-induced neutropenia. Although a potential concern regarding immunogenicity exists with biosimilars, immunogenicity is anticipated to be low to nonexistent with filgrastim biosimilars based on the lack of immunogenicity seen with the originator filgrastim biologics and the nature of filgrastim as an unglycosylated protein. In limited clinical studies of healthy volunteers or cancer patients, the incidence of antibodies binding to filgrastim-sndz reached 3% (11 out of 333 patients).[7] Further analysis of these patients showed no evidence of neutralizing antibodies, suggesting that there is no increased risk of immunogenic adverse events or reduction of efficacy.[40] A phase III trial of 218 patients with breast cancer receiving myelosuppressive chemotherapy with TAC (docetaxel, doxorubicin, and cyclophosphamide) showed no clinically meaningful differences regarding efficacy, safety, or immunogenicity between filgrastim and filgrastim-sndz, even in patients who alternated between the two in subsequent chemotherapy cycles.[30] A combined analysis of this and another phase III trial on the safety of filgrastim-sndz in breast cancer patients concluded that filgrastim-sndz has a safety profile consistent with previous studies of reference filgrastim.[41] Several retrospective studies also report similar efficacy between filgrastim-sndz and filgrastim for prophylaxis of chemotherapy-induced neutropenia.[42-45]

In July 2018, the FDA approved a second filgrastim biosimilar, filgrastim-aafi, for the same indications as filgrastim.[46] A phase III randomized equivalence study in 279 patients receiving docetaxel/doxorubicin chemotherapy for breast cancer found filgrastim-aafi to be bioequivalent to filgrastim in terms of efficacy and safety, with similar incidence of FN, treatment-related bone pain, and mean time to neutrophil recovery.[47] The prospective, non-interventional, longitudinal VENICE study, which observed the tolerability, safety, and efficacy of filgrastim-aafi in 386 cancer patients receiving chemotherapy, concluded that filgrastim-aafi was effective and well-tolerated in both the primary and secondary prophylactic settings.[48] The majority of patients (95.6%) experienced no change in chemotherapy dose or schedule due to FN and less than one-third (29.8%) of patients experienced one or more treatment-related adverse events. Two other non-interventional studies reached similar conclusions regarding the bioequivalence of filgrastim-aafi to reference filgrastim in both the prophylactic and therapeutic settings.[49,50]

Pegfilgrastim Biosimilars

In 2018, the FDA approved the first pegfilgrastim biosimilars, pegfilgrastim-jmdb and pegfilgrastim-cbqv, for the same indications as pegfilgrastim based on data showing highly similar pharmacokinetics, pharmacodynamics, and safety in healthy volunteers.[11,12,51-55] Pegfilgrastim-jmdb has been shown to have high analytical and functional similarity to pegfilgrastim, with similar structure, molecular mass, physicochemical characteristics, and G-CSF receptor binding affinity.[56,57] A phase I randomized equivalence trial concluded that pegfilgrastim-jmdb demonstrated similar pharmacokinetics, pharmacodynamics, and safety to

pegfilgrastim in healthy volunteers.[51] In a multicenter randomized phase III efficacy and safety trial, breast cancer patients receiving myelosuppressive chemotherapy with pegfilgrastim-jmdb support showed no difference in the duration of severe neutropenia, time to ANC nadir, duration of post-nadir recovery, or treatment-related adverse events compared to patients receiving reference pegfilgrastim.[58] Pegfilgrastim-jmdb has also demonstrated low immunogenic potential in healthy volunteers and in cancer patients receiving myelosuppressive chemotherapy.[59] Although data are limited, pegfilgrastim-cbqv was shown to have a similar safety profile and bioequivalent pharmacokinetics and pharmacodynamics to pegfilgrastim in 122 healthy volunteers in a multicenter randomized crossover study.[52,53] No serious treatment-related adverse events were observed with the use of pegfilgrastim-cbqv.

In late 2019, the FDA approved the third pegfilgrastim biosimilar, pegfilgrastim-bmez, for the same indications as pegfilgrastim.[13,60] Pegfilgrastim-bmez showed similar pharmacokinetics and pharmacodynamics to pegfilgrastim in healthy volunteers, with no clinically meaningful differences in safety, tolerability, or immunogenicity.[61] Two randomized phase III trials (PROTECT-1 and PROTECT-2) demonstrated equivalent efficacy and safety between pegfilgrastim-bmez and pegfilgrastim in breast cancer patients receiving myelosuppressive chemotherapy.[62,63] In PROTECT-1, breast cancer patients who were randomized to receive pegfilgrastim-bmez had equivalent duration of severe neutropenia during cycle 1 of chemotherapy as patients receiving pegfilgrastim (difference = .07 days; 95% CI: -0.12–0.26).[63] This was confirmed in PROTECT-2, which reported a difference in duration of severe neutropenia between patients receiving pegfilgrastim-bmez and those receiving pegfilgrastim of 0.16 days (95% CI: -0.40–0.08).[62] Pegfilgrastim-bmez also demonstrated highly similar safety and tolerability to pegfilgrastim across both trials, with no significant difference in adverse events reported.[64]

Epoetin Alfa Biosimilar

In May 2018, the FDA approved the first epoetin alfa biosimilar, epoetin alfa-epbx, for anemia associated with administration of myelosuppressive chemotherapy, chronic kidney disease (CKD), treatment of HIV, or to prevent the need for RBC transfusions for patients undergoing surgery.[22,23] Analytical studies and clinical pharmacology data from healthy volunteers have shown epoetin alfa-epbx to have highly similar protein structure, stability, pharmacokinetics, and pharmacodynamics to epoetin alfa.[65] Epoetin alfa-epbx was also shown to have similar efficacy, safety, and mechanism of action to epoetin alfa in two randomized phase III clinical trials involving patients with anemia secondary to CKD.[65] Additionally, the results of three independent studies conducted in patients with CKD and healthy volunteers showed similar rates and titers of anti-drug antibodies for both products, indicating there is no clinically meaningful difference in immunogenicity risk for epoetin alfa-epbx as compared to epoetin alfa. Although there are limited data on the efficacy of epoetin alfa-epbx in treating CIA, two studies concluded that there were no clinically meaningful differences in efficacy or safety between epoetin alfa-epbx and epoetin alfa in the treatment of anemia in patients with CKD.[66,67] Therefore, the FDA approved extrapolation of epoetin alfa-epbx for the treatment of anemia in patients undergoing treatment with myelosuppressive chemotherapy, as well as all other indications for the originator product.[23]

Management of Neutropenia

Benefits of MGFs

Many studies have shown that the prophylactic use of MGFs reduces the incidence, duration, and severity of FN, decreases the subsequent rates of infection and hospitalization, and improves the delivery of full dose-intensity chemotherapy on schedule in patients with various cancers.[68-96] In a meta-analysis by Clark et al, which included 13 studies involving a total of 1518 patients, a clear reduction in infection-related mortality (OR, 0.51;

95% CI, 0.26–1.00; *P* = .05), length of hospitalization (hazard ratio [HR], 0.63; 95% CI, 0.49–0.82; *P* = .0006), and time to neutrophil recovery (HR, 0.32; 95% CI, 0.23–0.46; *P* < .0001) was observed with the prophylactic use of MGFs.[93] In a systematic review of 17 randomized trials including 3493 patients with solid tumors and lymphoma, primary prophylaxis with G-CSF (defined as G-CSF administration within 5 days of beginning chemotherapy) reduced the risk of FN (relative risk [RR], 0.54; 95% CI, 0.43–0.67; *P* < .001) and significantly improved the relative dose intensity (RDI) of chemotherapy with an average difference in RDI of 8.4% between G-CSF–treated (mean RDI = 95.1%) and non-G-CSF–treated (mean RDI = 86.7) patients (*P* = .001).[95] This analysis also reported a substantial reduction in the risk of infection-related mortality (RR, 0.55; 95% CI, 0.33–0.90; *P* = .018) and early death during chemotherapy (RR, 0.60; 95% CI, 0.43–0.83; *P* = .002) with use of G-CSF. This survival advantage was confirmed in a systematic review of 25 randomized controlled trials that involved >12,000 patients undergoing chemotherapy with or without G-CSF support.[96] With an average follow-up of 5 years, G-CSF support was associated with a 3.4% reduction in absolute risk of mortality and an RR of 0.9 for all-cause mortality. Notably, the degree of survival benefit correlated with the chemotherapy dose intensity received by the patient.

The recommendations in the NCCN Guidelines regarding the use of MGFs are based on therapeutic efficacy and clinical benefit. However, in addition to evaluating the clinical benefits of MGF therapy, an increasing number of studies have assessed the financial implications of their use. Based on data analyzed in 2004, the higher cost of inpatient hospitalization resulted in a change of the FN risk threshold on a pure cost basis from 40% to approximately 20% for the cost-saving use of G-CSF prophylaxis.[97] Therefore, if the risk of FN is >20% in a given patient, the overall costs of treatment are substantially reduced with G-CSF prophylaxis. While the addition of MGFs to treatment regimens inevitably raises drug costs, it may equate to substantial savings in comparison to the costs of hospitalization and subsequent treatment of FN. Recently developed pharmacoeconomic models of MGF use have reflected these clinical observations by modeling sequential chemotherapy regimens to account for FN risk on a per-cycle basis, and by accounting for chemotherapy dose reductions and consequent survival losses.[98] Economic analyses of MGFs have yielded mixed results depending on the context of usage.[99-103] Selective use of MGFs in patients at an increased risk for neutropenic complications may also enhance cost-effectiveness.[97,104] Additionally, the use of biosimilars represents a new opportunity for cost containment in oncology care, as biosimilars are typically more affordable than their originator products.[26,105-108]

Risks of MGFs

While MGFs may result in improved outcomes, they are also associated with toxicities (see *Toxicity Risks with Myeloid Growth Factors* in the algorithm). The toxicities listed in the algorithm are from the FDA package inserts and are based on studies from different patient populations. For filgrastim, tbo-filgrastim, and filgrastim biosimilars, the toxicities are based on studies in patients with non-myeloid malignancies. For sargramostim, the toxicities are based primarily on studies from leukemia and transplant patients, and the listed toxicities may reflect the intravenous route of administration, which may differ from those of subcutaneous administration. Not all of the toxicities listed have been seen with each preparation, but similar toxicities are expected with filgrastim, tbo-filgrastim, pegfilgrastim, and biosimilars. See the full package inserts for specific product information.

Bone Pain

To date, the major consistently observed adverse event associated with G-CSF prophylaxis is mild to moderate bone pain in 10% to 30% of patients.[6,10,86,109-112] Currently, data for the treatment of G-CSF–related bone

pain is limited to case series, reviews, and small randomized trials. The available data support the use of naproxen 500 mg BID, or other similar non-steroidal anti-inflammatory drugs (NSAIDs), for 5 to 7 days after G-CSF administration.[110,113] However, use of NSAIDs may not be appropriate for all patients on chemotherapy receiving G-CSF support due to comorbidities, side effects, drug-drug interactions, and drug-disease interactions.[113] Additionally, some patients may experience bone pain that is refractory to NSAIDs.[110] As an alternative, loratadine 10 mg daily or similar anti-histamine can be used for 5 to 7 days after G-CSF administration to treat G-CSF–related bone pain.[114-117] Some studies have suggested that using a reduced dose of pegfilgrastim may be effective in managing G-CSF–related bone pain without increasing the risk for FN.[118-120] However, this strategy may not be feasible since pegfilgrastim comes in a pre-filled, non-graduated syringe designed and FDA-labeled for single-patient use. Therefore, use of reduced-dose pegfilgrastim is not currently recommended by the panel for management of G-CSF–related bone pain.

Splenic Rupture

Rare cases of splenic rupture have been reported with G-CSF use, some of which were fatal.[121-127] These cases occurred in patients with underlying hematopoietic disorders, patients with solid tumors, and healthy donors of peripheral blood progenitor cells (PBPCs). The exact mechanism of G-CSF–induced splenic rupture is unknown, but is thought to involve intrasplenic accumulation of circulating granulocytes and myeloid precursors.[62] Physicians should monitor patients closely for signs of splenic rupture, including abdominal pain (especially in the upper left quadrant), nausea, vomiting, and progressively worsening anemia. Prospective studies on health status, baseline spleen size, and complete blood count (CBC) may be required to identify risk factors for rupture in individual patients.[64]

Bleomycin-Induced Pulmonary Toxicity

The risk of bleomycin-induced pulmonary toxicity may be increased in patients treated with G-CSF. In a retrospective study of 141 patients with Hodgkin lymphoma receiving ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine) chemotherapy, the rate of bleomycin-induced pulmonary toxicity was 26% in patients receiving G-CSF compared with 9% in patients who did not receive it (P = .014).[128] The toxicity potential for patients following the BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone) regimen is less clear, although bleomycin is given every 3 weeks in this regimen as opposed to every 2 weeks in ABVD. Due to the risk of pulmonary complications, the routine use of G-CSF is not recommended in conjunction with the most common chemotherapy regimens for classical Hodgkin lymphoma (ABVD and Stanford V). Two studies have shown that ABVD can be safely administered at full dose without G-CSF support.[129,130] Due to the high incidence of toxicity and treatment delays, G-CSF support is recommended for patients with Hodgkin lymphoma treated with the escalated BEACOPP regimen.

AML and MDS

Although there have been suggestions of a potentially increased risk for development of AML and myelodysplastic syndrome (MDS) following MGF administration from epidemiologic studies, this has not been observed in individual randomized trials.[121,131-133] The meta-analysis by Lyman et al[96] reported a 0.41% increase in absolute risk (95% CI, 0.10%–0.72%; P = .009) and an estimated RR of 1.92 (95% CI, 1.19–3.07; P = .007) for the development of AML/MDS related to G-CSF use. While it was not possible from this meta-analysis to determine whether the risk for AML/MDS is secondary to G-CSF or related to higher total doses of chemotherapy, overall mortality was nevertheless decreased by the addition of G-CSF support. An updated meta-analysis and systematic literature review by

Lyman et al largely came to the same conclusions, reporting an increased risk for the development of secondary malignancies including AML/MDS (RR, 1.85; 95% CI, 1.19–2.88; *P* < .01) and improved survival (mortality RR, 0.86; 95% CI, 0.80–0.92; *P* < .0001) in patients receiving primary G-CSF support.[134] Analyses using data from the Surveillance, Epidemiology, and End Results (SEER) database have also shown a slightly elevated risk of developing AML/MDS in patients receiving G-CSF support.[133,135] However, these studies should be interpreted with caution since they cannot exclude the possibility that the increased risk was due to the use of G-CSF in cases that were more likely to progress into AML/MDS, regardless of the presence or absence of adjuvant therapy.

Other Toxicities

Some patients may develop allergic reactions to G-CSF involving the skin, respiratory system, or cardiovascular system. Other potential toxicities include acute respiratory distress syndrome, alveolar hemorrhage, and hemoptysis.[6,10,136] Sickle cell crisis, sometimes fatal, has been reported in patients with sickle cell disease receiving G-CSF, but not for patients with sickle cell trait.[137-139] Significant toxicity in amyloidosis patients following G-CSF administration has also been described in two case reports.[140,141] There has also been a low fraction of fatalities in amyloidosis patients undergoing stem cell mobilization with G-CSF.[142]

Adverse events have also been reported with GM-CSF use. In an early study, adverse reactions were seen in 65% of patients with advanced malignancy following administration of GM-CSFs, though they were not severe and were reversible. These reactions included mild myalgias, facial flushing, low-grade fever, headache, nausea, and dyspnea.[143] A side-effect profile of GM-CSF, completed several years later, reported a lower rate of 20% to 30% mild-to-moderate adverse events, and attributed this decline to improved dosing and delivery.[144] Though uncommon, severe side effects have also been reported with GM-CSF use. Less than 1% of patients develop blood clots, which may lead to pulmonary embolism or stroke in rare cases.[145-147] There have also been reports of capillary leak syndrome,[148-150] a condition in which fluids move from the vascular system into the interstitial space resulting in hypotension and reduced blood flow to internal organs.[145] While this is more common with GM-CSF use, it has also been reported to occur with G-CSF use.[151,152]

Data regarding the safety of MGF administration following infusion of chimeric antigen receptor (CAR)-modified T cells are limited and institutional practices widely vary.[153-155] The FDA label for tisagenlecleucel recommends avoiding use of MGFs, particularly GM-CSF, during the first 3 weeks after cell infusion or until cytokine release syndrome (CRS) has resolved.[156] Although data are not provided to support this recommendation, it is likely based on the potential for GM-CSF to promote antigen-presenting cell function that may exacerbate the severity or incidence of CRS.[153,157] Due to the high rates of neutropenic complications in patients undergoing CAR T cell therapies and the potential for promotion of CRS with the use of MGFs, more studies are needed to determine the safety of MGFs in this setting.

Prophylactic Use of MGFs

Risk Assessment

The risk of developing FN is related to the treatment regimen, delivered dose intensity, and patient-specific risk factors. FN risk should be evaluated prior to the first and each subsequent cycle of chemotherapy. The risk assessment should include disease type, chemotherapy regimen (high-dose, dose-dense, or standard-dose), patient-specific risk factors, and treatment intent (curative/adjuvant vs. palliative). Based on the chemotherapy regimen, the patient is assigned to an overall high-risk group (>20% risk of FN), intermediate-risk group (10%–20% risk), or low-risk group (<10% risk). Patients in the high-risk group should receive prophylactic G-CSF (category 1). Prophylactic G-CSF should also be

considered for patients in the intermediate-risk group based on patient-specific risk factors (see *Patient Risk Factors for Developing FN* below). Patients in the low-risk group should generally not receive prophylactic G-CSF.

There is currently no consensus nomogram for FN risk assessment. While the NCCN Panel outlines criteria to aid in the assessment of FN risk, independent clinical judgment should be exercised based on the individual patient's situation. The NCCN Panel recommends that patients receiving cytotoxic chemotherapy as part of a clinical trial be evaluated for prophylactic use of G-CSF based on both regimen-specific and patient-specific risk factors, unless precluded by trial specifications.

Chemotherapy Regimens and Risk for FN

The development of FN is directly related to the dose intensity of the chemotherapy regimen. Chemotherapy regimens for which clinical trial data show an incidence of FN >20% in chemotherapy-naive patients are considered by the panel to be high risk. It should be noted that the addition of monoclonal antibodies to chemotherapy regimens has the potential to increase the risk of FN. Of particular concern is rituximab, an anti-CD20 monoclonal antibody mainly used in treatment of CD20+ hematologic malignancies, which is known to have an independent potential to cause severe neutropenia. Rituximab has been associated with prolonged, delayed-onset neutropenia both with and without chemotherapy.[158]

The algorithm lists common chemotherapy regimens associated with a high or intermediate risk of developing FN based on published data (see *Examples of Disease Settings and Chemotherapy Regimens with a High/Intermediate Risk for Febrile Neutropenia* in the algorithm). These lists are not comprehensive and are meant to serve as examples only. Other agents/regimens may also have a high or intermediate risk for FN. In general, dose-dense regimens require MGF support to maintain dose intensity and schedule. It is emphasized that the chemotherapy regimen is only one component of risk assessment and needs to be combined with patient-specific risk factors and treatment setting to estimate the overall risk of FN.

Patient Risk Factors for Developing FN

Patient-specific risk factors are an important consideration in estimating the overall risk of FN, particularly when chemotherapy regimens are considered intermediate risk.[159] The presence of patient-specific risk factors may elevate the overall risk to a high-risk category, where prophylactic G-CSFs are more routinely recommended. Many regimens for breast and lung cancers are associated with an intermediate risk of neutropenic complications, making it important to identify which patients would be considered high risk for FN development based on individual risk factors. Even a low-risk regimen may warrant the use of G-CSF in a patient with one or more clinical risk factors.

The most important patient-specific risk factor for the development of FN is older age (>65 years; see NCCN Guidelines for Older Adult Oncology).[160-165] Other identified risk factors that might prompt the use of prophylactic G-CSF include prior exposure to chemotherapy or radiation therapy, persistent neutropenia, bone marrow involvement by the tumor, poor performance status, recent surgery and/or open wounds, renal or liver dysfunction, and HIV infection (see *Patient Risk Factors Assessment* in the algorithm).[166] Chronic immunosuppression in the post-transplant setting (including organ transplant) may also warrant the use of G-CSF. Most of these have been confirmed as independent risk factors for the development of neutropenic complications in a risk model developed by Lyman et al that was validated in a study population of 3760 patients with cancer beginning chemotherapy.[167] This model and its associated risk factors have been retrospectively validated both internally and externally in an independent patient population.[168] In the future, external validation of other proposed FN risk assessment models and novel patient-specific

risk factors may enhance identification of patients at high risk for developing FN.[104,169-172]

Patients at High Risk for FN

The NCCN Guidelines recommend prophylactic use of G-CSF if a patient's risk of developing FN is >20% (category 1). The most recent updates of the ASCO and EORTC guidelines have also adopted the 20% threshold for considering routine prophylactic MGF support.[173,174] This consistent recommendation is based on the results of several large randomized trials that have documented a significant reduction in FN incidence following primary G-CSF prophylaxis when the risk of FN without prophylaxis is >20%.[95,175] In one such example, a randomized, placebo-controlled, phase III trial in breast cancer patients receiving TC (docetaxel and cyclophosphamide) chemotherapy found that the incidence of FN was significantly lower for patients who received prophylactic G-CSF than those who received placebo (1.2% vs. 68.8%, respectively; $P < .001$).[175] Patients in the G-CSF group also had lower rates of hospitalization and antibiotic use. Furthermore, prophylactic use of G-CSF was associated with a 46% reduction in the relative risk of developing FN in a systematic review of 17 randomized controlled trials involving 3493 patients with solid tumors or malignant lymphoma receiving systemic chemotherapy.[95]

The NCCN Guidelines recognize a variety of circumstances in which patients treated with relatively non-myelosuppressive chemotherapy regimens are at a high risk for FN due to bone marrow compromise, comorbidities, or other patient-specific risk factors. Prophylactic G-CSF is recommended for any patient considered to be at high patient-specific risk, regardless of the treatment regimen or intent.

Patients at Intermediate Risk for FN

The NCCN Panel defines intermediate risk as a 10% to 20% probability of developing FN or a neutropenic event that would compromise treatment. For patients receiving intermediate-risk chemotherapy regimens, the panel recommends individualized consideration of prophylactic G-CSF use based on the presence of patient-specific risk factors. Patients with ≥1 risk factor should be considered for prophylactic G-CSF, while patients with no risk factors should be observed. The panel also recommends physician-patient discussion of the risk-benefit ratio of G-CSF use with respect to the likelihood of developing FN, the potential consequences of a neutropenic event, and the implications of reduced chemotherapy dose delivery.

When the intent of chemotherapy is palliative, the use of G-CSF is a difficult decision and requires careful discussion between the physician and patient. If the increased risk for FN is due to patient-specific risk factors, G-CSF use is reasonable. However, if the risk is due to the chemotherapy regimen, alternatives such as dose reduction or the use of less myelosuppressive chemotherapy, if of comparable benefit, should be explored.

Patients at Low Risk for FN

For patients receiving low-risk chemotherapy regimens, as defined by an FN risk of <10%, routine use of G-CSF prophylaxis is not recommended.[97,176,177] However, use of prophylactic G-CSF may be appropriate if the patient is receiving therapy with curative intent and is at significant patient-specific risk for developing FN.

Evaluation Prior to Subsequent Chemotherapy Cycles

After the first cycle of chemotherapy, patient evaluation should be performed prior to each subsequent cycle to determine the FN risk categorization. If the patient experienced an episode of FN or a dose-limiting neutropenic event (a nadir count or a day-of-treatment count

impacting the planned dose of chemotherapy) during the previous treatment cycle with the same dose and schedule planned for the current cycle, this patient is now in the high-risk group. Prophylactic G-CSF support should be considered for such patients who had not received prior G-CSF. In patients who did receive prior G-CSF, the panel recommends a chemotherapy dose reduction or a change in treatment regimen unless there is an impact on patient survival. If the patient did not develop FN or a dose-limiting neutropenic event in the first cycle and is thought to be benefiting from chemotherapy, the assessment of patient-specific risk factors should be repeated prior to each subsequent chemotherapy cycle and a decision rendered regarding the indication for prophylactic G-CSF.

Dosing and Administration

Filgrastim, tbo-filgrastim, filgrastim-sndz, filgrastim-aafi, pegfilgrastim, pegfilgrastim-jmdb, pegfilgrastim-cbqv, and pegfilgrastim-bmez are FDA-approved options for FN prophylaxis in patients with solid tumors receiving myelosuppressive chemotherapy. Sargramostim is not recommended in this setting. For information regarding prophylactic anti-infectives (ie, viral, fungal, bacterial), see the NCCN Guidelines for Prevention and Treatment of Cancer-Related Infections.

Filgrastim and Filgrastim Biosimilars

The subcutaneous administration of filgrastim, tbo-filgrastim, filgrastim-sndz, or filgrastim-aafi is a category 1 recommendation for the prevention of FN. Initial doses of filgrastim, tbo-filgrastim, or filgrastim biosimilars are administered the next day or up to 3 to 4 days after completion of myelosuppressive chemotherapy in a daily dose of 5 mcg/kg until post-nadir ANC recovery to normal or near-normal levels by laboratory standards. The dose may be rounded to the nearest vial size by institution-defined weight limits. Neutrophil counts should be monitored as indicated appropriate to the setting. The NCCN Panel recommends treatment of patients through post-nadir recovery since studies have shown shorter durations of G-CSF treatment to be less efficacious.[178]

Pegfilgrastim and Pegfilgrastim Biosimilars

Pegfilgrastim, pegfilgrastim-jmdb, pegfilgrastim-cbqv, and pegfilgrastim-bmez are pegylated versions of filgrastim designed to have a longer half-life, which allows for a single administration of 6 mg to be sufficient. Based on clinical trial data, pegfilgrastim or pegfilgrastim biosimilars should be administered the day following myelosuppressive chemotherapy (category 1).[179] Administration up to 3 to 4 days after myelosuppressive chemotherapy is also reasonable based on trials of filgrastim. The rationale for not giving same-day pegfilgrastim is the potential for exacerbation of neutropenia resulting from stimulation of hematopoietic progenitor cells at the time of cytotoxic chemotherapy active in dividing cells, resulting in loss of the progenitors.[180,181] A systematic literature review evaluating the relative merits of next-day versus same-day pegfilgrastim found that delivery of pegfilgrastim at least 24 hours after myelosuppressive chemotherapy resulted in improved patient outcomes across a variety of tumor types.[179] Additionally, a retrospective analysis found that administration of pegfilgrastim 24 to 72 hours after chemotherapy was significantly associated with maintenance of chemotherapy dose intensity in patients with various cancers.[182] Another retrospective evaluation found that 50% of all FN hospitalization episodes among cancer patients occurred in those who either did not receive pegfilgrastim or received pegfilgrastim on the same day as chemotherapy.[178] A large-scale retrospective evaluation of 53,814 patients receiving intermediate- or high-risk chemotherapy regimens also found the incidence of FN to be significantly higher in patients administered pegfilgrastim prophylaxis either the same day or 4 to 5 days after chemotherapy compared to those receiving pegfilgrastim on days 1 to 3 following chemotherapy.[183] In a direct comparison, Kaufman et al[184] administered either same-day or next-day pegfilgrastim in women with

breast cancer receiving chemotherapy with TAC. FN was observed in 33% of patients treated in the same-day group compared with only 11% of patients treated in the next-day group.[184] A similar trend was seen in a prospective, randomized trial of patients receiving CHOP or CHOP-like therapy for NHL, where same-day pegfilgrastim was associated with enhanced myelosuppression.[185]

Panelists recognize that some institutions have administered pegfilgrastim on the same day as chemotherapy for logistical reasons and to minimize travel burdens on long-distance patients.[186] The recent FDA approval of a delivery device that can be applied the same day as chemotherapy and set to deliver the full dose of pegfilgrastim the following day (approximately 27 hours after application) is an alternative to same-day administration for patients who cannot return to the clinic for next-day administration of pegfilgrastim.[187] However, this on-body delivery device is currently only available for use with originator pegfilgrastim and not pegfilgrastim biosimilars. The panel also discussed the use of pegfilgrastim in chemotherapy regimens of different cycle lengths. In general, there should be at least 12 days between the dose of pegfilgrastim and the next cycle of chemotherapy. If the treatment cycle includes chemotherapy administration on days 1 and 15, pegfilgrastim may be given after each chemotherapy treatment. Based on phase III clinical trials,[72,188] use of pegfilgrastim for chemotherapy regimens given every 3 weeks is a category 1 recommendation. Pegfilgrastim use is a category 2A recommendation for chemotherapy regimens given every 2 weeks, based on phase II studies.[189-194] There are insufficient data to support the use of pegfilgrastim for weekly regimens; therefore, pegfilgrastim should not be used. The panel has extended these recommendations to pegfilgrastim biosimilars.

Therapeutic Use of MGFs

Compared to prophylactic use, there is less evidence supporting the therapeutic use of MGFs for FN. While there are clinical benefits to G-CSF therapy for FN, such as shorter time to neutrophil recovery and shorter length of hospitalization, it remains unclear whether these benefits translate into a survival advantage.[93,195] The NCCN Panel recommends that patients presenting with FN who are receiving or have previously received prophylactic filgrastim, tbo-filgrastim, filgrastim-sndz, or filgrastim-aafi should continue G-CSF. However, since pegfilgrastim, pegfilgrastim-jmdb, pegfilgrastim-cbqv, and pegfilgrastim-bmez are long-acting, those who have received these agents prophylactically should not be treated with additional G-CSF.[196] There are no studies that address the therapeutic use of filgrastim for FN in patients who have already received prophylactic pegfilgrastim or a pegfilgrastim biosimilar. Pharmacokinetic data following treatment with pegfilgrastim demonstrate high levels during neutropenia and suggest that additional G-CSF use may not be beneficial. However, additional G-CSF support may be considered in patients with prolonged neutropenia (beyond 12–14 days) as the pegylated products are unlikely to endure beyond this window.

For patients presenting with FN who have not received prophylactic G-CSF, the NCCN Panel recommends an evaluation of risk factors for infection-related complications or poor clinical outcome. Features associated with poor outcome include age >65 years; sepsis syndrome; ANC <100 neutrophils/mcL; anticipated prolonged (>10 days) neutropenia; pneumonia or other clinically documented infection; invasive fungal infections; hospitalization at the time of fever; and prior episode(s) of FN. If risk factors are present, use of therapeutic MGFs should be considered. Filgrastim, tbo-filgrastim, filgrastim-sndz, filgrastim-aafi, or sargramostim may be administered in the therapeutic setting. Pegfilgrastim and pegfilgrastim biosimilars have only been studied for prophylactic use and are not recommended for therapeutic use at this time.

Filgrastim, pegfilgrastim, and sargramostim are also FDA-approved for the treatment of patients with radiation-induced myelosuppression following a radiologic/nuclear incident (H-ARS).[6,10,16,145,197] The panel also recommends use of tbo-filgrastim or FDA-approved filgrastim/pegfilgrastim biosimilars as appropriate options in this setting. The goals of using MGFs to treat radiation-induced myelosuppression are to shorten the duration of severe neutropenia, minimize the severity of neutropenia-associated complications, and increase survival.[198] According to U.S. Department of Health and Human Services Radiation Emergency Medical Management guidance, initiation of MGFs should be strongly considered for patients who received ≥2 Gy whole body exposure or ≥2 Gy significant partial body exposure and have an ANC ≤500 cells/mm^3, will likely have prolonged periods of significant neutropenia, or have trauma and/or burns, which worsen the clinical outcome compared to radiation exposure alone.[198] Most of the data in support of MGF used in this setting are derived from animal studies and case reports concerning patients involved in radiation accidents.[199-208]

Dosing and Administration

Filgrastim, tbo-filgrastim, filgrastim-sndz, filgrastim-aafi, and sargramostim are the recommended MGFs for the treatment of FN in select high-risk patients as outlined above who have not received prophylactic G-CSF. Filgrastim, tbo-filgrastim, filgrastim-aafi, or filgrastim-sndz should be given at a daily dose of 5 mcg/kg and sargramostim should be given at a daily dose of 250 mcg/m^2. Treatment should continue through post-nadir recovery. For patients presenting with H-ARS, filgrastim, tbo-filgrastim, filgrastim-aafi, or filgrastim-sndz should be given at a daily dose of 10 mcg/kg; pegfilgrastim, pegfilgrastim-jmdb, pegfilgrastim-cbqv, and pegfilgrastim-bmez should be given as a single dose of 6 mg; and sargramostim should be given at a daily dose of 250 mcg/m^2.[198] MGFs should be administered as soon as possible after acute radiation exposure.

MGFs in Mobilization and Post Hematopoietic Cell Transplant Care

MGFs are commonly administered in the HCT setting, either for mobilization of hematopoietic progenitor cells or as supportive care after transplantation. Mobilization of PBPCs by G-CSF-containing regimens has largely replaced bone marrow collection for HCT due to the ease of collection, avoidance of general anesthesia, and more rapid recovery of blood counts.[209] Additionally, PBPC transplants are associated with a more rapid recovery of granulocytes and platelets after transplantation and lower transplant-related mortality compared to bone marrow transplants.[209] Effective mobilization regimens include growth factor alone, chemotherapy and growth factor combined, and the incorporation of plerixafor with either approach.

Mobilization of Hematopoietic Progenitor Cells in the Autologous Setting

Studies have shown that single-agent filgrastim, tbo-filgrastim, and filgrastim biosimilars are effective in mobilizing hematopoietic progenitor cells in the autologous HCT setting.[210-214] Combination chemotherapy followed by filgrastim, tbo-filgrastim, or filgrastim biosimilars may result in higher collection yields with fewer days of apheresis, but at an increased rate of hospitalizations for neutropenic fever.[215-218] This approach may also reduce the burden of residual tumor. Several regimens are effective in chemomobilization of hematopoietic progenitor cells, including cyclophosphamide,[215] ICE,[216] DHAP,[216] VTD-PACE,[217] and others. Studies using GM-CSF as a single agent for mobilization or in sequential combination with G-CSF have also reported good yields of PBPCs in normal donors.[219-221] However, a randomized phase III trial comparing filgrastim, sargramostim, and sequential sargramostim and filgrastim following administration of myelosuppressive chemotherapy in the autologous HCT setting found that patients who received filgrastim alone yielded more CD34+ cells (median 7.1 vs. 2.0 x 10^6 kg per apheresis, *P* =

.0001) and had faster recovery of ANC (median 11 vs. 14 days, *P* = .0001) compared to patients receiving sargramostim alone. Importantly, there were no significant differences in outcomes between groups receiving filgrastim alone and the sequential regimen.[222] Therefore, the use of concurrent filgrastim or a filgrastim biosimilar with sargramostim is a category 2B recommendation. Use of single-agent sargramostim is not recommended.

The CXCR4 inhibitor plerixafor, in combination with G-CSF, is FDA-approved for mobilizing autologous hematopoietic progenitor cells to the peripheral blood in patients with NHL or multiple myeloma.[223] Numerous studies have shown that the addition of plerixafor to mobilization regimens accelerates the rise in PBPC count.[224-232] The addition of plerixafor as a preemptive ("just in time") strategy in patients with poor mobilization after administration of growth factor with or without chemotherapy has been highly successful.[226,227,233-235] Poor mobilization is generally defined as failure to achieve the target level of at least 2×10^6 CD34+ cells/kg body weight.[236] However, there are limited data on parameters for predicting poor mobilization and identifying which patients may benefit from upfront use of plerixafor. Risk factors that have been associated with poor mobilization include older age, extensive prior therapy, prior radiation to marrow-containing regions, or multiple cycles of certain agents such as fludarabine or lenalidomide.[228,237-245] Traditionally, parameters such as older age (>60 years) and low platelet count (<100,000) have been used to predict poor mobilization. However, recent data suggest that prior exposure to lenalidomide and low white blood cell count (<4000) are more strongly associated with poor mobilization than platelet count.[246] Additional studies have suggested there may also be genetic parameters that contribute to mobilization outcome.[247] Historically, predicting mobilization failure based on baseline patient characteristics or risk factors has been highly inaccurate.[228] Thus, there is increasing interest in developing new predictive models for poor mobilization to identify patients most likely to benefit from upfront plerixafor. Olivieri et al recently proposed a predicted poor mobilizer (pPM) score, using criteria such as increasing age, diagnosis of NHL, positive bone marrow biopsy, cytopenias before mobilization, and previous mobilization failure, to help identify patients at high risk for poor mobilization.[248] If validated in prospective trials, this model may become highly useful in avoiding likely mobilization failures. Another predictive model proposed by Musto et al used 4 parameters (age, baseline low peripheral blood cell count, use of lenalidomide, and hematologic toxicity developed during induction) to predict poor mobilization among multiple myeloma patients.[249] However, age and hematologic toxicity developed during induction were the only parameters that maintained statistical significance after multivariate analysis. Well-designed randomized trials are needed to validate the parameters proposed in predictive models for poor mobilization.

There are data to support the use of tbo-filgrastim and filgrastim biosimilars in the autologous HCT setting.[250-258] However, the panel acknowledges the limitations of these studies regarding long-term outcomes. Therefore, while it is reasonable to substitute with filgrastim biosimilars, clinicians should be aware of any complications presented in the literature or in their patients. Accurate and timely disclosure of any variation in expected outcome with the biosimilars compared to the originator filgrastim will be of paramount importance. While some small studies suggest that single-dose pegfilgrastim may have similar efficacy to filgrastim for mobilization,[259-264] there are limited high-quality data supporting the use of pegfilgrastim in this setting. Therefore, pegfilgrastim, pegfilgrastim-jmdb, and pegfilgrastim-cbqv are not recommended for mobilization at this time.

Dosing and Administration

The NCCN Panel recommends administration of filgrastim, filgrastim-sndz, filgrastim-aafi, or tbo-filgrastim as a single agent[210-212] or as part of a

chemomobilization regimen,[215-217] starting about 24 hours after completion of chemotherapy, at a dose of 10 to 32 mcg/kg per day in daily or twice-daily dosing. Apheresis usually commences on the fourth or fifth day of G-CSF initiation when it is used as a single agent. If used concurrently with sargramostim, filgrastim, filgrastim-sndz, or filgrastim-aafi should be administered at a dose of 7.5 mcg/kg each morning with sargramostim administered at a dose of 7.5 mcg/kg each evening. Leukapheresis should begin on day 5. If used in conjunction with plerixafor, filgrastim, filgrastim-sndz, filgrastim-aafi, or tbo-filgrastim should be administered at 10 mcg/kg per day for 5 days. On the evening of day 4, plerixafor should be administered by subcutaneous injection 11 hours prior to initiation of apheresis on day 5. Plerixafor dosing is based on patient weight and estimated creatinine clearance (See *Myeloid Growth Factors in Mobilization and Post Hematopoietic Cell Transplant* in the algorithm for more information).

Mobilization of Hematopoietic Progenitor Cells in the Allogeneic Setting

Initially, there were concerns about using G-CSF for mobilization in the allogeneic setting due to normal donor toxicity and the risk for graft-versus-host disease (GVHD) in the recipient. However, studies have demonstrated filgrastim to be well-tolerated by donors without an effect on long-term survival in the recipient.[265-267] Data supporting the use of filgrastim biosimilars in the allogeneic setting are sparse. Some studies have suggested that filgrastim-sndz is effective for mobilization in healthy donors with no short-term safety issues;[268-272] however, long-term data are needed. In a study by the World Marrow Donor Association (WMDA), mobilization of CD34+ cells and incidence of treatment-related adverse events were found to be similar between filgrastim-sndz and reference filgrastim in 1287 healthy volunteers,[273] although the authors cite a lack of long-term follow-up for both reference filgrastim and filgrastim-sndz. There was no evidence of a higher risk of filgrastim antibody formation using biosimilars. Based on these data, the NCCN Panel endorses the use of filgrastim biosimilars for the mobilization of PBPCs in healthy donors in the allogeneic HCT setting, but cautions physicians to closely follow patients during the follow-up period in order to identify any potential complications or unexpected outcomes. Tbo-filgrastim has also been shown to effectively mobilize PBPCs for allogeneic transplantation in healthy donors;[214,274,275] however, the data are limited to very small studies that only included related donors. Therefore, the use of tbo-filgrastim for PBPC mobilization in healthy allogeneic donors is currently a category 2B recommendation.

Dosing and Administration

The NCCN Panel recommends single-agent filgrastim (category 2A), filgrastim biosimilars (category 2A), or tbo-filgrastim (category 2B) for allogeneic donor PBPC mobilization at a dose of 10 to 16 mcg/kg per day by subcutaneous injection, with collection beginning on day 4 or 5. The use of plerixafor in healthy allogeneic donors (category 2B) is currently under study.[276-278] As previously mentioned, pegfilgrastim and pegfilgrastim biosimilars are not recommended for mobilization at this time. For granulocyte transfusion, the panel recommends filgrastim (category 2A), filgrastim biosimilars (category 2A), or tbo-filgrastim (category 2B) at a single subcutaneous dose of 5 mcg/kg with dexamethasone 10 mg PO administered 8 to 24 hours prior to collection.[279]

MGFs as Part of Supportive Care After HCT

Consensus is lacking on the use of MGFs in the post-transplant setting. Filgrastim administration after high-dose chemotherapy and autologous HCT has been shown to expedite neutrophil recovery in prospective randomized trials.[280-285] However, results were inconclusive on the impact of filgrastim on duration of post-HCT hospital stay, infections, and survival. Several studies comparing filgrastim and pegfilgrastim in the post-

autologous transplant setting concluded that the two are at least equally effective.[286-293] Data are conflicting on G-CSF use as a supportive care measure for allogeneic transplant recipients, with some studies associating G-CSF with worse clinical outcomes.[294] However, G-CSF has been used routinely to facilitate the recovery of blood counts after umbilical cord blood transplant, because there is a significant delay in the rate and kinetics of neutrophil and platelet engraftment after cord blood transplant as compared to marrow or mobilized PBPC grafts.[295]

Dosing and Administration

The NCCN Panel recommends the use of filgrastim,[285] filgrastim-sndz,[42] filgrastim-aafi, or tbo-filgrastim following autologous HCT, haploidentical transplant, or cord blood transplant at a dose of 5 mcg/kg per day beginning 5 to 7 days post-transplant until ANC recovery. Pegfilgrastim and pegfilgrastim biosimilars are also recommended in the supportive care setting for post-autologous HCT[257,259-264]

Severe Chronic Neutropenia

These guidelines focus on the management of neutropenia in the cancer setting; therefore, severe chronic neutropenia is only briefly discussed below. G-CSF is established as an effective treatment for cyclic, congenital, and idiopathic neutropenia based on a randomized controlled trial involving 123 patients.[296] In this study, daily treatment with subcutaneously administered G-CSF normalized neutrophils in most patients and prevented fever, mouth ulcers, and infections. Subsequent observational studies showed that patients with idiopathic and cyclic neutropenia generally responded to low-dose daily, alternate-day, or thrice-per-week subcutaneous G-CSF administration (1–3 mcg/kg per day). Congenital neutropenia patients generally require higher doses (3–10 mcg/kg per day). All patients should have doses adjusted to maintain a blood neutrophil level in the normal or low-normal range. Acute adverse effects include bone pain, arthralgias, and myalgias, which usually diminish in the first few weeks of treatment. The greatest concern is that patients with the diagnosis of severe congenital neutropenia are at risk for myelodysplasia and leukemia, with or without G-CSF treatment. More severely affected patients, as reflected by the requirement of higher doses of G-CSF, appear to be at greater risk. These considerations emphasize the importance of making a correct diagnosis and following these patients carefully. Currently, the only alternative therapy for severe chronic neutropenia is HCT. For further reading on severe chronic neutropenia, refer to the website developed by The Severe Chronic Neutropenia International Registry: http://depts.washington.edu/registry/index.html.

Summary

G-CSF can prevent the development of FN and are utilized in patients receiving myelosuppressive chemotherapy regimens with a high risk of FN and in patients with one or more patient-specific risk factors receiving regimens with an intermediate risk of FN. MGFs (G-CSF or GM-CSF) can also be used to treat FN or H-ARS in select individuals. Mild to moderate bone pain is the most commonly reported adverse event in patients receiving G-CSF while patients receiving GM-CSF commonly report mild myalgias, facial flushing, low-grade fever, headache, nausea, and dyspnea. MGFs are also commonly administered in the HCT setting, either for mobilization of hematopoietic progenitor cells or as supportive care after transplantation. An FDA-approved biosimilar is an appropriate substitution for filgrastim or pegfilgrastim for all indications.

Management of Cancer- and Chemotherapy-Induced Anemia

Etiology of Anemia Associated with Cancer and Myelosuppressive Chemotherapy

Causes of anemia in patients with cancer are often multifactorial.[297] Anemia may be attributed to underlying comorbidities such as bleeding, hemolysis, nutritional deficiencies, hereditary disease, renal insufficiency, hormone dysfunction, or a combination of these factors.[298,299] The malignancy itself can lead to or exacerbate anemia in a number of ways.[300] Cancer cells may directly suppress hematopoiesis through bone marrow infiltration. They may also produce cytokines that lead to iron sequestration, which decreases RBC production and may shorten RBC survival. Chronic blood loss at tumor sites from blood vessels or organ damage can also exacerbate anemia in patients with cancer. Additional indirect effects may include nutritional deficiencies caused by loss of appetite, hemolysis by immune-mediated antibodies, or changes in coagulation parameters. For this myriad of reasons, anemia is highly prevalent among patients with cancer at initial presentation, especially in patients with lung cancer.[19,301-303]

Many chemotherapy agents produce myelosuppression, which contributes to anemia.[303] Chemotherapeutic agents induce anemia by directly impairing hematopoiesis in the bone marrow, including disruption of RBC precursor production.[300] Additionally, the nephrotoxic effects of some cytotoxic agents (eg, platinum-containing agents) can result in decreased production of erythropoietin by the kidneys.[300] RT to the skeleton has also been associated with hematologic toxicity. In a retrospective analysis of 210 patients undergoing craniospinal RT for treatment of primary tumors of the central nervous system, approximately one-third of patients developed grade 3/4 hematologic toxicities including anemia.[304] Newer modalities such as immunotherapies may also produce anemia, though data are limited.[305-308] Clinicians should become familiar with the adverse effects of immunotherapy drugs, including hematologic toxicities, and be observant for other less-documented clinical conditions as these therapies become more prevalent in cancer care.

The myelosuppressive effects of particular cytotoxic agents are likely to accumulate over the course of repeated cycles of therapy, resulting in a steady increase in the rate and severity of anemia with additional chemotherapy cycles. In the European Cancer Anaemia Survey (ECAS),[302] the rate of anemia (Hb level <12 g/dL) was found to increase from 19.5% in cycle 1 to 46.7% by cycle 5.[302] An increase in the fraction of grade 2 to 3 anemia was also associated with a greater number of chemotherapy cycles. Other factors to consider when evaluating the risk for CIA include the nadir Hb level, the time to the nadir Hb level (roughly estimated at 2 weeks, but time can vary), and whether an Hb measurement is considered to be pre- or post-nadir.[300]

Initial Evaluation of Anemia

Given the wide variation in Hb levels among healthy subjects, a universal “normal” value is difficult to define. According to the NCCN Panel, an Hb level ≤11 g/dL should prompt an evaluation of anemia in patients with cancer. A drop ≥2 g/dL below baseline is also cause for concern and assessment. Importantly, clinicians should consider gender differences in Hb as part of the initial evaluation of anemia, since women typically have a lower baseline Hb level than men.[309] As discussed above, a patient with cancer may suffer from anemia as the result of a combination of causes, some of which may not be directly related to the cancer (reviewed by Gilreath et al[297]). The overall goals of evaluation are to characterize the anemia and identify any potentially correctable underlying comorbidities prior to initiating treatment.

Initial characterization of anemia involves a CBC with indices to determine if other cytopenias are present. A visual review of the peripheral blood

smear morphology is critical to confirm the size, shape, and Hb content of RBCs. A detailed history and physical exam must also be taken. The history should include the onset and duration of symptoms, comorbidities, family history, and whether there has been any exposure to antineoplastic drugs or radiation. Common complaints are syncope, exercise dyspnea, headache, vertigo, chest pain, fatigue that is disruptive to work and daily activities, and abnormal menstruation in female patients. Pallor may also be apparent. A key characteristic distinguishing fatigue related to cancer from fatigue in healthy individuals is that cancer-related fatigue is less likely to be ameliorated by rest (see NCCN Guidelines for Cancer-Related Fatigue).[310] The above clinical manifestations are neither sensitive nor specific to the type of anemia. Clinicians should watch for signs of underlying etiologies such as jaundice, splenic enlargement, neurologic symptoms, blood in the stool, petechiae, and heart murmur, among others.

Approaches to Evaluation

There are two common approaches to evaluating anemia: morphologic and kinetic. A complete evaluation should utilize both. The morphologic approach is a characterization of anemia by the mean corpuscular volume (MCV), or average RBC size, reported in the initial CBC and classified as follows:

- Microcytic (<80 fL)—most commonly caused by iron deficiency; other etiologies include thalassemia, anemia of chronic disease, and sideroblastic anemia.
- Macrocytic (>100 fL)—most commonly caused by medications[311] and alcoholism, both of which are forms of non-megaloblastic anemia. MDS also causes mild macrocytosis. Macrocytosis seen in megaloblastic anemia is most frequently caused by vitamin deficiency resulting from inadequate intake (folic acid or B_{12}) or inadequate absorption of B_{12} from lack of intrinsic factor or antibodies to parietal cells. Macrocytosis accompanies increased reticulocyte counts following brisk hemorrhage or hemolysis.
- Normocytic (80–100 fL)—may be due to hemorrhage, hemolysis, bone marrow failure, anemia of chronic inflammation, or renal insufficiency.

The kinetic approach focuses on the underlying mechanism of anemia, distinguishing among the production, destruction, and loss of RBCs. The most basic RBC index is the reticulocyte index (RI) that corrects the reticulocyte count against the degree of anemia as measured by Hct. The reticulocyte count, often represented as a percentage, reflects the number of reticulocytes (immature RBCs) per number of total RBCs. The RI is calculated based on the reticulocyte count and is an indicator of the RBC production capacity by the bone marrow. The normal RI ranges from 1.0 to 2.0.

- RI = Reticulocyte count (%) x [(observed Hct)/(expected Hct)], where the expected Hct is equal to 45%.

Reticulocytes normally persist in the circulation for 24 hours before becoming erythrocytes. However, as anemia increases, younger reticulocytes are released from the marrow requiring them to remain in circulation for 2 to 3 days before converting to erythrocytes, thereby giving a falsely high RI value. The reticulocyte production index (RPI) is an adjusted index that takes this into account and is calculated using the following formula:

- RPI = RI x (1/RMT), where RMT is the reticulocyte maturation time constant determined by the observed Hct (see Table 2).
- Low RI/RPI ratio (<1) indicates decreased RBC production, suggesting iron deficiency, B_{12}/folate deficiency, aplastic anemia, or bone marrow dysfunction due to cancer or cancer-related therapy (eg, radiation, myelosuppressive chemotherapy).

- High RI/RPI ratio (>1) indicates normal RBC production, suggesting blood loss or hemolysis in the anemic patient.

Table 2. Correction Factor for RPI Calculation

Hematocrit %	Reticulocyte maturation time (RMT) in days
40–45	1.0
35–39	1.5
25–34	2.0
15–24	2.5
<15	3.0

Additional signs and symptoms of common underlying ailments and/or informative diagnostic tests are as follows:

- Nutritional deficiency—low iron and elevated total iron-binding capacity (TIBC) and/or low vitamin B_{12} or red cell folate levels (commonly tested together with iron studies). Ferritin values are also useful in evaluating iron stores. Fasting values are preferred for serum iron and TIBC studies.
- Hemorrhage—stool guaiac positive, endoscopy findings.
- Hemolysis—direct antiglobulin test positive, disseminated intravascular coagulation panel positive, low haptoglobin levels, elevated indirect bilirubin, elevated lactate dehydrogenase (LDH).
- Renal dysfunction—glomerular filtration rate <60 mL/min/1.73 m^2 for ≥3 consecutive months.
- Inherited anemia—personal and/or family history.
- Sideroblastic anemia—sideroblasts present in bone marrow biopsy.
- Hormone dysfunction—hypogonadism, adrenal dysfunction, hyper/hypothyroidism.
- Chronic inflammation—increased C-reactive protein level and/or erythrocyte sedimentation rate.[312]

Any cause of anemia that is found to be independent of cancer or chemotherapy should be treated as indicated. When no such etiology is identified, the effects of cancer-related inflammation and/or myelosuppressive chemotherapy (if applicable) should be considered the cause of anemia. If this is the case, a risk assessment of the anemic patient is necessary to determine the initial intervention plan. The decision regarding the best treatment option is dependent on many factors. While PRBC transfusion is best for symptomatic patients requiring an immediate boost in Hb levels, consideration of ESA therapy with or without iron supplementation may be warranted for the long-term management of anemia in high-risk patients or in asymptomatic patients with comorbidities.

Red Blood Cell Transfusion

The decision to offer PRBC transfusion should not be made on the basis of whether the Hb level of the patient has reached a certain threshold or "trigger." Instead, the NCCN Panel outlines three general categories: 1) asymptomatic without significant comorbidities, for which observation and periodic re-evaluation are appropriate; 2) high risk (ie, progressive decline in Hb with recent intensive chemotherapy or radiation) or asymptomatic with comorbidities (eg, cardiac disease, chronic pulmonary disease, cerebral vascular disease), for which transfusion can be considered; and 3) symptomatic (physiologic), for which patients should receive transfusion. Physiologic symptoms warranting the use of PRBC transfusion include sustained tachycardia, tachypnea, chest pain, dyspnea on exertion, lightheadedness, syncope, or severe fatigue preventing work and usual activities.

The clinical manifestations of anemia are associated with the onset, severity, and duration of the anemia, as well as other factors influencing

tissue demands for oxygen. When anemia onset is acute, symptoms are likely to be more pronounced, whereas physiologic adjustments that compensate for the lower oxygen-carrying capacity of the blood can occur with the gradual onset of anemia. These adaptive measures include heightened cardiac output, increased coronary flow, altered blood viscosity, and changes in oxygen consumption and extraction. The presence of preexisting cardiovascular, pulmonary, or cerebral vascular disease may compromise the ability of a patient to tolerate anemia. Hence, decisions related to whether immediate correction of anemia is needed must be based on an assessment of individual patient characteristics, severity of anemia, presence and severity of comorbidities, and the clinical judgment of the physician. For example, even when an anemic patient has no physiologic symptoms or significant comorbidities, transfusion may be appropriate if there is an anticipated progressive decline in Hb level following anti-cancer treatment.

PRBCs are the blood product of choice for transfusion to correct anemia. These are concentrated from centrifuged whole blood donations or collected by apheresis. They are anticoagulated and may contain added preservatives. Further enhancements include leukoreduction, γ-irradiation, freezing, and washing. Patients who are immunocompromised may need PRBCs that are cytomegalovirus (CMV) negative. Leukoreduction is often sufficient to reduce the risk of CMV transmission. For example, patients who are candidates for or undergoing autologous or allogeneic HCT require blood products that have undergone leukocyte reduction and γ-irradiation to reduce the risks of transfusion-associated GVHD, viral transmission, and alloimmunization. One unit of PRBCs (~300 cc) can have an Hct ranging from 50% to 80%, and typically contains 42.5 to 80 g of Hb (with 147–278 mg of iron) and 128 to 240 mL of pure RBCs.[313]

Benefits and Risks of Red Blood Cell Transfusion

Benefits of Red Blood Cell Transfusion

The major benefit of transfusion with PRBCs, offered by no other anemia treatment, is a rapid increase in Hb and Hct levels and thus, a rapid improvement in anemia-related symptoms. Hence, PRBC transfusion is the best option for patients who require immediate correction of anemia. Transfusion of 1 unit (~300 cc) of PRBCs has been estimated to result in an average increase in Hb level by 1 g/dL or in Hct level by 3% in a normal-size adult who is not experiencing a simultaneous loss of blood.[313,314] It should be noted that patients receiving concomitant fluid resuscitation may not experience an Hb increase of 1 g/dL per unit of blood transfused.

Risks of Red Blood Cell Transfusion

Risks associated with PRBC transfusion include transfusion-related reactions (eg, hemolytic, non-hemolytic, febrile, lung injury), transfusion-associated circulatory overload (TACO), and bacterial contamination. The introduction of numerous safety interventions to screen the U.S. blood supply for infectious organisms has dramatically decreased the risk of transfusion-transmitted infections.[315,316] Bacterial infection was the most common form, and occurred as frequently as 1 in 3000 random-donor samples before the mandate of bacterial screening in 2004.[316] Since the implementation of screening, fewer than 10 deaths from bacterial sepsis per year have been reported in PRBC transfusion patients. Additionally, pre-storage leukoreduction has been shown to decrease the incidence of febrile non-hemolytic transfusion reactions, the most common adverse event.[317,318]

Red Blood Cell Transfusion Goals and Basic Principles

The overall goal of PRBC transfusion is to treat or prevent deficiencies in the oxygen-carrying capacity of the blood in order to improve oxygen

delivery to bodily tissues. In 2016, the AABB (formerly the American Association of Blood Banks) published clinical practice guidelines based on a systematic review of randomized controlled trials evaluating Hb thresholds for RBC transfusion.[319] AABB recommendations include: 1) using an Hb level of 7 g/dL as a threshold for hospitalized adult patients who are hemodynamically stable; 2) using an Hb level of 8 g/dL as a threshold for patients undergoing orthopedic surgery, cardiac surgery, or those with pre-existing cardiovascular disease; and 3) using RBC units selected at any point within their licensed dating period rather than limiting patients to transfusion of only fresh RBC units. However, there was a lack of evidence to provide specific recommendations for the cancer population. NCCN Panelists agree that no single target Hb level is appropriate for all cases and that the balance between transfusion risks and benefits should be evaluated on an individual basis. Clinicians are urged to exercise their clinical judgment based on patient symptoms, cancer course and treatment, comorbidities, and patient preference.

Prior to transfusion, PRBCs must be crossmatched to confirm compatibility with ABO and other antibodies in the recipient. There is no evidence to support routine premedication with acetaminophen or an antihistamine to prevent allergic and febrile non-hemolytic transfusion reactions.[320,321] However, if repeated transfusions are required, leukocyte-reduced blood and the use of premedication may minimize adverse transfusion reactions. In most instances, PRBCs should be transfused by the unit, and reassessment should be conducted after each transfusion. When considering PRBC transfusion, refer to the 2016 AABB clinical practice guidelines.[322]

Patients with CIA Who Refuse Blood Transfusions

Patients with CIA who refuse blood transfusions are occasionally seen in clinical practice. Religious beliefs or personal preferences may prohibit such patients from using blood products. For such patients, clinicians should consider the risk of anemia when making treatment decisions. Although there are limited available data on the best management of CIA in patients who refuse blood transfusions, several strategies can be employed to reduce anemia in this patient population, including minimizing blood loss,[323-327] use of ESAs,[326,328,329] or use of blood substitute products.[323,326,328-331] Strategies to reduce blood loss include batching routine laboratory testing, using pediatric blood collection tubes, minimizing phlebotomy, and returning discard in a closed system.[323-327] Additionally, consider daily folic acid and vitamin B_{12} supplementation prior to initiation of myelosuppressive chemotherapy. Nutritional sufficiency for iron, folate, and vitamin B_{12} should be evaluated and deficiencies corrected. Iron deficiency should be corrected using intravenous (IV) iron. Baseline coagulation abnormalities should also be fully evaluated and corrected prior to myelosuppressive treatment.

The majority of data regarding the use of ESAs in patients who refuse blood transfusions comes from published case reports and small cohort series involving patients who are Jehovah's Witnesses. These types of reports carry inherent bias and vary significantly in reporting of outcomes, regimens, and dosing.[328] A 2008 analysis of 14 case reports of Jehovah's Witness patients receiving ESA therapy in a variety of clinical situations concluded that while administration of ESAs enhanced Hb levels in each situation, time to the start of treatment, dosage, route of administration, and treatment duration varied widely among included studies.[332] Additionally, there was a lack of data regarding Jehovah's Witness patients with CIA. More recent case reports on Jehovah's Witness patients, including three involving patients with cancer, have reported similar results on the effectiveness of ESAs in increasing Hb levels.[333-339] In one case report, a 57-year-old male Jehovah's Witness diagnosed with CIA secondary to aggressive NHL was administered darbepoetin alfa once per week. This therapy increased his Hb level from 7.5 g/dL to 11.5 g/dL within 1 month and enabled completion of intensive chemotherapy.[333]

Although there is a lack of prospective data, ESAs should be considered given that there is no option for transfusion in such patients.[326,328] However, ESAs are not recommended for patients with cancer who are not receiving chemotherapy or patients receiving non-myelosuppressive chemotherapy. If ESAs are prescribed off-label for these indications, patients should be made aware of the potential increased risks of thrombosis and tumor progression and should know that under these circumstances the ESAs are being used off-label. It should be noted that the effects of ESA therapy on Hb level may not be evident for several days after administration. Therefore, in extreme cases of severe, life-threatening anemia, pure oxygen (400 mm Hg, S_AO_2 = 1.0) by mechanical ventilation can be used to increase blood oxygenation.[340]

Although not FDA-approved, clinicians may obtain access to investigational blood substitute products, also known as Hb-based oxygen carriers (HBOCs), for single-patient compassionate use under the FDA's Expanded Access program.[323,326,328-331,341] HBOCs are cell-free Hb molecules typically derived from animals that offer advantages over transfusions, including transportability, the lack of need for refrigeration or crossmatching, and reduced risks of infectious and allergic complications.[328] Despite these benefits, few products have advanced to phase III trials and no products have produced a significant decrease in the need for transfusions (in patients who accept transfusion support). The use of HBOCs has been associated with serious adverse reactions.[331] A 2008 meta-analysis by Natanson et al concluded that patients treated with an HBOC had a 1.3- and 2.7-fold increased risk of mortality and myocardial infarction, respectively, when compared with patients who had undergone conventional treatment with or without blood products.[342] However, with compassionate use, HBOCs have successfully treated Jehovah's Witnesses with severe anemia in emergent settings.[330,343-347] Therefore, while HBOCs may represent a lifesaving modality in the setting of severe anemia in patients who refuse blood transfusions, further evaluation of these products in clinical trials is needed. Since a case series evaluation has suggested that delay in receipt of HBOCs is independently associated with mortality in patients who refuse blood transfusions, clinicians should consider starting the regulatory process for procurement of HBOCs early on in the course of treatment.[348]

Erythropoietic Therapy

ESAs have been shown to stimulate erythropoiesis in patients with low RBC levels, though not all patients have disease that responds to ESA therapy. In a study of 2192 patients with cancer receiving ESA therapy, an Hb increase of ≥1 g/dL was attained in 65% of patients.[349] Unlike transfusion, which immediately boosts the Hb level, ESAs can take weeks to elicit an Hb response, but they are effective at maintaining a target Hb level with repeated administration. Iron studies (serum iron, TIBC, and serum ferritin) should accompany ESA therapy to monitor the development of iron deficiency (See *Iron Monitoring and Supplementation* below for more information).

Benefits of ESA Therapy

A gradual improvement in anemia-related symptoms and avoidance of transfusion are the main goals of ESA therapy. In a randomized, placebo-controlled study, epoetin alfa was shown to increase Hb levels (2.2 g/dL vs. 0.5 g/dL, $P < .001$) and reduce transfusion requirements (24.7% vs. 39.5%, $P = .0057$) in patients with anemia receiving chemotherapy.[350] In a randomized phase III study, lung cancer patients with Hb ≤11 g/dL receiving chemotherapy and darbepoetin alfa required fewer transfusions (27% vs. 52%; 95% CI, 14%–36%; $P < .001$) than patients receiving chemotherapy and placebo.[351] The ability of ESAs to reduce transfusions was one endpoint used in a Cochrane review that enrolled a total of 20,102 patients undergoing treatment for cancer with concomitant ESA therapy.[352] A decreased RR for transfusion was observed in patients

receiving ESAs (RR, 0.65; 95% CI, 0.62–0.68).[352] Of the patients treated with ESAs, 25 out of 100 subsequently received a transfusion versus 39 out of 100 patients in the untreated group, equating to a one-unit reduction in transfusion in ESA-treated patients. The first patient-level meta-analysis evaluating the efficacy of darbepoetin alfa treatment when initiated at Hb ≤10 g/dL in patients with CIA found that more patients who received darbepoetin alfa than placebo achieved an Hb increase of ≥1 g/dL (fixed-effects HR = 2.07; 95% CI, 1.62–2.63) or ≥2 g/dL (HR = 2.91; 95% CI, 2.09–4.06).[353] Transfusions were also less common in these patients (HR = 0.58; 95% CI, 0.44–0.77).

Risks of ESA Therapy

ESAs have associated toxicities, including increased thrombotic events, possible decreased survival, and shortened time to tumor progression. When considering ESAs, discuss the risks of ESA therapy with patients including the potential for tumor growth, death, blood clots, and hypertension.

Possible Increased Mortality and Tumor Progression

Since their approval in 2007, the FDA has made substantial revisions to the label information and regulations regarding epoetin alfa and darbepoetin alfa,[20,21] including the addition of black-box warnings. These strengthened FDA restrictions were based on the results of 8 randomized studies that individually showed a decrease in OS and/or locoregional disease control with ESA usage in breast, cervical, head and neck, lymphoid, non-myeloid, and non-small cell lung cancers (NSCLCs).[354-361] Of the 8 studies, 4 investigated ESAs in patients who underwent chemotherapy, 2 studies involved patients receiving RT alone, and 2 studies involved patients receiving neither chemotherapy nor RT. All 8 trials had an off-label target Hb level >12 g/dL. Additional meta-analyses of randomized controlled trials have confirmed worsened health outcomes associated with the use of ESAs when targeting Hb levels >12 g/dL.[352,362-365] Data from the Cochrane Database also reported increased mortality associated with ESA use in patients when targeting Hb levels >12 g/dL.[352] It should be noted that the risks of shortened survival and tumor progression have not been excluded when ESAs have been dosed to a target Hb of <12 g/dL. Data from a systematic review by the Agency for Healthcare Research and Quality (AHRQ) showed that delaying ESA treatment until Hb is <10 g/dL resulted in fewer thromboembolic events and a reduced mortality.[365]

The association between increased mortality and ESA therapy has been debated in other meta-analyses, including two studies reporting no statistically significant effect of ESAs on mortality or disease progression.[366,367] Pharmacovigilance trials have also reported no adverse effects on survival in patients with CIA receiving ESAs.[368,369] Several prospective trials have reported similar outcomes. The phase III WSG-ARA trial that included 1234 patients with early-stage breast cancer receiving adjuvant ESA therapy evaluated survival as the primary endpoint.[370] In this study, no impact on event-free survival (EFS) (darbepoetin alfa, 89.3% vs. no darbepoetin alfa, 87.5%; $P_{\text{log-rank}} = 0.55$) or overall survival (OS) (darbepoetin alfa, 95.5% vs. no darbepoetin alfa, 95.4%; $P_{\text{log-rank}} = 0.77$) was observed with the use of ESAs. In the AGO-ETC trial, which included 1284 high-risk breast cancer patients, epoetin alfa resulted in improved Hb levels and decreased transfusions without an impact on relapse-free survival or OS.[371] Additionally, data from randomized studies showed no increase in mortality in patients receiving chemotherapy for small cell lung cancer when ESAs were given according to the prescribing label.[372-374] While these data suggest that use of ESAs may not be associated with decreased survival or increased disease progression as previously thought, additional prospective trials designed and powered to measure survival of patients with cancer are needed to provide clinicians with data to guide optimal use of ESAs.

Thromboembolism

Increased thromboembolic events, including venous thromboembolism (VTE), have been associated with ESA therapy in patients with cancer.[352,362,364-367] The cause of VTE in cancer patients is complex with a heightened baseline risk related to both the malignancy itself and to the chemotherapy regimen used (see NCCN Guidelines for Cancer-Associated Venous Thromboembolic Disease).[375-378] Risk factors for VTE in patients with cancer include prior history of VTE, inherited or acquired mutations, hypercoagulability, elevated pre-chemotherapy platelet counts, recent surgery, hormonal agents, prolonged immobility, steroid use, and comorbidities such as hypertension.[379] Patients with risk factors may be at a higher risk for thrombosis with the use of ESAs. Therefore, risk factors should be evaluated in each patient before administration of ESA therapy. The NCCN Panel cautions physicians to be alert to the signs and symptoms of thromboembolism in patients with cancer receiving ESAs.

In an analysis of phase III trials comparing ESAs with placebo for the treatment of CIA, the absolute risk of VTE was 7.5% in patients treated with ESAs compared with 4.9% in control patients.[362] Additionally, an increased risk of stroke was associated with darbepoetin alfa in a clinical trial of patients with CKD (RR, 1.92; 95% CI, 1.38–2.68; absolute risk; 5% vs. 2.6% in the placebo group).[380] ESA use was also associated with a significantly increased risk of stroke (OR, 1.83; 95% CI, 1.26–2.65) in a retrospective case-controlled study of CKD patients with cancer.[381] It is important to note that the thrombotic potential of ESAs is independent of Hb levels.[382]

Hypertension

An increased risk for hypertension with ESA usage in patients with cancer was reported by a Cochrane review (RR, 1.30; 95% CI, 1.08–1.56).[352] Blood pressure should be controlled in all patients prior to initiating ESA therapy and must be monitored regularly throughout treatment. Hb levels should be monitored before and during the use of ESAs to decrease the risk of hypertension.

Pure Red Cell Aplasia

Pure red cell aplasia (PRCA) is a rare syndrome of anemia characterized by a low reticulocyte count and loss of bone marrow erythroblasts caused by the development of neutralizing antibodies against erythropoietin. A marked rise in incidence (197 cases) of PRCA was observed between 1998 and 2004, though over 90% of cases occurred with an epoetin alfa product used outside of the United States.[383,384] Causation was attributed to formulations without human serum albumin, subcutaneous administration, and use of uncoated rubber stoppers.[385] Interventions, designed accordingly to address these issues, reduced the incidence of PRCA by 83%. In 2005, the FDA's interpretation of anemia associated with neutralizing antibodies evolved to include both PRCA and severe anemia, resulting in a class label change for all ESAs.[20,21] Since 2005, FDA safety databases have included information on 30 new cases of antibody-associated PRCA, primarily associated with subcutaneous administration of epoetin alfa and darbepoetin alfa in patients with chronic renal failure.[385] Therefore, patients who develop a loss of response to ESAs should be evaluated for possible PRCA, and if present, all ESA drugs should be discontinued.[383]

Considerations for the Use of ESAs

In 2017, the FDA determined that the ESA Risk Evaluation and Mitigation Strategy (REMS) program is no longer necessary to ensure that the benefits of ESA therapy outweigh its risks.[386] The FDA made this determination based on an evaluation of the results of the REMS Assessments and additional FDA analyses. For patients with cancer, the black box warning on the revised FDA label states that ESAs should only be used to treat CIA and should be discontinued once the chemotherapy

course is complete.[20] As discussed previously, randomized trial data suggest that ESAs may promote tumor growth in an off-target manner. For this reason, the FDA states that these agents should not be used when the treatment intent is curative. This includes primary and adjuvant chemotherapy for malignancies such as early-stage breast cancer, NSCLC, lymphomas, and testicular cancer, among others. An exception to this may be small cell lung cancer, for which there are trials demonstrating no negative impact on survival or disease progression with ESA use.[372-374] Additionally, ESAs are not recommended for use in patients with cancer who are not receiving therapy or in patients receiving non-myelosuppressive therapy. Patients undergoing palliative treatment may be considered for ESA therapy, PRBC transfusion, or participation in a clinical trial, depending on their preferences and personal values. The NCCN Panel recognizes that it is not always clear whether a chemotherapy regimen is considered curative. Under these circumstances, if no other cause of anemia has been identified, physicians should first consider PRBC transfusion or clinical trial enrollment, if available, for anemia management. Upon the decision to use an ESA, physicians are advised to use the lowest dose necessary to eliminate symptoms and avoid transfusion.

CKD is an independent indication for ESA therapy. Controlled clinical trials have associated increased risks of mortality and adverse cardiovascular outcomes with ESA use in CKD patients when targeted to Hb levels >11 g/dL.[380-382,387-389] Hence, the FDA label mandates individualized dosing to reduce the need for PRBC transfusions. Since almost one-third of patients with end-stage renal disease are also afflicted with cancer, they represent a unique subgroup that requires personalized use of ESAs based on very careful evaluation of risks and benefits (reviewed by Bennett et al[390]). In a study comparing darbepoetin alfa to placebo, a significant increase in cancer-related death was seen in CKD patients with pre-existing cancer at baseline treated with ESA therapy (P = .002).[380] Additionally, data from Seliger et al indicated that ESA treatment in patients with CKD was not associated with an overall increased risk for stroke, except in the subpopulation diagnosed with cancer.[381] CKD patients not receiving active therapy for a malignancy should try to avoid ESAs, while those receiving palliative chemotherapy may favor carefully dosed ESAs over transfusion to treat severe anemia. In the scenario where the patient with CKD has a curable solid tumor, ESAs should not be administered during chemotherapy. However, they may be used with caution after chemotherapy is complete, keeping in mind the possibility of recurring disease.

Dosing Schedules

Epoetin alfa, epoetin alfa-epbx, and darbepoetin alfa are recommended equivalently by the NCCN Panel. Head-to-head comparisons of epoetin alfa versus darbepoetin alfa are inconclusive with regard to the superiority of one agent over the other.[365,391,392] Recommended dosing schedules for patients receiving chemotherapy are summarized in the algorithm (see *Erythropoietic Therapy – Dosing, Titration, and Adverse Effects*). The panel recommends two initial dosing schedules for epoetin alfa and epoetin alfa-epbx: 150 units/kg 3 times weekly[350,393] or 40,000 units once weekly[357,360,361,394] administered by subcutaneous injection. Other dosing ranges and schedules of epoetin alfa may be considered, including an extended dose of 80,000 units administered every 2 weeks[395] and a dose of 120,000 units administered once every 3 weeks.[396]

Although darbepoetin alfa doses were initially administered at 2.25 mcg/kg every week,[351,355,397] there has been interest in implementing either fixed doses or higher doses at decreased frequency. A randomized trial comparing weekly dosing at 2.25 mcg/kg versus fixed dosing at 500 mcg every 3 weeks in 705 anemic patients with non-myeloid malignancies showed that the percentage of patients achieving the target Hb level (≥11 g/dL) was higher in the weekly arm compared to patients receiving

darbepoetin alfa every 3 weeks (84% vs. 77%).[397] Dosing once every 3 weeks was further refined in 2 studies, which reduced the dose to 300 mcg. Initially, a multicenter study of 1493 patients showed that 79% of patients receiving this dose achieved a target Hb level ≥11 g/dL.[398] A head-to-head comparison with 500 mcg in a phase II randomized study further confirmed the efficacy of 300 mcg. In this study, no difference in the proportion of patients who achieved target Hb levels (≥11 g/dL) was seen between those receiving 300 mcg versus 500 mcg darbepoetin alfa (75% vs. 78%, respectively).[399] Alternative dosing schedules for darbepoetin alfa include a fixed weekly dose of 100 mcg[351] and a fixed dose of 200 mcg every 2 weeks.[400] The NCCN Panel recommends these alternative regimens to support the delivery of the lowest ESA dose possible while maintaining maximal efficacy.

Response Assessment and Dose Titration

Response to ESA therapy should be assessed to determine whether the initial dose should be reduced, escalated, or withheld. Decisions related to ESA dose adjustment are based on the goal of maintaining the lowest Hb level sufficient to avoid transfusion. ESAs require at least 2 weeks of treatment before there is an increase in the number of RBCs. Hb level should be measured weekly until stabilized. Dose reduction (generally 25% for epoetin alfa or epoetin alfa-epbx and 40% for darbepoetin alfa) should be implemented once Hb reaches a level sufficient to avoid transfusion or if the Hb level increases by ≥1 g/dL during a 2-week period.

Conversely, the ESA dose should be increased according to the algorithm for patients receiving chemotherapy who show no response (defined as Hb increase <1 g/dL that remains below 10 g/dL) following 4 weeks of epoetin alfa or epoetin alfa-epbx treatment or following 6 weeks of darbepoetin alfa treatment. A subsequent response at 8 weeks may necessitate a dose escalation to avoid transfusion. Iron supplementation should be considered to improve response to ESA therapy. A recent Cochrane Database review concluded that the addition of iron to ESA therapy offers superior hematopoietic response, reduces the risk of transfusions, improves Hb levels, and appears to be well tolerated.[401] A meta-analysis of randomized controlled trials also showed that the addition of parenteral iron reduces the risk of transfusions by 23% and increases the chance of hematopoietic response by 29% when compared with ESAs alone.[402] ESA therapy should be discontinued and PRBC transfusion should be considered in patients showing no response despite iron supplementation after 8 weeks of therapy. ESAs should also be discontinued when chemotherapy is completed or withdrawn.

Iron Monitoring and Supplementation

Iron Deficiency Evaluation and Definitions of Iron Status

Iron deficiency is reported in 32% to 60% of patients with cancer, most of whom are also anemic.[403] Iron studies, including serum iron, TIBC, and serum ferritin, should be performed prior to ESA treatment in order to rule out absolute iron deficiency, which may respond to oral or IV iron monotherapy. Serum iron and TIBC levels may be falsely elevated by diet (reviewed in Collings et al[404]); therefore, fasting is recommended to provide more accurate measurements. Transferrin saturation (TSAT) should be calculated from these values using the following formula:

- TSAT = (serum iron level x 100)/TIBC

Treatment for iron deficiency is guided by iron status, defined in these guidelines as absolute iron deficiency, functional iron deficiency, possible functional iron deficiency, or no iron deficiency. In the absence of a universal numerical definition of iron deficiency in relevant studies, the NCCN Panel recognizes that ferritin and TSAT values defining absolute and functional iron deficiencies represent moving targets.[297] However, as general guidance, definitions and characteristics of each iron status group are discussed below.

Absolute Iron Deficiency

Absolute iron deficiency refers to the depletion of total body iron stores. It is characterized by low Hb, low serum iron, and high TIBC that result in a TSAT level <20% and a ferritin level <30 ng/mL. If the TSAT and ferritin parameters are discordant, a low ferritin value should take precedence in determining whether iron supplementation will be beneficial. The reference interval for serum ferritin depends on the specific laboratory used, but in general, the lower the level, the more probable that true iron deficiency is present. However, in the cancer setting, clinicians should be aware of a chronic inflammatory state, which may falsely elevate serum ferritin levels.

Although IV iron is preferred, either IV or oral iron products alone (without an ESA) are recommended for patients with cancer who develop absolute iron deficiency. Hb levels should increase after 4 weeks of treatment. Periodic evaluation of ferritin and TSAT levels is required as some patients, especially those with continued internal bleeding, may suffer a relapse. If the patient initially receives oral iron and the anticipated response is not seen after 4 weeks, a trial of IV iron should be considered. If Hb is not improved after 4 weeks following IV iron supplementation, the patient should be evaluated for functional iron deficiency. Although data are conflicting in the literature, concerns exist regarding the possibility of IV iron promoting inflammation and bacterial growth.[405] Hence, IV iron supplementation is not recommended for patients with an active infection.

For further discussion of absolute iron deficiency, see *Clinical Examples of Iron Status, case scenarios 1 and 2* below.

Functional Iron Deficiency

Functional iron deficiency is a condition in which stored iron is sufficient but bioavailable iron necessary for erythroblast production is deficient. This may occur when infection or inflammation blocks iron transport to the bone marrow, as seen in anemia of chronic inflammation. Functional iron deficiency is defined in these guidelines as a ferritin level between 30 and 500 ng/mL and a TSAT level <50%. IV iron supplementation with erythropoietic therapy should be considered for these patients. Although oral iron has been used more commonly, IV iron has superior efficacy and should be considered for supplementation in this setting (see *Intravenous Versus Oral Iron* below). However, there are insufficient data to routinely recommend IV iron as monotherapy without an ESA for the treatment of functional iron deficiency. Functional iron deficiency often arises following continued ESA use, resulting in a blunted erythropoietic response to anemia. Hence, iron supplementation will eventually be required in most patients in order to maintain optimal erythropoiesis.[406,407]

For further discussion of functional iron deficiency, see *Clinical Examples of Iron Status, case scenario 3.*

Possible Functional Iron Deficiency

Possible functional iron deficiency is a condition in which stored iron is sufficient but bioavailable iron necessary for erythroblast production *may* be deficient. These patients are defined by a TSAT level <50% and a ferritin level of 500 to 800 ng/mL. Although clinical trials suggest that these patients may have functional iron deficiency, there are insufficient data to support the routine use of IV iron in this setting. The panel recommends no iron supplementation or the consideration of IV iron supplementation for select patients. Administration of IV iron to these patients should be individualized with the goal of avoiding transfusion. ESA therapy is not recommended in this setting.

For further discussion of possible functional iron deficiency, see *Clinical Examples of Iron Status, case scenarios 4 and 5.*

No Iron Deficiency

Patients with ferritin values >800 ng/mL or a TSAT ≥50% are not iron deficient. These patients do not require iron supplementation or ESA therapy.

Intravenous Versus Oral Iron

Iron can be administered orally or intravenously. Although oral iron is appropriate for most iron-deficient anemic patients, many patients with CIA either do not respond to oral iron, may be intolerant of oral iron, or may require higher iron doses than achievable with oral iron, making IV iron therapy a valuable option.[408] Evidence from several published studies utilizing iron in conjunction with an ESA suggest that IV iron is superior to oral iron in improving Hb response rates in patients with CIA.[409-414] In 2011, a trial published by Steensma et al challenged these positive results.[415] In this study, patients with CIA (n = 502) were randomized to receive IV iron, oral iron, or oral placebo in combination with ESA therapy. Initial analysis of the data led the authors to conclude that IV iron failed to confer any benefit in terms of Hb response, transfusion requirement, or quality of life compared to oral iron or placebo. However, the lack of response to IV iron observed in this study may have been attributable to problems with the study design, including a suboptimal IV iron dosing regimen and a high proportion of participant dropouts.[416] Indeed, reanalysis of study data indicated that trial participants who received at least 80% of the planned IV iron dosage had Hb response rates similar to participants in other IV iron trials.[417] It should be noted that patients with a baseline TSAT level <20% have a higher response rate to IV iron supplementation when given in addition to an ESA. As the TSAT level increases from 20% to 50%, the response rate to IV iron is diminished and the time to response is prolonged. Hence, for patients with TSAT levels between 20% and 50%, the decision to offer IV iron should be reserved for those in whom the benefits are likely to outweigh the risks. Future studies on the parameters that make patients more or less likely to benefit from IV iron, as well as studies of alternative dose schedules of IV iron, are needed.

None of the studies on iron supplementation in conjunction with ESAs provided instruction on how or when to re-dose iron after the initial cumulative dose has been given. Generally, repeat iron studies are not recommended within 3 to 4 weeks of administration. Clinicians may consider repeating iron studies when the MCV declines or hypochromic RBCs are seen on the peripheral blood smear. Additionally, repeat iron studies can be considered for patients with anemia that fails to respond to iron supplementation 4 to 6 weeks after administration of the total intended dose.[411,415] If evidence exists of iron overload, do not administer IV iron. Subsequent doses of iron should be withheld if the serum ferritin exceeds 800 ng/mL or if the TSAT exceeds 50%.[410-412]

Since the majority of studies show that IV iron is superior to oral iron, the panel recommends that IV iron supplementation be used in most clinical circumstances. Low-molecular-weight iron dextran, ferric gluconate, iron sucrose, ferric carboxymaltose, and ferumoxytol are the recommended IV iron preparations. Common adverse events following FDA-approved doses of IV iron include hypotension, hypertension, nausea, vomiting, diarrhea, pain, fever, dyspnea, pruritus, headaches, and dizziness.[418-420] Dosage details for administering IV iron therapy are listed in the algorithm (see *Recommendations for Administering Parenteral Iron Products* in the algorithm).

Low-Molecular-Weight Iron Dextran

A prospective, multicenter trial randomized 157 patients with CIA on epoetin alfa to receive: 1) no iron; 2) oral iron; 3) iron dextran IV bolus; or 4) iron dextran total dose infusion (TDI).[409] Increases in Hb concentration were greater with IV iron dextran (groups 3 and 4) compared to oral iron or no iron ($P < .02$). Importantly, there was no difference between the oral and no iron groups ($P = .21$). Additionally, there was no statistically

significant difference between groups 3 and 4 (*P* = .53), suggesting that lower, intermittent doses of IV iron dextran are equally as efficacious as TDI. Most adverse events associated with iron dextran, such as headaches, dizziness, nausea, vomiting, and diarrhea, occurred with high-molecular-weight iron dextran.[421] Therefore, the recommended iron dextran product is low-molecular-weight iron dextran.[422] Test doses are required for iron dextran (25 mg slow IV push over 1–2 minutes; if tolerated, follow with 75 mg IV bolus for a total dose of 100 mg).[409] As reactions to the IV iron dextran test dose may be severe, pre-medication of the patient should occur prior to administration of the test dose. Anaphylaxis-like reactions occur within minutes of the test dose but respond readily to IV epinephrine, diphenhydramine, and corticosteroids. It should be noted that patients may develop a reaction to IV iron dextran with later doses, and clinicians should be prepared to administer appropriate treatment. Delayed reactions to iron dextran may result in adverse events up to 24 to 48 hours following injection.[423]

Ferric Gluconate

In a multicenter trial, 187 patients with CIA on chemotherapy and epoetin alfa were randomized to receive no iron, oral ferrous sulfate 3 times daily, or weekly IV ferric gluconate.[412] The Hb response rate (≥2 g/dL increase) was higher in the IV ferric gluconate arm (73%; *P* = .0099 vs. oral iron; *P* = .0029 vs. no iron) compared to the oral (45%; *P* = .6687 vs. no iron) or no iron (41%) arms. In another study, 149 patients with solid tumors and CIA were randomly assigned to receive weekly darbepoetin alfa with or without IV ferric gluconate.[413] The IV ferric gluconate group showed a higher hematopoietic response rate compared to the no iron group (93% vs. 70%, respectively; *P* = .0033). In a study evaluating 396 CIA patients with non-myeloid malignancies undergoing chemotherapy, patients were treated with darbepoetin alfa with or without IV ferric gluconate every 3 weeks for 16 weeks.[410] Erythropoietic responses were improved in the IV ferric gluconate arm. Most significantly, this was the first study to associate IV iron with fewer RBC transfusions in patients with cancer (9% vs. 20%, *P* = .005). Prior to administration, test doses are recommended at physician discretion for patients receiving ferric gluconate based on the risk for reaction.

Iron Sucrose

A randomized controlled trial involving 64 patients with gynecologic cancers compared the efficacy of IV iron sucrose to oral ferrous fumarate for the primary prevention of anemia (ie, patients did not present with anemia).[424] In this study, patients were given a single dose of 200 mg iron sucrose following each course of chemotherapy infusion for 6 cycles. The number of patients requiring a blood transfusion was double in the oral iron group compared to the IV iron sucrose group (56.3% vs. 28.1%; *P* = .02). Furthermore, patients receiving IV iron sucrose who did receive transfusion required fewer median number of PRBC units (0 vs. 0.5 units; *P* = .05). Another study randomized 67 patients with lymphoproliferative malignancies not undergoing chemotherapy to receive weekly ESA therapy with or without IV iron sucrose.[411] Although an oral iron arm was not included, IV iron sucrose resulted in a higher mean change in Hb level from baseline (2.76 g/dL vs. 1.56 g/dL, *P* = .0002) and a higher Hb level response rate (≥2 g/dL increase; 87% vs. 53%, *P* = .0014) compared to the no iron group. Prior to administration, test doses are recommended at physician discretion for patients receiving iron sucrose based on the risk for reaction.

Ferric Carboxymaltose

An observational study by Steinmetz et al[425] evaluated the use of ferric carboxymaltose with and without an ESA in patients with cancer. Of the 233 patients treated with ferric carboxymaltose alone, a median Hb increase of 1.4 g/dL (range, 1.3–1.5 g/dL) was observed with an overall increase in median Hb levels to >11 g/dL within 5 weeks of treatment.[425]

Similar results were seen in patients receiving concomitant treatment with ferric carboxymaltose and an ESA (1.6 g/dL increase; range, 0.7–2.4 g/dL; n = 46). Another observational study of 367 patients with solid tumors or hematologic malignancies also demonstrated improved median Hb levels following administration of ferric carboxymaltose alone or in combination with an ESA (1.3 g/dL vs. 1.4 g/dL, respectively) when measured over a 3-month period.[426] A retrospective analysis of 303 anemic patients with gastrointestinal cancers found that IV administration of ferric carboxymaltose resulted in a significant increase in Hb levels, with a median change between baseline and follow-up Hb of 0.5 (interquartile range [IQR]: -0.1–1.6) g/dL.[427] In the randomized clinical IVICA trial, which included 116 anemic colorectal cancer patients, preoperative administration of ferric carboxymaltose resulted in higher Hb levels after surgery compared to oral ferrous sulfate (11.9 g/dL vs. 11.0 g/dL; $P = .002$).[428] A follow-up study indicated that patients who had received ferric carboxymaltose had significantly improved quality-of-life scores, as measured by the Functional Assessment of Cancer Therapy-Anemia (FACT-An) subscale, compared to patients who had received oral iron.[429] Preoperative treatment with ferric carboxymaltose in patients with colon cancer and anemia was also shown to significantly reduce RBC transfusion requirements (9.9% vs. 38.7%; $P < .001$) and length of hospital stay (8.4 ± 6.8 days vs. 10.9 ± 12.4 days to discharge; $P < .001$) compared to patients not receiving IV iron.[430]

Ferric carboxymaltose has been associated with severe phosphate deficiency that is often asymptomatic.[431-435] Lack of awareness of this complication causes delayed time to diagnosis and results in significant morbidity.[431] Therefore, patients receiving ferric carboxymaltose should be closely monitored for hypophosphatemia. Prior to administration, test doses are recommended at physician discretion for patients receiving ferric carboxymaltose based on the risk for reaction.

Ferumoxytol

Ferumoxytol is a colloidal iron oxide that is indicated for the treatment of iron-deficiency anemia in patients with CKD or an intolerance or poor response to oral iron.[255,436-438] However, ferumoxytol has not been prospectively evaluated in patients with CIA.[439] In a phase III trial involving patients with anemia due to various causes, 81.1% of patients treated with ferumoxytol achieved an Hb increase ≥2.0 g/dL at week 5 compared to only 5.5% of patients given placebo ($P < .0001$).[438] However, only a small percentage of patients in this study had cancer (n = 39).[438] Although a positive trend in favor of ferumoxytol was demonstrated in the cancer subgroup compared with placebo (ferumoxytol, 51.7% vs. placebo, 30.0%; $P < .2478$), the difference was not statistically significant.[438] In a randomized phase III study of patients with iron-deficiency anemia that had not responded to oral iron, ferumoxytol was noninferior to iron sucrose as measured by the proportion of patients who had ≥2 g/dL increase in Hb from baseline to week 5 (84% with ferumoxytol vs. 81.4% with iron sucrose).[437] However, noninferiority was not reached in the cancer subgroup (n = 31), potentially due to the small sample size. A recent post-hoc analysis of pooled data from these two trials found that both ferumoxytol and iron sucrose produced significant increases in Hb from baseline compared to placebo (1.8 g/dL, $P < .0001$ and 1.9 g/dL, $P = .002$, respectively) in a subgroup of 98 patients with cancer.[439]

It should be noted that ferumoxytol may cause interference with MRI scans causing potential false interpretation of organ iron overload.[440] This is especially pertinent for populations at risk for serious organ-threatening iron deposition and should be a consideration when selecting the agent for iron supplementation. Prior to administration, test doses are recommended at physician discretion for patients receiving ferumoxytol based on the risk for reaction.

Clinical Examples of Iron Status

The following clinical scenarios illustrate how iron studies may guide iron supplementation and ESA treatment of patients with CIA.

Patient Case

A 59-year-old female with no significant medical history presented to her primary care provider after acute onset of bloody stools in addition to a 2-month history of early satiety and 9 kg weight loss. Abdominal imaging revealed a colonic mass and mesenteric lesions. She was referred to an oncologist. Biopsy of the mass demonstrated a poorly differentiated adenocarcinoma. Her oncologist has begun palliative treatment with FOLFOX plus bevacizumab, a myelosuppressive regimen. After 2 cycles of chemotherapy, her CBC results are as follows: Hb 8.8 g/dL, Hct 26.7%, MCV 73 fL, reticulocytes 0.8%, mean corpuscular Hb 25 pg, red cell distribution width 18.2%, and platelets 398000/µL. She does not have CKD. Serum folate, vitamin B_{12} levels, indirect bilirubin, and serum LDH are within normal limits. Bleeding has ceased, but given her baseline anemia and red cell indices, iron studies have been ordered. Five different scenarios are provided below to illustrate the potential management of this patient depending on various ferritin and TSAT combinations.

Scenario 1: Serum Ferritin 5 ng/mL & TSAT 4%

With a ferritin level <30 ng/mL and a TSAT level <20%, this patient has absolute iron deficiency and would benefit from iron repletion. Reducing transfusion requirements remains the goal of therapy. With a baseline Hb of 8.8 g/dL, imminent chemotherapy initiation, and very low iron stores, IV iron repletion is preferred. Oral iron may not supply bioavailable iron rapidly enough in certain patients.[409]

Scenario 2: Serum Ferritin 10 ng/mL & TSAT 22%

With low ferritin and normal TSAT levels, we can postulate that iron stores are becoming depleted. Iron is being mobilized, but signs of iron-restricted erythropoiesis are beginning to emerge. If the ferritin and TSAT levels are discordant, the low ferritin level should take precedence to determine if IV iron therapy would be beneficial. Iron would be beneficial in this patient as these laboratory values reflect a transition from an iron-replete to an iron-deficient state. For the same reasons as discussed in scenario 1, IV iron is preferred over oral iron. It is also possible for TIBC to be low secondary to malnutrition, resulting in a normal TSAT level despite definitive absolute iron deficiency. ESA use should be considered only after iron repletion.

Scenario 3: Serum Ferritin 580 ng/mL & TSAT 12%

With normal or elevated ferritin and low TSAT levels, we can assume that iron is either not bioavailable or that the ferritin level reflects an acute-phase response, potentially secondary to cancer-related inflammation (functional iron deficiency). Functional iron deficiency may cause iron-restricted erythropoiesis, and there is no ferritin threshold at which we can assume iron supply is adequate for erythropoiesis if the TSAT level is low. Thus, patients with ferritin levels >100 ng/mL could be treated with IV iron. However, an ESA should be considered first because as the ferritin level moves across the spectrum from absolute iron deficiency to iron overload, the response to either an ESA or IV iron will diminish. Concomitant IV iron can be considered as it may increase the percentage of patients who respond to the ESA as well as reduce the time to response.

Scenario 4: Serum Ferritin 100 ng/mL & TSAT 30%

As the TSAT level increases from 20% to 50%, the percentage of patients with anemia that responds to iron decreases; therefore, this patient may not necessarily require IV iron until the TSAT level trends downward as a result of ESA use. If the anticipated response to ESA therapy is not

realized by 4 to 6 weeks, consider repeating iron studies. If TSAT and/or ferritin levels decrease, consider giving IV iron. If iron studies remain unchanged, continue the ESA for a total of 8 weeks. Discontinue thereafter if lack of response persists and consider RBC transfusion.

Scenario 5: Serum Ferritin 500 ng/mL & TSAT 40%

These ferritin and TSAT parameters suggest that functional iron deficiency is unlikely. Therefore, this patient is unlikely to benefit from iron therapy since she is iron replete. In this scenario, an ESA may be considered. ESA use induces functional iron deficiency by increasing iron utilization without the compensatory ability to mobilize stored iron in a timely manner. Therefore, iron repletion can be initiated if a response to ESA therapy is not seen and the patient remains transfusion-dependent. Of note, improved response is generally expected as the TSAT level decreases from 50% to 20%. Ultimately, clinical judgment must be used to determine whether the potential benefits of iron administration are likely to outweigh the risks.

Summary

ESAs can improve symptoms of CIA and are utilized in scenarios to avoid RBC transfusion. There have been cases of possible tumor progression, so they are only used during cancer chemotherapy. There is potential utility in using ESAs in cancer patients who do not consent to transfusion support. Iron supplementation may be needed to optimize the response to ESAs.

References

1. Tabbara IA, Robinson BE. Hematopoietic growth factors. Anticancer Res 1991;11:81-90. Available at: https://www.ncbi.nlm.nih.gov/pubmed/1708221.

2. Freifeld AG, Bow EJ, Sepkowitz KA, et al. Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 update by the Infectious Diseases Society of America. Clin Infect Dis 2011;52:427-431. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21205990.

3. Lyman GH, Kuderer NM. Epidemiology of febrile neutropenia. Support Cancer Ther 2003;1:23-35. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18628128.

4. Lalami Y, Klastersky J. Impact of chemotherapy-induced neutropenia (CIN) and febrile neutropenia (FN) on cancer treatment outcomes: an overview about well-established and recently emerging clinical data. Crit Rev Oncol Hematol 2017;120:163-179. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29198330.

5. Fortner BV, Schwartzberg L, Tauer K, et al. Impact of chemotherapy-induced neutropenia on quality of life: a prospective pilot investigation. Support Care Cancer 2005;13:522-528. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15678345.

6. U.S. Food and Drug Administration. Filgrastim label information. 2015. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/103353s5183lbl.pdf. Accessed December 16, 2019.

7. U.S. Food and Drug Administration. Filgrastim-sndz label information. 2015. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/125553lbl.pdf. Accessed December 16, 2019.

8. U.S. Food and Drug Administration. Tbo-filgrastim label information. 2012. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/125294s000lbl.pdf. Accessed December 16, 2019.

9. U.S. Food and Drug Administration. Filgrastim-aafi label information. 2018. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/761080s000lbl.pdf. Accessed December 16, 2019.

10. U.S. Food and Drug Administration. Pegfilgrastim label information. 2015. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/125031s180lbl.pdf. Accessed December 16, 2019.

11. U.S. Food and Drug Administration. Pegfilgrastim-jmdb label information. 2018. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/761075s000lbl.pdf. Accessed December 16, 2019.

12. U.S. Food and Drug Administration. Pegfilgrastim-cbqv label information. 2018. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/761039s000lbl.pdf. Accessed December 16, 2019.

13. U.S. Food and Drug Administration. Pegfilgrastim-bmez label information. 2019. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/761045lbl.pdf. Accessed December 16, 2019.

14. U.S. Food and Drug Administration. FDA Medical Imaging Drugs Advisory Committee and the Oncologic Drugs Advisory Committee Advisory Committee Briefing Materials: Available for public release. Tbo-filgrastim. 2013. Available at: https://wayback.archive-it.org/7993/20170405222000/https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/MedicalImagingDrugsAdvisoryCommittee/UCM350157.pdf. Accessed December 16, 2019.

15. Dorr RT. Clinical properties of yeast-derived versus Escherichia coli-derived granulocyte-macrophage colony-stimulating factor. Clin Ther

1993;15:19-29. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8458048.

16. Farese AM, MacVittie TJ. Filgrastim for the treatment of hematopoietic acute radiation syndrome. Drugs Today (Barc) 2015;51:537-548. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26488033.

17. DiCarlo AL, Horta ZP, Aldrich JT, et al. Use of growth factors and other cytokines for treatment of injuries during a radiation public health emergency. Radiat Res 2019;192:99-120. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31081742.

18. Knight K, Wade S, Balducci L. Prevalence and outcomes of anemia in cancer: a systematic review of the literature. Am J Med 2004;116 Suppl 7A:11S-26S. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15050883.

19. Xu H, Xu L, Page JH, et al. Incidence of anemia in patients diagnosed with solid tumors receiving chemotherapy, 2010-2013. Clin Epidemiol 2016;8:61-71. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27186078.

20. U.S. Food and Drug Administration. Epoetin alfa label information. 2011. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/103234Orig1s5166_103234Orig1s5266lbl.pdf. Accessed December 16, 2019.

21. U.S. Food and Drug Administration. Darbepoetin alfa label information. 2011. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/103951Orig1s5173_103951Orig1s5258lbl.pdf. Accessed December 16, 2019.

22. U.S. Food and Drug Administration. FDA approves first epoetin alfa biosimilar for the treatment of anemia. 2018. Available at: https://www.fda.gov/newsevents/newsroom/pressannouncements/ucm607703.htm. Accessed December 16, 2019.

23. U.S. Food and Drug Administration. Epoetin alfa-epbx label information. 2018. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/125545s000lbl.pdf. Accessed December 16, 2019.

24. U.S. National Library of Medicine Key MEDLINE® Indicators Available at: http://www.nlm.nih.gov/bsd/bsd_key.html.

25. U.S. Food and Drug Administration. Implementation of the Biologics Price Competition and Innovation Act of 2009. 2010. Available at: https://www.fda.gov/drugs/guidancecomplianceregulatoryinformation/ucm215089.htm. Accessed December 16, 2019.

26. Lyman GH, Zon R, Harvey RD, Schilsky RL. Rationale, opportunities, and reality of biosimilar medications. N Engl J Med 2018;378:2036-2044. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29791832.

27. Awad M, Singh P, Hilas O. Zarxio (Filgrastim-sndz): the first biosimilar approved by the FDA. P T 2017;42:19-23. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28090158.

28. U.S. Food and Drug Administration. Biosimilar and Interchangeable Products. 2017. Available at: https://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/ucm580419.htm. Accessed December 16, 2019.

29. Kleinberg M, Mosdell KW. Current and future considerations for the new classes of biologicals. Am J Health Syst Pharm 2004;61:695-708. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15119576.

30. Blackwell K, Gascon P, Krendyukov A, et al. Safety and efficacy of alternating treatment with EP2006, a filgrastim biosimilar, and reference filgrastim: a phase 3, randomised, double-blind clinical study in the prevention of severe neutropenia in patients with breast cancer receiving myelosuppressive chemotherapy. Ann Oncol 2018;29:244-249. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29091995.

31. del Giglio A, Eniu A, Ganea-Motan D, et al. XM02 is superior to placebo and equivalent to Neupogen in reducing the duration of severe neutropenia and the incidence of febrile neutropenia in cycle 1 in breast

cancer patients receiving docetaxel/doxorubicin chemotherapy. BMC Cancer 2008;8:332. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19014494.

32. Engert A, Griskevicius L, Zyuzgin Y, et al. XM02, the first granulocyte colony-stimulating factor biosimilar, is safe and effective in reducing the duration of severe neutropenia and incidence of febrile neutropenia in patients with non-Hodgkin lymphoma receiving chemotherapy. Leuk Lymphoma 2009;50:374-379. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19347726.

33. Gatzemeier U, Ciuleanu T, Dediu M, et al. XM02, the first biosimilar G-CSF, is safe and effective in reducing the duration of severe neutropenia and incidence of febrile neutropenia in patients with small cell or non-small cell lung cancer receiving platinum-based chemotherapy. J Thorac Oncol 2009;4:736-740. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19404210.

34. Engert A, del Giglio A, Bias P, et al. Incidence of febrile neutropenia and myelotoxicity of chemotherapy: a meta-analysis of biosimilar G-CSF studies in breast cancer, lung cancer, and non-Hodgkin's lymphoma. Onkologie 2009;32:599-604. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19816079.

35. Lubenau H, Bias P, Maly AK, et al. Pharmacokinetic and pharmacodynamic profile of new biosimilar filgrastim XM02 equivalent to marketed filgrastim Neupogen: single-blind, randomized, crossover trial. BioDrugs 2009;23:43-51. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19344191.

36. Lubenau H, Sveikata A, Gumbrevicius G, et al. Bioequivalence of two recombinant granulocyte colony-stimulating factor products after subcutaneous injection in healthy volunteers. Int J Clin Pharmacol Ther 2009;47:275-282. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19356394.

37. Zou L, Buchner A, Field JA, et al. Immunogenicity assessment of tbo-filgrastim in cancer patients receiving chemotherapy. Bioanalysis 2018;10:1221-1228. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30058363.

38. Sorgel F, Lerch H, Lauber T. Physicochemical and biologic comparability of a biosimilar granulocyte colony-stimulating factor with its reference product. BioDrugs 2010;24:347-357. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20873878.

39. U.S. Food and Drug Administration. EP2006, a proposed biosimilar to Neupogen (R) (filgrastim). BLA 125553. 2015. Available at: https://wayback.archive-it.org/7993/20170405222922/https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/OncologicDrugsAdvisoryCommittee/UCM428780.pdf. Accessed December 16, 2019.

40. Mellstedt H. Anti-neoplastic biosimilars-the same rules as for cytotoxic generics cannot be applied. Ann Oncol 2013;24 Suppl 5:v23-28. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23975701.

41. Harbeck N, Gascon P, Krendyukov A, et al. Safety profile of biosimilar filgrastim (Zarzio/Zarxio): a combined analysis of phase III studies. Oncologist 2018;23:403-409. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29317553.

42. Zecchini J, Yum K, Steinberg A, et al. A single-center, retrospective analysis to compare the efficacy and safety of filgrastim-sndz to filgrastim for prophylaxis of chemotherapy-induced neutropenia and for neutrophil recovery following autologous stem cell transplantation. Support Care Cancer 2017;26:1013-1016. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28990128.

43. Schwartzberg LS, Lal LS, Balu S, et al. Incidence of febrile neutropenia during chemotherapy among patients with nonmyeloid cancer receiving filgrastim vs a filgrastim biosimilar. Clinicoecon Outcomes Res 2018;10:493-500. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30214262.

44. Schwartzberg LS, Lal LS, Balu S, et al. Clinical outcomes of treatment with filgrastim versus a filgrastim biosimilar and febrile neutropenia-

associated costs among patients with nonmyeloid cancer undergoing chemotherapy. J Manag Care Spec Pharm 2018;24:976-984. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29687743.

45. Chen X, Agiro A, Barron J, et al. Early adoption of biosimilar growth factors in supportive cancer care. JAMA Oncol 2018;4:1779-1781. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30383135.

46. The Center for Biosimilars. FDA approves second neupogen biosimilar, Nivestym. 2018. Available at: https://www.centerforbiosimilars.com/news/fda-approves-second-neupogen-biosimilar-nivestym. Accessed December 16, 2019.

47. Waller CF, Semiglazov VF, Tjulandin S, et al. A phase III randomized equivalence study of biosimilar filgrastim versus Amgen filgrastim in patients receiving myelosuppressive chemotherapy for breast cancer. Onkologie 2010;33:504-511. Available at: https://www.ncbi.nlm.nih.gov/pubmed/20926897.

48. Fruehauf S, Otremba B, Stotzer O, Rudolph C. Compatibility of biosimilar filgrastim with cytotoxic chemotherapy during the treatment of malignant diseases (VENICE): a prospective, multicenter, non-interventional, longitudinal study. Adv Ther 2016;33:1983-2000. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27743353.

49. Brito M, Esteves S, Andre R, et al. Comparison of effectiveness of biosimilar filgrastim (Nivestim), reference Amgen filgrastim and pegfilgrastim in febrile neutropenia primary prevention in breast cancer patients treated with neo(adjuvant) TAC: a non-interventional cohort study. Support Care Cancer 2016;24:597-603. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26111956.

50. Frederic M, Stephane L, Didier K, et al. Biosimilar filgrastim in the treatment and the prevention of chemotherapy-induced neutropenia: The next study [abstract]. J Geriatr Oncol 2014;5:S71. Available at: https://doi.org/10.1016/j.jgo.2014.09.129.

51. Waller CF, Tiessen RG, Lawrence TE, et al. A pharmacokinetics and pharmacodynamics equivalence trial of the proposed pegfilgrastim biosimilar, MYL-1401H, versus reference pegfilgrastim. J Cancer Res Clin Oncol 2018;144:1087-1095. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29671069.

52. Glaspy JA, O'Connor PG, Tang H, Finck B. Randomized, single-blind, crossover study to assess the pharmacokinetic and pharmacodynamic bioequivalence of CHS-1701 to pegfilgrastim in healthy subjects. J Clin Oncol 2017;35:e21693. Available at: http://ascopubs.org/doi/abs/10.1200/JCO.2017.35.15_suppl.e21693.

53. O'Conner P, Tang H, Civoli F, et al. Proposed pegfilgrastim biosimilar CHS-1701 demonstrates pharmacokinetic and pharmacodynamic similarity to marketed pegfilgrastim in a rat neutropenia model and in healthy subjects [abstract]. Proceedings of the 22nd Congress of the European Hematology Association 2017. Available at: https://learningcenter.ehaweb.org/eha/2017/22nd/180923/paula.oconnor.proposed.pegiflgrastim.biosimilar.chs-1701.demonstrates.html.

54. U.S. Food and Drug Administration. FDA approves first biosimilar to Neulasta to help reduce the risk of infection during cancer treatment. 2018. Available at: https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm609805.htm. Accessed December 16, 2019.

55. The Center for Biosimilars. FDA approves Coherus' pegfilgrastim biosimilar, Udenyca. 2018. Available at: https://www.centerforbiosimilars.com/news/fda-approves-coherus-pegfilgrastim-biosimilar-udenyca. Accessed December 16, 2019.

56. Hoy SM. Pegfilgrastim-jmdb/MYL-1401H: a pegfilgrastim biosimilar. BioDrugs 2019;33:117-120. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30701419.

57. Sankaran PK, Palanivelu DV, Nair R, et al. Characterization and similarity assessment of a pegfilgrastim biosimilar MYL-1401H. J Clin Oncol 2018;36:e19028. Available at: http://ascopubs.org/doi/abs/10.1200/JCO.2018.36.15_suppl.e19028.

58. Waller CF, Ranganna GM, Pennella EJ, et al. Randomized phase 3 efficacy and safety trial of proposed pegfilgrastim biosimilar MYL-1401H in the prophylactic treatment of chemotherapy-induced neutropenia. Ann Hematol 2019;98:1217-1224. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30824956.

59. Waller C, Ranganna GM, Pennella E, et al. Comparison of immunogenicity between the proposed pegfilgrastim biosimilar MYL-1401H and reference pegfilgrastim. Blood 2017;130:3568. Available at: https://ashpublications.org/blood/article/130/Supplement%201/3568/114870.

60. The Center for Biosimilars. FDA approves Sandoz's pegfilgrastim biosimilar, Ziextenzo. 2019. Available at: https://www.centerforbiosimilars.com/news/fda-approves-sandozs-pegfilgrastim-biosimilar-ziextenzo. Accessed December 16, 2019.

61. Nakov R, Gattu S, Wang J, et al. Proposed biosimilar pegfilgrastim shows similarity in pharmacokinetics and pharmacodynamics to reference pegfilgrastim in healthy subjects. Br J Clin Pharmacol 2018;84:2790-2801. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30079636.

62. Blackwell K, Donskih R, Jones CM, et al. A comparison of proposed biosimilar LA-EP2006 and reference pegfilgrastim for the prevention of neutropenia in patients with early-stage breast cancer receiving myelosuppressive adjuvant or neoadjuvant chemotherapy: pegfilgrastim randomized oncology (supportive care) trial to evaluate comparative treatment (PROTECT-2), a phase III, randomized, double-blind trial. Oncologist 2016;21:789-794. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27091420.

63. Harbeck N, Lipatov O, Frolova M, et al. Randomized, double-blind study comparing proposed biosimilar LA-EP2006 with reference pegfilgrastim in breast cancer. Future Oncol 2016;12:1359-1367. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27020170.

64. Harbeck N, Wang J, Otto GP, et al. Safety analysis of proposed pegfilgrastim biosimilar in Phase I and Phase III studies. Future Oncol 2019;15:1313-1322. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30834780.

65. U.S. Food and Drug Administration. FDA Oncologic Drugs Advisory Committee Briefing Materials: "Epoetin Hospira", a proposed biosimilar to US-licensed Epogen/Procrit 2017. Available at: https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/OncologicDrugsAdvisoryCommittee/UCM561560.pdf. Accessed December 16, 2019.

66. Fishbane S, Singh B, Kumbhat S, et al. Intravenous epoetin alfa-epbx versus epoetin alfa for treatment of anemia in end-stage kidney disease. Clin J Am Soc Nephrol 2018;13:1204-1214. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29921734.

67. Thadhani R, Guilatco R, Hymes J, et al. Switching from epoetin alfa (Epogen(R)) to epoetin alfa-epbx (RetacritTM) using a specified dosing algorithm: a randomized, non-inferiority study in adults on hemodialysis. Am J Nephrol 2018;48:214-224. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30196301.

68. Gisselbrecht C, Haioun C, Lepage E, et al. Placebo-controlled phase III study of lenograstim (glycosylated recombinant human granulocyte colony-stimulating factor) in aggressive non-Hodgkin's lymphoma: factors influencing chemotherapy administration. Groupe d'Etude des Lymphomes de l'Adulte. Leuk Lymphoma 1997;25:289-300. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9168439.

69. Trillet-Lenoir V, Green J, Manegold C, et al. Recombinant granulocyte colony stimulating factor reduces the infectious complications of cytotoxic chemotherapy. Eur J Cancer 1993;29A:319-324. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7691119.

70. Bui BN, Chevallier B, Chevreau C, et al. Efficacy of lenograstim on hematologic tolerance to MAID chemotherapy in patients with advanced soft tissue sarcoma and consequences on treatment dose-intensity. J Clin Oncol 1995;13:2629-2636. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7595717.

71. Timmer-Bonte JN, de Boo TM, Smit HJ, et al. Prevention of chemotherapy-induced febrile neutropenia by prophylactic antibiotics plus or minus granulocyte colony-stimulating factor in small-cell lung cancer: a Dutch Randomized Phase III Study. J Clin Oncol 2005;23:7974-7984. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16258098.

72. Vogel CL, Wojtukiewicz MZ, Carroll RR, et al. First and subsequent cycle use of pegfilgrastim prevents febrile neutropenia in patients with breast cancer: a multicenter, double-blind, placebo-controlled phase III study. J Clin Oncol 2005;23:1178-1184. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15718314.

73. Chevallier B, Chollet P, Merrouche Y, et al. Lenograstim prevents morbidity from intensive induction chemotherapy in the treatment of inflammatory breast cancer. J Clin Oncol 1995;13:1564-1571. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7541448.

74. Crawford J, Ozer H, Stoller R, et al. Reduction by granulocyte colony-stimulating factor of fever and neutropenia induced by chemotherapy in patients with small-cell lung cancer. N Engl J Med 1991;325:164-170. Available at: http://www.ncbi.nlm.nih.gov/pubmed/1711156.

75. Gatzemeier U, Kleisbauer JP, Drings P, et al. Lenograstim as support for ACE chemotherapy of small-cell lung cancer: a phase III, multicenter, randomized study. Am J Clin Oncol 2000;23:393-400. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10955871.

76. Muhonen T, Jantunen I, Pertovaara H, et al. Prophylactic filgrastim (G-CSF) during mitomycin-C, mitoxantrone, and methotrexate (MMM) treatment for metastatic breast cancer. A randomized study. Am J Clin Oncol 1996;19:232-234. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8638531.

77. Osby E, Hagberg H, Kvaloy S, et al. CHOP is superior to CNOP in elderly patients with aggressive lymphoma while outcome is unaffected by filgrastim treatment: results of a Nordic Lymphoma Group randomized trial. Blood 2003;101:3840-3848. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12531794.

78. Pettengell R, Gurney H, Radford JA, et al. Granulocyte colony-stimulating factor to prevent dose-limiting neutropenia in non-Hodgkin's lymphoma: a randomized controlled trial. Blood 1992;80:1430-1436. Available at: http://www.ncbi.nlm.nih.gov/pubmed/1381626.

79. Zinzani PL, Pavone E, Storti S, et al. Randomized trial with or without granulocyte colony-stimulating factor as adjunct to induction VNCOP-B treatment of elderly high-grade non-Hodgkin's lymphoma. Blood 1997;89:3974-3979. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9166835.

80. Burdach SE, Muschenich M, Josephs W, et al. Granulocyte-macrophage-colony stimulating factor for prevention of neutropenia and infections in children and adolescents with solid tumors. Results of a prospective randomized study. Cancer 1995;76:510-516. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8625134.

81. Eguchi K, Kabe J, Kudo S, et al. Efficacy of recombinant human granulocyte-macrophage colony-stimulating factor for chemotherapy-induced leukopenia in patients with non-small-cell lung cancer. Cancer Chemother Pharmacol 1994;34:37-43. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8174201.

82. Jones SE, Schottstaedt MW, Duncan LA, et al. Randomized double-blind prospective trial to evaluate the effects of sargramostim versus placebo in a moderate-dose fluorouracil, doxorubicin, and cyclophosphamide adjuvant chemotherapy program for stage II and III breast cancer. J Clin Oncol 1996;14:2976-2983. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8918495.

83. Arnberg H, Letocha H, Nou F, et al. GM-CSF in chemotherapy-induced febrile neutropenia-a double-blind randomized study. Anticancer Res 1998;18:1255-1260. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9615797.

84. Gerhartz HH, Engelhard M, Meusers P, et al. Randomized, double-blind, placebo-controlled, phase III study of recombinant human granulocyte-macrophage colony-stimulating factor as adjunct to induction treatment of high-grade malignant non-Hodgkin's lymphomas. Blood

1993;82:2329-2339. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7691256.

85. Agiro A, Ma Q, Acheson AK, et al. Risk of neutropenia-related hospitalization in patients who received colony-stimulating factors with chemotherapy for breast cancer. J Clin Oncol 2016;34:3872-3879. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27646945.

86. Dale DC, Crawford J, Klippel Z, et al. A systematic literature review of the efficacy, effectiveness, and safety of filgrastim. Support Care Cancer 2018;26:7-20. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28939926.

87. Weycker D, Bensink M, Lonshteyn A, et al. Use of colony-stimulating factor primary prophylaxis and incidence of febrile neutropenia from 2010-2016: a longitudinal assessment. Curr Med Res Opin 2019;35:1073-1080. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30550346.

88. Rowe JM, Andersen JW, Mazza JJ, et al. A randomized placebo-controlled phase III study of granulocyte-macrophage colony-stimulating factor in adult patients (> 55 to 70 years of age) with acute myelogenous leukemia: a study of the Eastern Cooperative Oncology Group (E1490). Blood 1995;86:457-462. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7605984.

89. Doorduijn JK, van der Holt B, van Imhoff GW, et al. CHOP compared with CHOP plus granulocyte colony-stimulating factor in elderly patients with aggressive non-Hodgkin's lymphoma. J Clin Oncol 2003;21:3041-3050. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12915593.

90. Fossa SD, Kaye SB, Mead GM, et al. Filgrastim during combination chemotherapy of patients with poor-prognosis metastatic germ cell malignancy. European Organization for Research and Treatment of Cancer, Genito-Urinary Group, and the Medical Research Council Testicular Cancer Working Party, Cambridge, United Kingdom. J Clin Oncol 1998;16:716-724. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9469362.

91. Bohlius J, Herbst C, Reiser M, et al. Granulopoiesis-stimulating factors to prevent adverse effects in the treatment of malignant lymphoma. Cochrane Database Syst Rev 2008:CD003189. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18843642.

92. Sung L, Nathan PC, Alibhai SM, et al. Meta-analysis: effect of prophylactic hematopoietic colony-stimulating factors on mortality and outcomes of infection. Ann Intern Med 2007;147:400-411. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17876022.

93. Clark OA, Lyman GH, Castro AA, et al. Colony-stimulating factors for chemotherapy-induced febrile neutropenia: a meta-analysis of randomized controlled trials. J Clin Oncol 2005;23:4198-4214. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15961767.

94. Mhaskar R, Clark OA, Lyman G, et al. Colony-stimulating factors for chemotherapy-induced febrile neutropenia. Cochrane Database Syst Rev 2014:CD003039. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25356786.

95. Kuderer NM, Dale DC, Crawford J, Lyman GH. Impact of primary prophylaxis with granulocyte colony-stimulating factor on febrile neutropenia and mortality in adult cancer patients receiving chemotherapy: a systematic review. J Clin Oncol 2007;25:3158-3167. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17634496.

96. Lyman GH, Dale DC, Wolff DA, et al. Acute myeloid leukemia or myelodysplastic syndrome in randomized controlled clinical trials of cancer chemotherapy with granulocyte colony-stimulating factor: a systematic review. J Clin Oncol 2010;28:2914-2924. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20385991.

97. Lyman GH, Kuderer NM. The economics of the colony-stimulating factors in the prevention and treatment of febrile neutropenia. Crit Rev Oncol Hematol 2004;50:129-146. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15157662.

98. Fust K, Parthan A, Maschio M, et al. Granulocyte colony-stimulating factors in the prevention of febrile neutropenia: review of cost-

effectiveness models. Expert Rev Pharmacoecon Outcomes Res 2017;17:39-52. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28064553.

99. Cosler LE, Eldar-Lissai A, Culakova E, et al. Therapeutic use of granulocyte colony-stimulating factors for established febrile neutropenia: effect on costs from a hospital perspective. Pharmacoeconomics 2007;25:343-351. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17402806.

100. Doorduijn JK, Buijt I, van der Holt B, et al. Economic evaluation of prophylactic granulocyte colony stimulating factor during chemotherapy in elderly patients with aggressive non-Hodgkin's lymphoma. Haematologica 2004;89:1109-1117. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15377472.

101. Eldar-Lissai A, Cosler LE, Culakova E, Lyman GH. Economic analysis of prophylactic pegfilgrastim in adult cancer patients receiving chemotherapy. Value Health 2008;11:172-179. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18380630.

102. Numnum TM, Kimball KJ, Rocconi RP, et al. Pegfilgrastim for the prevention of febrile neutropenia in patients with epithelial ovarian carcinoma-a cost-effectiveness analysis. Int J Gynecol Cancer 2007;17:1019-1024. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17386043.

103. Timmer-Bonte JN, Adang EM, Termeer E, et al. Modeling the cost effectiveness of secondary febrile neutropenia prophylaxis during standard-dose chemotherapy. J Clin Oncol 2008;26:290-296. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18182670.

104. Pawloski PA, Thomas AJ, Kane S, et al. Predicting neutropenia risk in patients with cancer using electronic data. J Am Med Inform Assoc 2017;24:e129-e135. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27638907.

105. McBride A, Balu S, Campbell K, et al. Expanded access to cancer treatments from conversion to neutropenia prophylaxis with biosimilar filgrastim-sndz. Future Oncol 2017;13:2285-2295. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28870106.

106. McBride A, Campbell K, Bikkina M, et al. Cost-efficiency analyses for the US of biosimilar filgrastim-sndz, reference filgrastim, pegfilgrastim, and pegfilgrastim with on-body injector in the prophylaxis of chemotherapy-induced (febrile) neutropenia. J Med Econ 2017;20:1083-1093. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28722494.

107. Grewal S, Ramsey S, Balu S, Carlson JJ. Cost-savings for biosimilars in the United States: a theoretical framework and budget impact case study application using filgrastim. Expert Rev Pharmacoecon Outcomes Res 2018;18:447-454. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29757040.

108. Lyman GH, Balaban E, Diaz M, et al. American Society of Clinical Oncology Statement: Biosimilars in Oncology. J Clin Oncol 2018;36:1260-1265. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29443651.

109. Bennett CL, Djulbegovic B, Norris LB, Armitage JO. Colony-stimulating factors for febrile neutropenia during cancer therapy. N Engl J Med 2013;368:1131-1139. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23514290.

110. Kirshner JJ, Heckler CE, Janelsins MC, et al. Prevention of pegfilgrastim-induced bone pain: a phase III double-blind placebo-controlled randomized clinical trial of the University of Rochester Cancer Center clinical community oncology program research base. J Clin Oncol 2012;30:1974-1979. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22508813.

111. Kubista E, Glaspy J, Holmes FA, et al. Bone pain associated with once-per-cycle pegfilgrastim is similar to daily filgrastim in patients with breast cancer. Clin Breast Cancer 2003;3:391-398. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12636878.

112. Kroschinsky F, Holig K, Ehninger G. The role of pegfilgrastim in mobilization of hematopoietic stem cells. Transfus Apher Sci 2008;38:237-244. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18490197.

113. Moore DC, Pellegrino AE. Pegfilgrastim-induced bone pain: a review on incidence, risk factors, and evidence-based management. Ann Pharmacother 2017;51:797-803. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28423916.

114. Romeo C, Li Q, Copeland L. Severe pegfilgrastim-induced bone pain completely alleviated with loratadine: A case report. J Oncol Pharm Pract 2015;21:301-304. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24664474.

115. Moore K, Haroz R. When hydromorphone is not working, try loratadine: an emergency department case of loratadine as abortive therapy for severe pegfilgrastim-induced bone pain. J Emerg Med 2017;52:e29-e31. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27751704.

116. Duggan C, Murphy L, Costello V, et al. Oral loratadine in the management of G-CSF-induced bone pain: a pilot study. Br J Nurs 2019;28:S4-S11. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30811242.

117. Kirshner JJ, McDonald MC, 3rd, Kruter F, et al. NOLAN: a randomized, phase 2 study to estimate the effect of prophylactic naproxen or loratadine vs no prophylactic treatment on bone pain in patients with early-stage breast cancer receiving chemotherapy and pegfilgrastim. Support Care Cancer 2018;26:1323-1334. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29147854.

118. Ramaekers RC, Olsen J, Obermiller AM, et al. Efficacy and safety of half-dose pegfilgrastim in cancer patients receiving cytotoxic chemotherapy. J Clin Oncol 2012;30:9110. Available at: https://ascopubs.org/doi/abs/10.1200/jco.2012.30.15_suppl.9110.

119. Lower EE, Charif M, Bartelt M. Reduced dose pegfilgrastim is associated with less bone pain without increased neutropenia: a retrospective study. Cancer Chemother Pharmacol 2018;82:165-170. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29869680.

120. Kim E, Jin R, Choi K, et al. Safety and efficacy of low-dose pegfilgrastim (pegfil) in maintaining chemotherapy (CT) dose density in patients (pts) receiving docetaxel/doxorubicin/cyclophosphamide (TAC) or doxorubicin/cyclophosphamide (AC) as neoadjuvant chemotherapy (NCT) for stage II-III breast cancer (BC). J Clin Oncol 2010;28:e19561. Available at: https://ascopubs.org/doi/abs/10.1200/jco.2010.28.15_suppl.e19561.

121. Tigue CC, McKoy JM, Evens AM, et al. Granulocyte-colony stimulating factor administration to healthy individuals and persons with chronic neutropenia or cancer: an overview of safety considerations from the Research on Adverse Drug Events and Reports project. Bone Marrow Transplant 2007;40:185-192. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17563736.

122. Akyol G, Pala C, Yildirim A, et al. A rare but severe complication of filgrastim in a healthy donor: splenic rupture. Transfus Apher Sci 2014;50:53-55. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24360843.

123. Funes C, Garcia-Candel F, Majado MJ, et al. Splenic rupture in a plasma cell leukemia, mobilized with G-CSF for autologous stem cell transplant. J Clin Apher 2010;25:223-225. Available at: https://www.ncbi.nlm.nih.gov/pubmed/20818717.

124. O'Malley DP, Whalen M, Banks PM. Spontaneous splenic rupture with fatal outcome following G-CSF administration for myelodysplastic syndrome. Am J Hematol 2003;73:294-295. Available at: https://www.ncbi.nlm.nih.gov/pubmed/12879437.

125. Veerappan R, Morrison M, Williams S, Variakojis D. Splenic rupture in a patient with plasma cell myeloma following G-CSF/GM-CSF administration for stem cell transplantation and review of the literature. Bone Marrow Transplant 2007;40:361-364. Available at: https://www.ncbi.nlm.nih.gov/pubmed/17563733.

126. Watring NJ, Wagner TW, Stark JJ. Spontaneous splenic rupture secondary to pegfilgrastim to prevent neutropenia in a patient with non-small-cell lung carcinoma. Am J Emerg Med 2007;25:247-248. Available at: https://www.ncbi.nlm.nih.gov/pubmed/17276841.

127. Becker PS, Wagle M, Matous S, et al. Spontaneous splenic rupture following administration of granulocyte colony-stimulating factor (G-CSF): occurrence in an allogeneic donor of peripheral blood stem cells. Biol Blood Marrow Transplant 1997;3:45-49. Available at: https://www.ncbi.nlm.nih.gov/pubmed/9209740.

128. Martin WG, Ristow KM, Habermann TM, et al. Bleomycin pulmonary toxicity has a negative impact on the outcome of patients with Hodgkin's lymphoma. J Clin Oncol 2005;23:7614-7620. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16186594.

129. Evens AM, Cilley J, Ortiz T, et al. G-CSF is not necessary to maintain over 99% dose-intensity with ABVD in the treatment of Hodgkin lymphoma: low toxicity and excellent outcomes in a 10-year analysis. Br J Haematol 2007;137:545-552. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17459049.

130. Boleti E, Mead GM. ABVD for Hodgkin's lymphoma: full-dose chemotherapy without dose reductions or growth factors. Ann Oncol 2007;18:376-380. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17071938.

131. Relling MV, Boyett JM, Blanco JG, et al. Granulocyte colony-stimulating factor and the risk of secondary myeloid malignancy after etoposide treatment. Blood 2003;101:3862-3867. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12531808.

132. Smith RE, Bryant J, DeCillis A, et al. Acute myeloid leukemia and myelodysplastic syndrome after doxorubicin-cyclophosphamide adjuvant therapy for operable breast cancer: the National Surgical Adjuvant Breast and Bowel Project Experience. J Clin Oncol 2003;21:1195-1204. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12663705.

133. Hershman D, Neugut AI, Jacobson JS, et al. Acute myeloid leukemia or myelodysplastic syndrome following use of granulocyte colony-stimulating factors during breast cancer adjuvant chemotherapy. J Natl Cancer Inst 2007;99:196-205. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17284714.

134. Lyman GH, Yau L, Nakov R, Krendyukov A. Overall survival and risk of second malignancies with cancer chemotherapy and G-CSF support. Ann Oncol 2018;29:1903-1910. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30099478.

135. Calip GS, Moran KM, Sweiss KI, et al. Myelodysplastic syndrome and acute myeloid leukemia after receipt of granulocyte colony-stimulating factors in older patients with non-Hodgkin lymphoma. Cancer 2019;125:1143-1154. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30548485.

136. D'Souza A, Jaiyesimi I, Trainor L, Venuturumili P. Granulocyte colony-stimulating factor administration: adverse events. Transfus Med Rev 2008;22:280-290. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18848155.

137. Adler BK, Salzman DE, Carabasi MH, et al. Fatal sickle cell crisis after granulocyte colony-stimulating factor administration. Blood 2001;97:3313-3314. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11368061.

138. Grigg AP. Granulocyte colony-stimulating factor-induced sickle cell crisis and multiorgan dysfunction in a patient with compound heterozygous sickle cell/beta+ thalassemia. Blood 2001;97:3998-3999. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11405211.

139. Kang EM, Areman EM, David-Ocampo V, et al. Mobilization, collection, and processing of peripheral blood stem cells in individuals with sickle cell trait. Blood 2002;99:850-855. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11806986.

140. Gertz MA, Lacy MQ, Bjornsson J, Litzow MR. Fatal pulmonary toxicity related to the administration of granulocyte colony-stimulating factor in amyloidosis: a report and review of growth factor-induced pulmonary toxicity. J Hematother Stem Cell Res 2000;9:635-643. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11091487.

141. Bashir Q, Langford LA, Parmar S, et al. Primary systemic amyloid light chain amyloidosis decompensating after filgrastim-induced

mobilization and stem-cell collection. J Clin Oncol 2011;29:e79-80. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21060030.

142. Tsai SB, Seldin DC, Quillen K, et al. High-dose melphalan and stem cell transplantation for patients with AL amyloidosis: trends in treatment-related mortality over the past 17 years at a single referral center. Blood 2012;120:4445-4446. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23175664.

143. Herrmann F, Schulz G, Lindemann A, et al. Yeast-expressed granulocyte-macrophage colony-stimulating factor in cancer patients: a phase Ib clinical study. Behring Inst Mitt 1988:107-118. Available at: http://www.ncbi.nlm.nih.gov/pubmed/2467645.

144. Stern AC, Jones TC. The side-effect profile of GM-CSF. Infection 1992;20 Suppl 2:S124-127. Available at: http://www.ncbi.nlm.nih.gov/pubmed/1493936.

145. U.S. Food and Drug Administration. Sargramostim label information. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/103362s5240lbl.pdf. Accessed December 16, 2019.

146. Amato RJ, Hernandez-McClain J, Henary H. Phase 2 study of granulocyte-macrophage colony-stimulating factor plus thalidomide in patients with hormone-naive adenocarcinoma of the prostate. Urol Oncol 2009;27:8-13. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18367123.

147. Winer ES, Miller KB, Chan GW. GM-CSF and low-dose cytosine arabinoside in high-risk, elderly patients with AML or MDS. Oncology (Williston Park) 2005;19:11-14. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15934494.

148. Arning M, Kliche KO, Schneider W. GM-CSF therapy and capillary-leak syndrome. Ann Hematol 1991;62:83-83. Available at: https://www.ncbi.nlm.nih.gov/pubmed/2031971.

149. Al-Homaidhi A, Prince HM, Al-Zahrani H, et al. Granulocyte-macrophage colony-stimulating factor-associated histiocytosis and capillary-leak syndrome following autologous bone marrow transplantation: two case reports and a review of the literature. Bone Marrow Transplant 1998;21:209-214. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9489640.

150. Emminger W, Emminger-Schmidmeier W, Peters C, et al. Capillary leak syndrome during low dose granulocyte-macrophage colony-stimulating factor (rh GM-CSF) treatment of a patient in a continuous febrile state. Blut 1990;61:219-221. Available at: http://www.ncbi.nlm.nih.gov/pubmed/2224143.

151. Deeren DH, Zachee P, Malbrain ML. Granulocyte colony-stimulating factor-induced capillary leak syndrome confirmed by extravascular lung water measurements. Ann Hematol 2005;84:89-94. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15365768.

152. Vial T, Descotes J. Clinical toxicity of cytokines used as haemopoietic growth factors. Drug Saf 1995;13:371-406. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8652081.

153. Mahmoudjafari Z, Hawks KG, Hsieh AA, et al. American Society for Blood and Marrow Transplantation Pharmacy Special Interest Group survey on chimeric antigen receptor T cell therapy administrative, logistic, and toxicity management practices in the United States. Biol Blood Marrow Transplant 2019;25:26-33. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30266675.

154. Brudno JN, Kochenderfer JN. Toxicities of chimeric antigen receptor T cells: recognition and management. Blood 2016;127:3321-3330. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27207799.

155. Neelapu SS, Tummala S, Kebriaei P, et al. Chimeric antigen receptor T-cell therapy - assessment and management of toxicities. Nat Rev Clin Oncol 2018;15:47-62. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28925994.

156. U.S. Food and Drug Administration. Tisagenlecleucel label information. 2017. Available at: https://www.fda.gov/files/vaccines%2C%20blood%20%26%20biologics/published/Package-Insert---KYMRIAH.pdf. Accessed December 6, 2019.

157. Mehta HM, Malandra M, Corey SJ. G-CSF and GM-CSF in neutropenia. J Immunol 2015;195:1341-1349. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26254266.

158. Moore DC. Drug-induced neutropenia: a focus on rituximab-induced late-onset neutropenia. P T 2016;41:765-768. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27990078.

159. Lyman GH, Lyman CH, Agboola O. Risk models for predicting chemotherapy-induced neutropenia. Oncologist 2005;10:427-437. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15967836.

160. Aslani A, Smith RC, Allen BJ, et al. The predictive value of body protein for chemotherapy-induced toxicity. Cancer 2000;88:796-803. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10679649.

161. Chrischilles E, Delgado DJ, Stolshek BS, et al. Impact of age and colony-stimulating factor use on hospital length of stay for febrile neutropenia in CHOP-treated non-Hodgkin's lymphoma. Cancer Control 2002;9:203-211. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12060818.

162. Lyman GH, Dale DC, Friedberg J, et al. Incidence and predictors of low chemotherapy dose-intensity in aggressive non-Hodgkin's lymphoma: a nationwide study. J Clin Oncol 2004;22:4302-4311. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15381684.

163. Lyman GH, Delgado DJ. Risk and timing of hospitalization for febrile neutropenia in patients receiving CHOP, CHOP-R, or CNOP chemotherapy for intermediate-grade non-Hodgkin lymphoma. Cancer 2003;98:2402-2409. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14635075.

164. Lyman GH, Morrison VA, Dale DC, et al. Risk of febrile neutropenia among patients with intermediate-grade non-Hodgkin's lymphoma receiving CHOP chemotherapy. Leuk Lymphoma 2003;44:2069-2076. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14959849.

165. Morrison VA, Picozzi V, Scott S, et al. The impact of age on delivered dose intensity and hospitalizations for febrile neutropenia in patients with intermediate-grade non-Hodgkin's lymphoma receiving initial CHOP chemotherapy: a risk factor analysis. Clin Lymphoma 2001;2:47-56. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11707870.

166. Lyman GH, Abella E, Pettengell R. Risk factors for febrile neutropenia among patients with cancer receiving chemotherapy: A systematic review. Crit Rev Oncol Hematol 2014;90:190-199. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24434034.

167. Lyman GH, Kuderer NM, Crawford J, et al. Predicting individual risk of neutropenic complications in patients receiving cancer chemotherapy. Cancer 2011;117:1917-1927. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21509769.

168. Lyman GH, Poniewierski MS. A patient risk model of chemotherapy-induced febrile neutropenia: lessons learned from the ANC study group. J Natl Compr Canc Netw 2017;15:1543-1550. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29223991.

169. Razzaghdoust A, Mofid B, Moghadam M. Development of a simplified multivariable model to predict neutropenic complications in cancer patients undergoing chemotherapy. Support Care Cancer 2018;26:3691-3699. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29736867.

170. Aagaard T, Roen A, Reekie J, et al. Development and validation of a risk score for febrile neutropenia after chemotherapy in patients with cancer: the FENCE score. JNCI Cancer Spectr 2018;2:pky053. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31360873.

171. Aagaard T, Reekie J, Roen A, et al. Development and validation of a cycle-specific risk score for febrile neutropenia during chemotherapy cycles 2-6 in patients with solid cancers: the (CSR) FENCE score. Int J

Cancer 2019;146:321-328. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30839100.

172. Family L, Li Y, Chen LH, et al. A study of novel febrile neutropenia risk factors related to bone marrow or immune suppression, barrier function, and bacterial flora. J Natl Compr Canc Netw 2018;16:1201-1208. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30323090.

173. Smith TJ, Bohlke K, Lyman GH, et al. Recommendations for the use of WBC growth factors: American Society of Clinical Oncology clinical practice guideline update. J Clin Oncol 2015;33:3199-3212. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26169616.

174. Aapro MS, Bohlius J, Cameron DA, et al. 2010 update of EORTC guidelines for the use of granulocyte-colony stimulating factor to reduce the incidence of chemotherapy-induced febrile neutropenia in adult patients with lymphoproliferative disorders and solid tumours. Eur J Cancer 2011;47:8-32. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21095116.

175. Kosaka Y, Rai Y, Masuda N, et al. Phase III placebo-controlled, double-blind, randomized trial of pegfilgrastim to reduce the risk of febrile neutropenia in breast cancer patients receiving docetaxel/cyclophosphamide chemotherapy. Support Care Cancer 2015;23:1137-1143. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25576433.

176. Crawford J, Dale DC, Lyman GH. Chemotherapy-induced neutropenia: risks, consequences, and new directions for its management. Cancer 2004;100:228-237. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14716755.

177. Lyman GH. Risk assessment in oncology clinical practice. From risk factors to risk models. Oncology (Williston Park) 2003;17:8-13. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14682113.

178. Weycker D, Li X, Tzivelekis S, et al. Burden of chemotherapy-induced febrile neutropenia hospitalizations in US clinical practice, by use and patterns of prophylaxis with colony-stimulating factor. Support Care Cancer 2016:439-447. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27734153.

179. Lyman GH, Allcott K, Garcia J, et al. The effectiveness and safety of same-day versus next-day administration of long-acting granulocyte colony-stimulating factors for the prophylaxis of chemotherapy-induced neutropenia: a systematic review. Support Care Cancer 2017;25:2619-2629. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28484882.

180. Meropol NJ, Miller LL, Korn EL, et al. Severe myelosuppression resulting from concurrent administration of granulocyte colony-stimulating factor and cytotoxic chemotherapy. J Natl Cancer Inst 1992;84:1201-1203. Available at: http://www.ncbi.nlm.nih.gov/pubmed/1378905.

181. Rowinsky EK, Grochow LB, Sartorius SE, et al. Phase I and pharmacologic study of high doses of the topoisomerase I inhibitor topotecan with granulocyte colony-stimulating factor in patients with solid tumors. J Clin Oncol 1996;14:1224-1235. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8648378.

182. Kanbayashi Y, Ishikawa T, Kanazawa M, et al. Predictive factors in patients eligible for pegfilgrastim prophylaxis focusing on RDI using ordered logistic regression analysis. Med Oncol 2018;35:55. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29549536.

183. Weycker D, Bensink M, Lonshteyn A, et al. Risk of chemotherapy-induced febrile neutropenia by day of pegfilgrastim prophylaxis in US clinical practice from 2010-2015. Curr Med Res Opin 2017;33:2107-2113. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28958157.

184. Kaufman PA, Paroly W, Rinaldi D. Randomized double blind phase 2 study evaluating same-day vs. next-day administration of pegfilgrastim with docetaxel, doxorubicin and cyclophosphamide (TAC) in women with early stage and advanced breast cancer. Breast Cancer Res Treat 2004;88:S59. Available at: https://insights.ovid.com/breast-cancer-research-treatment/bcart/2004/88/001/randomized-double-blind-phase-study-evaluating/167/00001803.

185. Saven A, Schwartzberg L, Kaywin P, et al. Randomized, double-blind, phase 2, study evaluating same-day vs next-day administration of pegfilgrastim with R-CHOP in non-Hodgkin's lymphoma patients. J Clin Oncol 2006;24:7570. Available at: http://ascopubs.org/doi/abs/10.1200/jco.2006.24.18_suppl.7570.

186. American Society of Clinical Oncology. Letter to CMS regarding "Neulasta administered same day as chemotherapy". 2012. Available at: http://www.asco.org/sites/default/files/letter_to_cms_rac_audit_on_neulasta_110912_lthd.pdf. Accessed December 16, 2019.

187. Yang BB, Morrow PK, Wu X, et al. Comparison of pharmacokinetics and safety of pegfilgrastim administered by two delivery methods: on-body injector and manual injection with a prefilled syringe. Cancer Chemother Pharmacol 2015;75:1199-1206. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25894719.

188. Green MD, Koelbl H, Baselga J, et al. A randomized double-blind multicenter phase III study of fixed-dose single-administration pegfilgrastim versus daily filgrastim in patients receiving myelosuppressive chemotherapy. Ann Oncol 2003;14:29-35. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12488289.

189. Watanabe T, Tobinai K, Shibata T, et al. Phase II/III study of R-CHOP-21 versus R-CHOP-14 for untreated indolent B-cell non-Hodgkin's lymphoma: JCOG 0203 trial. J Clin Oncol 2011;29:3990-3998. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21931035.

190. Hecht JR, Pillai M, Gollard R, et al. A randomized, placebo-controlled phase II study evaluating the reduction of neutropenia and febrile neutropenia in patients with colorectal cancer receiving pegfilgrastim with every-2-week chemotherapy. Clin Colorectal Cancer 2010;9:95-101. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20378503.

191. Brusamolino E, Rusconi C, Montalbetti L, et al. Dose-dense R-CHOP-14 supported by pegfilgrastim in patients with diffuse large B-cell lymphoma: a phase II study of feasibility and toxicity. Haematologica 2006;91:496-502. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16537117.

192. Burstein HJ, Parker LM, Keshaviah A, et al. Efficacy of pegfilgrastim and darbepoetin alfa as hematopoietic support for dose-dense every-2-week adjuvant breast cancer chemotherapy. J Clin Oncol 2005;23:8340-8347. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16293865.

193. Jones RL, Walsh G, Ashley S, et al. A randomised pilot phase II study of doxorubicin and cyclophosphamide (AC) or epirubicin and cyclophosphamide (EC) given 2 weekly with pegfilgrastim (accelerated) vs 3 weekly (standard) for women with early breast cancer. Br J Cancer 2009;100:305-310. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19165198.

194. Pirker R, Ulsperger E, Messner J, et al. Achieving full-dose, on-schedule administration of ACE chemotherapy every 14 days for the treatment of patients with extensive small-cell lung cancer. Lung 2006;184:279-285. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17235728.

195. Estcourt LJ, Stanworth SJ, Hopewell S, et al. Granulocyte transfusions for treating infections in people with neutropenia or neutrophil dysfunction. Cochrane Database Syst Rev 2016;4:CD005339. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27128488.

196. Johnston E, Crawford J, Blackwell S, et al. Randomized, dose-escalation study of SD/01 compared with daily filgrastim in patients receiving chemotherapy. J Clin Oncol 2000;18:2522-2528. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10893282.

197. U.S. Food and Drug Administration. FDA Approves Radiation Medical Countermeasure. 2015. Available at: https://www.fda.gov/emergency-preparedness-and-response/about-mcmi/fda-approves-radiation-medical-countermeasure. Accessed November 4, 2019.

198. U. S. Department of Health and Human Services, Radiation Emergency Medical Management. Myeloid cytokines for acute exposure to myelosuppressive doses of radiation (hematopoietic subsyndrome of ARS). 2018. Available at: https://www.remm.nlm.gov/cytokines.htm.

199. Chua HL, Plett PA, Sampson CH, et al. Survival efficacy of the PEGylated G-CSFs Maxy-G34 and neulasta in a mouse model of lethal H-ARS, and residual bone marrow damage in treated survivors. Health Phys 2014;106:21-38. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24276547.

200. Farese AM, Brown CR, Smith CP, et al. The ability of filgrastim to mitigate mortality following LD50/60 total-body irradiation is administration time-dependent. Health Phys 2014;106:39-47. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24276548.

201. Farese AM, Cohen MV, Katz BP, et al. Filgrastim improves survival in lethally irradiated nonhuman primates. Radiat Res 2013;179:89-100. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23210705.

202. Hankey KG, Farese AM, Blaauw EC, et al. Pegfilgrastim improves survival of lethally irradiated nonhuman primates. Radiat Res 2015;183:643-655. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26035709.

203. MacVittie TJ, Bennett AW, Farese AM, et al. The effect of radiation dose and variation in Neupogen initiation schedule on the mitigation of myelosuppression during the concomitant GI-ARS and H-ARS in a nonhuman primate model of high-dose exposure with marrow sparing. Health Phys 2015;109:427-439. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26425903.

204. Rafael-Hurtado M, Alanis A, Raul-Alvarez T, et al. Recombinant human granulocyte/macrophage colony-stimulating factor for the treatment of bone marrow aplasia in accidentally irradiated (60Co) patients: report of three new cases. . In: MacVittie T, Weiss J, Browne D, eds. Advances in the Treatment of Radiation Injuries: Advances in the Biosciences. Vol. 94. Tarrytown, NY: Pergamon: Elsevier Science Ltd; 1996:295-301.

205. Baranov AE, Selidovkin GD, Butturini A, Gale RP. Hematopoietic recovery after 10-Gy acute total body radiation. Blood 1994;83:596-599. Available at: https://www.ncbi.nlm.nih.gov/pubmed/8286754.

206. The radiological accident in Istanbul. International Atomic Energy Agency 2000. Available at: http://www-pub.iaea.org/books/IAEABooks/6071/The-Radiological-Accident-in-Istanbul.

207. The radiological accident in Nueva Aldea. International Atomic Energy Agency 2009. Available at: http://www-pub.iaea.org/books/IAEABooks/8117/The-Radiological-Accident-in-Nueva-Aldea.

208. Gourmelon P, Benderitter M, Bertho JM, et al. European consensus on the medical management of acute radiation syndrome and analysis of the radiation accidents in Belgium and Senegal. Health Phys 2010;98:825-832. Available at: https://www.ncbi.nlm.nih.gov/pubmed/20445389.

209. Hosing C. Hematopoietic stem cell mobilization with G-CSF. Methods Mol Biol 2012;904:37-47. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22890920.

210. Kroger N, Zeller W, Fehse N, et al. Mobilizing peripheral blood stem cells with high-dose G-CSF alone is as effective as with Dexa-BEAM plus G-CSF in lymphoma patients. Br J Haematol 1998;102:1101-1106. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9734664.

211. Elayan MM, Horowitz JG, Magraner JM, et al. Tbo-filgrastim versus filgrastim during mobilization and neutrophil engraftment for autologous stem cell transplantation. Biol Blood Marrow Transplant 2015;21:1921-1925. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26033279.

212. Trifilio S, Zhou Z, Galvin J, et al. Filgrastim versus TBO-filgrastim to reduce the duration of neutropenia after autologous hematopoietic stem cell transplantation: TBO, or not TBO, that is the question. Clin Transplant 2015;29:1128-1132. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26493022.

213. Neme K, Henkin D, Mikulandric N, et al. Outcomes of tbo-filgrastim, filgrastim-sndz or filgrastim for mobilization in patients undergoing an autologous hematopoietic stem cell transplant: A single center experience.

J Clin Oncol 2019;37:e19000. Available at: https://ascopubs.org/doi/abs/10.1200/JCO.2019.37.15_suppl.e19000.

214. Schmitt M, Hoffmann JM, Lorenz K, et al. Mobilization of autologous and allogeneic peripheral blood stem cells for transplantation in haematological malignancies using biosimilar G-CSF. Vox Sang 2016;111:178-186. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27509033.

215. Haynes A, Hunter A, McQuaker G, et al. Engraftment characteristics of peripheral blood stem cells mobilised with cyclophosphamide and the delayed addition of G-CSF. Bone Marrow Transplant 1995;16:359-363. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8535307.

216. Matasar MJ, Czuczman MS, Rodriguez MA, et al. Ofatumumab in combination with ICE or DHAP chemotherapy in relapsed or refractory intermediate grade B-cell lymphoma. Blood 2013;122:499-506. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23692856.

217. Barlogie B, Anaissie E, van Rhee F, et al. Incorporating bortezomib into upfront treatment for multiple myeloma: early results of total therapy 3. Br J Haematol 2007;138:176-185. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17593024.

218. Chao NJ, Grima DT, Carrum G, et al. Chemo-mobilization provides superior mobilization and collection in autologous stem cell transplants but with less predictability and at a higher cost. Blood 2011;118:4040-4048. Available at: https://ashpublications.org/blood/article/118/21/4048/68992/Chemo-Mobilization-Provides-Superior-Mobilization.

219. Lane TA, Ho AD, Bashey A, et al. Mobilization of blood-derived stem and progenitor cells in normal subjects by granulocyte-macrophage- and granulocyte-colony-stimulating factors. Transfusion 1999;39:39-47. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9920165.

220. Lonial S, Akhtari M, Kaufman J, et al. Mobilization of hematopoietic progenitors from normal donors using the combination of granulocyte-macrophage colony-stimulating factor and granulocyte colony-stimulating factor results in fewer plasmacytoid dendritic cells in the graft and enhanced donor T cell engraftment with Th1 polarization: results from a randomized clinical trial. Biol Blood Marrow Transplant 2013;19:460-467. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23201472.

221. Sohn SK, Kim JG, Seo KW, et al. GM-CSF-based mobilization effect in normal healthy donors for allogeneic peripheral blood stem cell transplantation. Bone Marrow Transplant 2002;30:81-86. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12132046.

222. Weaver CH, Schulman KA, Buckner CD. Mobilization of peripheral blood stem cells following myelosuppressive chemotherapy: a randomized comparison of filgrastim, sargramostim, or sequential sargramostim and filgrastim. Bone Marrow Transplant 2001;27 Suppl 2:S23-29. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11436117.

223. U.S. Food and Drug Administration. Plerixafor label information. 2017. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/022311s018lbl.pdf. Accessed December 16, 2019.

224. Chaudhary L, Awan F, Cumpston A, et al. Peripheral blood stem cell mobilization in multiple myeloma patients treat in the novel therapy-era with plerixafor and G-CSF has superior efficacy but significantly higher costs compared to mobilization with low-dose cyclophosphamide and G-CSF. J Clin Apher 2013;28:359-367. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23765597.

225. Dugan MJ, Maziarz RT, Bensinger WI, et al. Safety and preliminary efficacy of plerixafor (Mozobil) in combination with chemotherapy and G-CSF: an open-label, multicenter, exploratory trial in patients with multiple myeloma and non-Hodgkin's lymphoma undergoing stem cell mobilization. Bone Marrow Transplant 2010;45:39-47. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19483760.

226. Gopal AK, Karami M, Mayor J, et al. The effective use of plerixafor as a real-time rescue strategy for patients poorly mobilizing autologous CD34(+) cells. J Clin Apher 2012;27:81-87. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22298418.

227. Milone G, Tripepi G, Martino M, et al. Early measurement of CD34+ cells in peripheral blood after cyclophosphamide and granulocyte colony-stimulating factor treatment predicts later CD34+ mobilisation failure and is a possible criterion for guiding "on demand" use of plerixafor. Blood Transfus 2013;11:94-101. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23114516.

228. Giralt S, Costa L, Schriber J, et al. Optimizing autologous stem cell mobilization strategies to improve patient outcomes: consensus guidelines and recommendations. Biol Blood Marrow Transplant 2014;20:295-308. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24141007.

229. Becker PS. Optimizing stem cell mobilization: lessons learned. J Natl Compr Canc Netw 2014;12:1443-1449. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25313183.

230. DiPersio JF, Micallef IN, Stiff PJ, et al. Phase III prospective randomized double-blind placebo-controlled trial of plerixafor plus granulocyte colony-stimulating factor compared with placebo plus granulocyte colony-stimulating factor for autologous stem-cell mobilization and transplantation for patients with non-Hodgkin's lymphoma. J Clin Oncol 2009;27:4767-4773. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19720922.

231. DiPersio JF, Stadtmauer EA, Nademanee A, et al. Plerixafor and G-CSF versus placebo and G-CSF to mobilize hematopoietic stem cells for autologous stem cell transplantation in patients with multiple myeloma. Blood 2009;113:5720-5726. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19363221.

232. Duong HK, Savani BN, Copelan E, et al. Peripheral blood progenitor cell mobilization for autologous and allogeneic hematopoietic cell transplantation: guidelines from the American Society for Blood and Marrow Transplantation. Biol Blood Marrow Transplant 2014;20:1262-1273. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24816581.

233. Micallef IN, Stiff PJ, DiPersio JF, et al. Successful stem cell remobilization using plerixafor (mozobil) plus granulocyte colony-stimulating factor in patients with non-hodgkin lymphoma: results from the plerixafor NHL phase 3 study rescue protocol. Biol Blood Marrow Transplant 2009;15:1578-1586. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19896082.

234. Li J, Hamilton E, Vaughn L, et al. Effectiveness and cost analysis of "just-in-time" salvage plerixafor administration in autologous transplant patients with poor stem cell mobilization kinetics. Transfusion 2011;51:2175-2182. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21492180.

235. Worel N, Fritsch G, Agis H, et al. Plerixafor as preemptive strategy results in high success rates in autologous stem cell mobilization failure. J Clin Apher 2017;32:224-234. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27578390.

236. Ataca Atilla P, Bakanay Ozturk SM, Demirer T. How to manage poor mobilizers for high dose chemotherapy and autologous stem cell transplantation? Transfus Apher Sci 2017;56:190-198. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28034547.

237. Tournilhac O, Cazin B, Lepretre S, et al. Impact of frontline fludarabine and cyclophosphamide combined treatment on peripheral blood stem cell mobilization in B-cell chronic lymphocytic leukemia. Blood 2004;103:363-365. Available at: https://www.ncbi.nlm.nih.gov/pubmed/12969985.

238. Kuittinen T, Nousiainen T, Halonen P, et al. Prediction of mobilisation failure in patients with non-Hodgkin's lymphoma. Bone Marrow Transplant 2004;33:907-912. Available at: https://www.ncbi.nlm.nih.gov/pubmed/15034543.

239. Kumar S, Giralt S, Stadtmauer EA, et al. Mobilization in myeloma revisited: IMWG consensus perspectives on stem cell collection following initial therapy with thalidomide-, lenalidomide-, or bortezomib-containing regimens. Blood 2009;114:1729-1735. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19561323.

240. Micallef IN, Apostolidis J, Rohatiner AZ, et al. Factors which predict unsuccessful mobilisation of peripheral blood progenitor cells following G-

CSF alone in patients with non-Hodgkin's lymphoma. Hematol J 2000;1:367-373. Available at: https://www.ncbi.nlm.nih.gov/pubmed/11920216.

241. Hosing C, Saliba RM, Ahlawat S, et al. Poor hematopoietic stem cell mobilizers: a single institution study of incidence and risk factors in patients with recurrent or relapsed lymphoma. Am J Hematol 2009;84:335-337. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19384931.

242. Wuchter P, Ran D, Bruckner T, et al. Poor mobilization of hematopoietic stem cells-definitions, incidence, risk factors, and impact on outcome of autologous transplantation. Biol Blood Marrow Transplant 2010;16:490-499. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19925876.

243. Paripati H, Stewart AK, Cabou S, et al. Compromised stem cell mobilization following induction therapy with lenalidomide in myeloma. Leukemia 2008;22:1282-1284. Available at: https://www.ncbi.nlm.nih.gov/pubmed/18216870.

244. Mazumder A, Kaufman J, Niesvizky R, et al. Effect of lenalidomide therapy on mobilization of peripheral blood stem cells in previously untreated multiple myeloma patients. Leukemia 2008;22:1280-1282. Available at: https://www.ncbi.nlm.nih.gov/pubmed/18033320.

245. Waterman J, Rybicki L, Bolwell B, et al. Fludarabine as a risk factor for poor stem cell harvest, treatment-related MDS and AML in follicular lymphoma patients after autologous hematopoietic cell transplantation. Bone Marrow Transplant 2012;47:488-493. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21572461.

246. Ogunniyi A, Rodriguez M, Devlin S, et al. Upfront use of plerixafor and granulocyte-colony stimulating factor (GCSF) for stem cell mobilization in patients with multiple myeloma: efficacy and analysis of risk factors associated with poor stem cell collection efficiency. Leuk Lymphoma 2017;58:1123-1129. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27735212.

247. Shin S, Kim J, Kim-Wanner SZ, et al. A novel association between relaxin receptor polymorphism and hematopoietic stem cell yield after mobilization. PLoS One 2017;12:e0179986. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28666004.

248. Olivieri J, Attolico I, Nuccorini R, et al. Predicting failure of hematopoietic stem cell mobilization before it starts: the predicted poor mobilizer (pPM) score. Bone Marrow Transplant 2018;53:461-473. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29330395.

249. Musto P, Simeon V, Grossi A, et al. Predicting poor peripheral blood stem cell collection in patients with multiple myeloma receiving pre-transplant induction therapy with novel agents and mobilized with cyclophosphamide plus granulocyte-colony stimulating factor: results from a Gruppo Italiano Malattie EMatologiche dell'Adulto Multiple Myeloma Working Party study. Stem Cell Res Ther 2015;6:64. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25889496.

250. Czerw T, Kruzel T, Sadus-Wojciechowska M, et al. Comparison of two formulations of filgrastim, Neupogen (Amgen) and Zarzio (Sandoz), used to accelerate neutrophil recovery after autologous peripheral blood stem cell transplantation. Bone Marrow Transplant 2012;47:P872. Available at: http://www.nature.com/bmt/journal/v47/n1s/pdf/bmt201237a.pdf.

251. Manko J, Walter-Croneck A, Jawniak D, et al. A clinical comparison of the efficacy and safety of biosimilar G-CSF and originator G-CSF in haematopoietic stem cell mobilization. Pharmacol Rep 2014;66:239-242. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24911076.

252. Yafour N, Brahimi M, Osmani S, et al. Biosimilar G-CSF (filgrastim) is effective for peripheral blood stem cell mobilization and non-cryopreserved autologous transplantation. Transfus Clin Biol 2013;20:502-504. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23916573.

253. Remenyi P, Gopcsa L, Marton I, et al. Peripheral blood stem cell mobilization and engraftment after autologous stem cell transplantation with biosimilar rhG-CSF. Adv Ther 2014;31:451-460. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24687301.

254. Cioch M, Jawniak D, Kotwica K, et al. Biosimilar granulocyte colony-stimulating factor is effective in reducing the duration of neutropenia after autologous peripheral blood stem cell transplantation. Transplant Proc 2014;46:2882-2884. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25380941.

255. Lefrere F, Brignier AC, Elie C, et al. First experience of autologous peripheral blood stem cell mobilization with biosimilar granulocyte colony-stimulating factor. Adv Ther 2011;28:304-310. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21400232.

256. Lanza F, Saraceni F, Pezzi A, et al. A comparative analysis of biosimilar vs. originator filgrastim in combination with plerixafor for stem cell mobilization in lymphoma and multiple myeloma: a propensity-score weighted multicenter approach. Am J Hematol 2017;92:557-559. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28612372.

257. Andreola G, Babic A, Rabascio C, et al. Plerixafor and Filgrastim XM02 (Tevagastrim) as a first line peripheral blood stem cell mobilisation strategy in patients with multiple myeloma and lymphoma candidated to autologous bone marrow transplantation. Eur J Haematol 2012;88:154-158. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21992403.

258. Wicherska-Pawlowska K, Rybka J, Prajs I, et al. The comparison of effectiveness and safety between different biosimilars of G-CSF in the mobilization of peripheral blood stem cells (PBSCs) for autologous transplantation (autologous peripheral blood stem cell transplantation, auto-PBSCT). J Clin Apher 2019. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31663634.

259. Kobbe G, Bruns I, Fenk R, et al. Pegfilgrastim for PBSC mobilization and autologous haematopoietic SCT. Bone Marrow Transplant 2009;43:669-677. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19308043.

260. Costa LJ, Kramer C, Hogan KR, et al. Pegfilgrastim- versus filgrastim-based autologous hematopoietic stem cell mobilization in the setting of preemptive use of plerixafor: efficacy and cost analysis. Transfusion 2012;52:2375-2381. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22404694.

261. Herbert KE, Demosthenous L, Wiesner G, et al. Plerixafor plus pegfilgrastim is a safe, effective mobilization regimen for poor or adequate mobilizers of hematopoietic stem and progenitor cells: a phase I clinical trial. Bone Marrow Transplant 2014;49:1056-1062. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24887382.

262. Abid MB, De Mel S, Abid MA, et al. Pegylated filgrastim versus filgrastim for stem cell mobilization in multiple myeloma after novel agent induction. Clin Lymphoma Myeloma Leuk 2018;18:174-179. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29398647.

263. Herbert KE, Gambell P, Link EK, et al. Pegfilgrastim compared with filgrastim for cytokine-alone mobilization of autologous haematopoietic stem and progenitor cells. Bone Marrow Transplant 2013;48:351-356. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22858510.

264. Partanen A, Valtola J, Ropponen A, et al. Preemptive plerixafor injection added to pegfilgrastim after chemotherapy in non-Hodgkin lymphoma patients mobilizing poorly. Ann Hematol 2017;96:1897-1906. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28879595.

265. Bensinger WI, Weaver CH, Appelbaum FR, et al. Transplantation of allogeneic peripheral blood stem cells mobilized by recombinant human granulocyte colony-stimulating factor. Blood 1995;85:1655-1658. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7534140.

266. Cavallaro AM, Lilleby K, Majolino I, et al. Three to six year follow-up of normal donors who received recombinant human granulocyte colony-stimulating factor. Bone Marrow Transplant 2000;25:85-89. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10654020.

267. Rinaldi C, Savignano C, Pasca S, et al. Efficacy and safety of peripheral blood stem cell mobilization and collection: a single-center experience in 190 allogeneic donors. Transfusion 2012;52:2387-2394. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22452363.

268. Azar N, Choquet S, Garnier A. Use of a biosimilar G-CSF in allogeneic stem cell mobilisation. Bone Marrow Transplant 2012;47:S316 (P727). Available at: http://www.nature.com/bmt/journal/v47/n1s/pdf/bmt201237a.pdf.

269. Antelo M, Zabalza A, Sanchez P. Safety and efficacy of a G-CSF biosimilar (Zarzio(R)) for haematopoietic progenitor cell mobilization in allogeneic healthy donors. Bone Marrow Transplant 2013;48:S102 (P491). Available at: http://www.nature.com/bmt/journal/v48/n2s/pdf/bmt201323a.pdf.

270. Becker P, Schwebig A, Brauninger S, et al. Healthy donor hematopoietic stem cell mobilization with biosimilar granulocyte-colony-stimulating factor: safety, efficacy, and graft performance. Transfusion 2016;56:3055-3064. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27633122.

271. Antelo ML, Zabalza A, Sanchez Anton MP, et al. Mobilization of hematopoietic progenitor cells from allogeneic healthy donors using a new biosimilar G-CSF (Zarzio(R)). J Clin Apher 2016;31:48-52. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26011178.

272. Farhan R, Urbanowska E, Zborowska H, et al. Biosimilar G-CSF versus filgrastim and lenograstim in healthy unrelated volunteer hematopoietic stem cell donors. Ann Hematol 2017;96:1735-1739. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28801752.

273. Pahnke S, Egeland T, Halter J, et al. Current use of biosimilar G-CSF for haematopoietic stem cell mobilisation. Bone Marrow Transplant 2019;54:858-866. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30283148.

274. Schmitt M, Xu X, Hilgendorf I, et al. Mobilization of PBSC for allogeneic transplantation by the use of the G-CSF biosimilar XM02 in healthy donors. Bone Marrow Transplant 2013;48:922-925. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23318540.

275. Danylesko I, Sareli R, Bloom-Varda N, et al. Biosimilar filgrastim (Tevagrastim, XMO2) for allogeneic hematopoietic stem cell mobilization and transplantation in patients with acute myelogenous leukemia/myelodysplastic syndromes. Biol Blood Marrow Transplant 2016;22:277-283. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26343949.

276. Gattillo S, Marktel S, Rizzo L, et al. Plerixafor on demand in ten healthy family donors as a rescue strategy to achieve an adequate graft for stem cell transplantation. Transfusion 2015;55:1993-2000. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25721167.

277. Schriber J, Fauble V, Sproat LO, Briggs A. Plerixafor 'just in time' for stem cell mobilization in a normal donor. Bone Marrow Transplant 2011;46:1026-1027. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20921944.

278. Schroeder MA, Rettig MP, Lopez S, et al. Mobilization of allogeneic peripheral blood stem cell donors with intravenous plerixafor mobilizes a unique graft. Blood 2017;129:2680-2692. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28292947.

279. Stroncek DF, Matthews CL, Follmann D, Leitman SF. Kinetics of G-CSF-induced granulocyte mobilization in healthy subjects: effects of route of administration and addition of dexamethasone. Transfusion 2002;42:597-602. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12084168.

280. Linch DC, Milligan DW, Winfield DA, et al. G-CSF after peripheral blood stem cell transplantation in lymphoma patients significantly accelerated neutrophil recovery and shortened time in hospital: results of a randomized BNLI trial. Br J Haematol 1997;99:933-938. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9432046.

281. Klumpp TR, Mangan KF, Goldberg SL, et al. Granulocyte colony-stimulating factor accelerates neutrophil engraftment following peripheral-blood stem-cell transplantation: a prospective, randomized trial. J Clin Oncol 1995;13:1323-1327. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7538555.

282. Lee SM, Radford JA, Dobson L, et al. Recombinant human granulocyte colony-stimulating factor (filgrastim) following high-dose chemotherapy and peripheral blood progenitor cell rescue in high-grade non-Hodgkin's lymphoma: clinical benefits at no extra cost. Br J Cancer 1998;77:1294-1299. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9579836.

283. Spitzer G, Adkins DR, Spencer V, et al. Randomized study of growth factors post-peripheral-blood stem-cell transplant: neutrophil recovery is improved with modest clinical benefit. J Clin Oncol 1994;12:661-670. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7512124.

284. Kawano Y, Takaue Y, Mimaya J, et al. Marginal benefit/disadvantage of granulocyte colony-stimulating factor therapy after autologous blood stem cell transplantation in children: results of a prospective randomized trial. The Japanese Cooperative Study Group of PBSCT. Blood 1998;92:4040-4046. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9834207.

285. Trivedi M, Martinez S, Corringham S, et al. Review and revision of clinical practice of using G-CSF after autologous and allogeneic hematopoietic stem cell transplantation at UCSD. J Oncol Pharm Pract 2011;17:85-90. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20015929.

286. Sebban C, Lefranc A, Perrier L, et al. A randomised phase II study of the efficacy, safety and cost-effectiveness of pegfilgrastim and filgrastim after autologous stem cell transplant for lymphoma and myeloma (PALM study). Eur J Cancer 2012;48:713-720. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22248711.

287. Ziakas PD, Kourbeti IS. Pegfilgrastim vs. filgrastim for supportive care after autologous stem cell transplantation: can we decide? Clin Transplant 2012;26:16-22. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22035044.

288. Castagna L, Bramanti S, Levis A, et al. Pegfilgrastim versus filgrastim after high-dose chemotherapy and autologous peripheral blood stem cell support. Ann Oncol 2010;21:1482-1485. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20007996.

289. Wannesson L, Luthi F, Zucca E, et al. Pegfilgrastim to accelerate neutrophil engraftment following peripheral blood stem cell transplant and reduce the duration of neutropenia, hospitalization, and use of intravenous antibiotics: a phase II study in multiple myeloma and lymphoma and comparison with filgrastim-treated matched controls. Leuk Lymphoma 2011;52:436-443. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21323524.

290. Samaras P, Blickenstorfer M, Siciliano RD, et al. Pegfilgrastim reduces the length of hospitalization and the time to engraftment in multiple myeloma patients treated with melphalan 200 and auto-SCT compared with filgrastim. Ann Hematol 2011;90:89-94. Available at: https://www.ncbi.nlm.nih.gov/pubmed/20706722.

291. Samaras P, Buset EM, Siciliano RD, et al. Equivalence of pegfilgrastim and filgrastim in lymphoma patients treated with BEAM followed by autologous stem cell transplantation. Oncology 2010;79:93-97. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21079406.

292. Rifkin R, Spitzer G, Orloff G, et al. Pegfilgrastim appears equivalent to daily dosing of filgrastim to treat neutropenia after autologous peripheral blood stem cell transplantation in patients with non-Hodgkin lymphoma. Clin Lymphoma Myeloma Leuk 2010;10:186-191. Available at: https://www.ncbi.nlm.nih.gov/pubmed/20511163.

293. Gerds A, Fox-Geiman M, Dawravoo K, et al. Randomized phase III trial of pegfilgrastim versus filgrastim after autologus peripheral blood stem cell transplantation. Biol Blood Marrow Transplant 2010;16:678-685. Available at: https://www.ncbi.nlm.nih.gov/pubmed/20045479.

294. Battiwalla M, McCarthy PL. Filgrastim support in allogeneic HSCT for myeloid malignancies: a review of the role of G-CSF and the implications for current practice. Bone Marrow Transplant 2009;43:351-356. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19182834.

295. Delaney C, Ratajczak MZ, Laughlin MJ. Strategies to enhance umbilical cord blood stem cell engraftment in adult patients. Expert Rev Hematol 2010;3:273-283. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20835351.

296. Dale DC, Bonilla MA, Davis MW, et al. A randomized controlled phase III trial of recombinant human granulocyte colony-stimulating factor (filgrastim) for treatment of severe chronic neutropenia. Blood 1993;81:2496-2502. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8490166.

297. Gilreath JA, Stenehjem DD, Rodgers GM. Diagnosis and treatment of cancer-related anemia. Am J Hematol 2014;89:203-212. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24532336.

298. Schwartz RN. Anemia in patients with cancer: incidence, causes, impact, management, and use of treatment guidelines and protocols. Am J Health Syst Pharm 2007;64:S5-13. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17244886.

299. Steensma DP. Is anemia of cancer different from chemotherapy-induced anemia? J Clin Oncol 2008;26:1022-1024. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18227523.

300. Wilson J, Yao GL, Raftery J, et al. A systematic review and economic evaluation of epoetin alpha, epoetin beta and darbepoetin alpha in anaemia associated with cancer, especially that attributable to cancer treatment. Health Technol Assess 2007;11:1-202, iii-iv. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17408534.

301. Moullet I, Salles G, Ketterer N, et al. Frequency and significance of anemia in non-Hodgkin's lymphoma patients. Ann Oncol 1998;9:1109-1115. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9834824.

302. Ludwig H, Van Belle S, Barrett-Lee P, et al. The European Cancer Anaemia Survey (ECAS): a large, multinational, prospective survey defining the prevalence, incidence, and treatment of anaemia in cancer patients. Eur J Cancer 2004;40:2293-2306. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15454256.

303. Groopman JE, Itri LM. Chemotherapy-induced anemia in adults: incidence and treatment. J Natl Cancer Inst 1999;91:1616-1634. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10511589.

304. Jefferies S, Rajan B, Ashley S, et al. Haematological toxicity of cranio-spinal irradiation. Radiother Oncol 1998;48:23-27. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9756168.

305. May MB, Glode A. Blinatumomab: A novel, bispecific, T-cell engaging antibody. Am J Health Syst Pharm 2016;73:e6-e13. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26683683.

306. Weber JS, Yang JC, Atkins MB, Disis ML. Toxicities of immunotherapy for the practitioner. J Clin Oncol 2015;33:2092-2099. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25918278.

307. Petrelli F, Ardito R, Borgonovo K, et al. Haematological toxicities with immunotherapy in patients with cancer: a systematic review and meta-analysis. Eur J Cancer 2018;103:7-16. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30196108.

308. Delanoy N, Michot JM, Comont T, et al. Haematological immune-related adverse events induced by anti-PD-1 or anti-PD-L1 immunotherapy: a descriptive observational study. Lancet Haematol 2019;6:e48-e57. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30528137.

309. Murphy WG. The sex difference in haemoglobin levels in adults - mechanisms, causes, and consequences. Blood Rev 2014;28:41-47. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24491804.

310. Glaus A, Crow R, Hammond S. A qualitative study to explore the concept of fatigue/tiredness in cancer patients and in healthy individuals. Support Care Cancer 1996;4:82-96. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8673356.

311. Hesdorffer CS, Longo DL. Drug-induced megaloblastic anemia. N Engl J Med 2015;373:1649-1658. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26488695.

312. Ganz T. Anemia of inflammation. N Engl J Med 2019;381:1148-1157. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31532961.

313. Miller Y, Bachowski G, Benjamin R, et al. Practice guidelines for blood transfusion: a compilation from recent peer-reviewed literature. American Red Cross 2007;2nd ed. Available at: http://www.sld.cu/galerias/pdf/sitios/anestesiologia/practical_guidelines_blood_transfusion.pdf.

314. Wiesen AR, Hospenthal DR, Byrd JC, et al. Equilibration of hemoglobin concentration after transfusion in medical inpatients not actively bleeding. Ann Intern Med 1994;121:278-230. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8037410.

315. Carson JL, Carless PA, Hebert PC. Transfusion thresholds and other strategies for guiding allogeneic red blood cell transfusion. Cochrane Database Syst Rev 2012;4:CD002042. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22513904.

316. Blajchman MA, Vamvakas EC. The continuing risk of transfusion-transmitted infections. N Engl J Med 2006;355:1303-1305. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17005947.

317. King KE, Shirey RS, Thoman SK, et al. Universal leukoreduction decreases the incidence of febrile nonhemolytic transfusion reactions to RBCs. Transfusion 2004;44:25-29. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14692963.

318. Yazer MH, Podlosky L, Clarke G, Nahirniak SM. The effect of prestorage WBC reduction on the rates of febrile nonhemolytic transfusion reactions to platelet concentrates and RBC. Transfusion 2004;44:10-15. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14692961.

319. Carson JL, Guyatt G, Heddle NM, et al. Clinical Practice Guidelines from the AABB: Red blood cell transfusion thresholds and storage. JAMA 2016;316:2025-2035. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27732721.

320. Geiger TL, Howard SC. Acetaminophen and diphenhydramine premedication for allergic and febrile nonhemolytic transfusion reactions: good prophylaxis or bad practice? Transfus Med Rev 2007;21:1-12. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17174216.

321. Marti-Carvajal AJ, Sola I, Gonzalez LE, et al. Pharmacological interventions for the prevention of allergic and febrile non-haemolytic transfusion reactions. Cochrane Database Syst Rev 2010:CD007539. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20556779.

322. Tobian AA, Heddle NM, Wiegmann TL, Carson JL. Red blood cell transfusion: 2016 clinical practice guidelines from AABB. Transfusion 2016;56:2627-2630. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27739152.

323. Scharman CD, Burger D, Shatzel JJ, et al. Treatment of individuals who cannot receive blood products for religious or other reasons. Am J Hematol 2017;92:1370-1381. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28815690.

324. Resar LM, Frank SM. Bloodless medicine: what to do when you can't transfuse. Hematology Am Soc Hematol Educ Program 2014;2014:553-558. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25696910.

325. Resar LM, Wick EC, Almasri TN, et al. Bloodless medicine: current strategies and emerging treatment paradigms. Transfusion 2016;56:2637-2647. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27473810.

326. Panico ML, Jenq GY, Brewster UC. When a patient refuses life-saving care: issues raised when treating a Jehovah's Witness. Am J Kidney Dis 2011;58:647-653. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21862193.

327. Joseph NS, Kaufman JL, Boise LH, et al. Safety and survival outcomes for bloodless transplantation in patients with myeloma. Cancer 2019;125:185-193. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30480777.

328. McConachie SM, Almadrahi Z, Wahby KA, Wilhelm SM. Pharmacotherapy in acutely anemic Jehovah's Witnesses: an evidence-based review. Ann Pharmacother 2018;52:910-919. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29592539.

329. Posluszny JA, Jr., Napolitano LM. How do we treat life-threatening anemia in a Jehovah's Witness patient? Transfusion 2014;54:3026-3034. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25330835.

330. McConachie S, Wahby K, Almadrahi Z, Wilhelm S. Early experiences eith PEGylated carboxyhemoglobin bovine in anemic Jehovah's Witnesses: a case series and review of the literature. J Pharm Pract 2018. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30518297.

331. Chen JY, Scerbo M, Kramer G. A review of blood substitutes: examining the history, clinical trial results, and ethics of hemoglobin-based oxygen carriers. Clinics (Sao Paulo) 2009;64:803-813. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19690667.

332. Ball AM, Winstead PS. Recombinant human erythropoietin therapy in critically ill Jehovah's Witnesses. Pharmacotherapy 2008;28:1383-1390. Available at: https://www.ncbi.nlm.nih.gov/pubmed/18956998.

333. Agapidou A, Vakalopoulou S, Papadopoulou T, et al. Successful treatment of severe anemia using erythropoietin in a Jehovah Witness with non-Hodgkin lymphoma. Hematol Rep 2014;6:5600. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25568760.

334. Arora N, Gupta A, Li HC, Sadeghi N. Use of platelet and erythroid growth factors during induction chemotherapy for acute lymphoblastic leukaemia in a Jehovah's Witness. BMJ Case Rep 2018;11. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30567199.

335. de Araujo Azi LM, Lopes FM, Garcia LV. Postoperative management of severe acute anemia in a Jehovah's Witness. Transfusion 2014;54:1153-1157. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24117834.

336. Tasch J, Gonzalez-Zayaz P. Ceftriaxone-induced hemolytic anemia in a Jehovah's Witness. Am J Case Rep 2017;18:431-435. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28428532.

337. Chojnowski K, Janus A, Blizniewska K, et al. Long-lasting extreme anemia during the therapy of acute lymphoblastic leukemia in a Jehovah's Witness patient. Transfusion 2016;56:2438-2442. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27385671.

338. Rebel A, Beck A, Efron P, et al. Successful rescue therapy for severe acute anemia: managing the critically ill Jehovah's Witness. Am Surg 2015;81:E263-265. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26031262.

339. Perol L, Grignano E, Contejean A, et al. High-dose chemotherapy without transfusion for Philadelphia chromosome negative B-cell acute lymphoblastic leukemia in two Jehovah's Witnesses patients: a feasible option in the age of hematopoietic growth factors. Leuk Lymphoma 2019:1-4. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30773115.

340. Dicpinigaitis PV. Optimization of tissue oxygenation in critically ill Jehovah's Witness patients. Am J Med 2010;123:e17; author reply e19. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20670703.

341. Weiskopf RB. Hemoglobin-based oxygen carriers: compassionate use and compassionate clinical trials. Anesth Analg 2010;110:659-662. Available at: https://www.ncbi.nlm.nih.gov/pubmed/20185643.

342. Natanson C, Kern SJ, Lurie P, et al. Cell-free hemoglobin-based blood substitutes and risk of myocardial infarction and death: a meta-analysis. JAMA 2008;299:2304-2312. Available at: https://www.ncbi.nlm.nih.gov/pubmed/18443023.

343. Lundy JB, Lewis CJ, Cancio LC, Cap AP. Experience with the use of Hemopure in the care of a massively burned adult. Int J Burns Trauma 2014;4:45-48. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24624314.

344. Fitzgerald MC, Chan JY, Ross AW, et al. A synthetic haemoglobin-based oxygen carrier and the reversal of cardiac hypoxia secondary to severe anaemia following trauma. Med J Aust 2011;194:471-473. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21534906.

345. Gannon CJ, Napolitano LM. Severe anemia after gastrointestinal hemorrhage in a Jehovah's Witness: new treatment strategies. Crit Care Med 2002;30:1893-1895. Available at: https://www.ncbi.nlm.nih.gov/pubmed/12163811.

346. Jordan SD, Alexander E. Bovine hemoglobin: a nontraditional approach to the management of acute anemia in a Jehovah's Witness patient with autoimmune hemolytic anemia. J Pharm Pract 2013;26:257-260. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22869910.

347. Donahue LL, Shapira I, Shander A, et al. Management of acute anemia in a Jehovah's Witness patient with acute lymphoblastic leukemia with polymerized bovine hemoglobin-based oxygen carrier: a case report and review of literature. Transfusion 2010;50:1561-1567. Available at: https://www.ncbi.nlm.nih.gov/pubmed/20456679.

348. Mackenzie CF, Moon-Massat PF, Shander A, et al. When blood is not an option: factors affecting survival after the use of a hemoglobin-based oxygen carrier in 54 patients with life-threatening anemia. Anesth Analg 2010;110:685-693. Available at: https://www.ncbi.nlm.nih.gov/pubmed/20042443.

349. Ludwig H, Aapro M, Bokemeyer C, et al. Treatment patterns and outcomes in the management of anaemia in cancer patients in Europe: findings from the Anaemia Cancer Treatment (ACT) study. Eur J Cancer 2009;45:1603-1615. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19278851.

350. Littlewood TJ, Bajetta E, Nortier JW, et al. Effects of epoetin alfa on hematologic parameters and quality of life in cancer patients receiving nonplatinum chemotherapy: results of a randomized, double-blind, placebo-controlled trial. J Clin Oncol 2001;19:2865-2874. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11387359.

351. Vansteenkiste J, Pirker R, Massuti B, et al. Double-blind, placebo-controlled, randomized phase III trial of darbepoetin alfa in lung cancer patients receiving chemotherapy. J Natl Cancer Inst 2002;94:1211-1220. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12189224.

352. Tonia T, Mettler A, Robert N, et al. Erythropoietin or darbepoetin for patients with cancer. Cochrane Database Syst Rev 2012;12:CD003407. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23235597.

353. Pirker R, Hedenus M, Vansteenkiste J, et al. Effectiveness of darbepoetin alfa for chemotherapy-induced anemia when initiated at hemoglobin </=10 g/dL. Clin Ther 2016;38:122-135. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26730453.

354. Untch M, von Minckwitz G, Konecny GE, et al. PREPARE trial: a randomized phase III trial comparing preoperative, dose-dense, dose-intensified chemotherapy with epirubicin, paclitaxel, and CMF versus a standard-dosed epirubicin-cyclophosphamide followed by paclitaxel with or without darbepoetin alfa in primary breast cancer--outcome on prognosis. Ann Oncol 2011;22:1999-2006. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21382868.

355. Hedenus M, Adriansson M, San Miguel J, et al. Efficacy and safety of darbepoetin alfa in anaemic patients with lymphoproliferative malignancies: a randomized, double-blind, placebo-controlled study. Br J Haematol 2003;122:394-403. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12877666.

356. Henke M, Laszig R, Rube C, et al. Erythropoietin to treat head and neck cancer patients with anaemia undergoing radiotherapy: randomised, double-blind, placebo-controlled trial. Lancet 2003;362:1255-1260. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14575968.

357. Leyland-Jones B, Semiglazov V, Pawlicki M, et al. Maintaining normal hemoglobin levels with epoetin alfa in mainly nonanemic patients with metastatic breast cancer receiving first-line chemotherapy: a survival study. J Clin Oncol 2005;23:5960-5972. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16087945.

358. Overgaard J, Hoff CM, Hansen HS, et al. DAHANCA 10 - Effect of darbepoetin alfa and radiotherapy in the treatment of squamous cell carcinoma of the head and neck. A multicenter, open-label, randomized, phase 3 trial by the Danish head and neck cancer group. Radiother Oncol 2018;127:12-19. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29523409.

359. Smith RE, Jr., Aapro MS, Ludwig H, et al. Darbepoetin alfa for the treatment of anemia in patients with active cancer not receiving chemotherapy or radiotherapy: results of a phase III, multicenter, randomized, double-blind, placebo-controlled study. J Clin Oncol 2008;26:1040-1050. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18227526.

360. Thomas G, Ali S, Hoebers FJ, et al. Phase III trial to evaluate the efficacy of maintaining hemoglobin levels above 12.0 g/dL with erythropoietin vs above 10.0 g/dL without erythropoietin in anemic patients receiving concurrent radiation and cisplatin for cervical cancer. Gynecol Oncol 2008;108:317-325. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18037478.

361. Wright JR, Ung YC, Julian JA, et al. Randomized, double-blind, placebo-controlled trial of erythropoietin in non-small-cell lung cancer with disease-related anemia. J Clin Oncol 2007;25:1027-1032. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17312332.

362. Bennett CL, Silver SM, Djulbegovic B, et al. Venous thromboembolism and mortality associated with recombinant erythropoietin and darbepoetin administration for the treatment of cancer-associated anemia. JAMA 2008;299:914-924. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18314434.

363. Bohlius J, Schmidlin K, Brillant C, et al. Recombinant human erythropoiesis-stimulating agents and mortality in patients with cancer: a meta-analysis of randomised trials. Lancet 2009;373:1532-1542. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19410717.

364. Tonelli M, Hemmelgarn B, Reiman T, et al. Benefits and harms of erythropoiesis-stimulating agents for anemia related to cancer: a meta-analysis. CMAJ 2009;180:E62-71. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19407261.

365. Grant MD, Piper M, J. B, et al. Epoetin and darbepotin for managing anemia in patients undergoing cancer treatment: Comparative effectiveness update (available at: http://www.ncbi.nlm.nih.gov/books/NBK143013/). Rockville MD: Agency for Healthcare Research and Quality; 2013.

366. Ludwig H, Crawford J, Osterborg A, et al. Pooled analysis of individual patient-level data from all randomized, double-blind, placebo-controlled trials of darbepoetin alfa in the treatment of patients with chemotherapy-induced anemia. J Clin Oncol 2009;27:2838-2847. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19380447.

367. Glaspy J, Crawford J, Vansteenkiste J, et al. Erythropoiesis-stimulating agents in oncology: a study-level meta-analysis of survival and other safety outcomes. Br J Cancer 2010;102:301-315. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20051958.

368. Engert A, Josting A, Haverkamp H, et al. Epoetin alfa in patients with advanced-stage Hodgkin's lymphoma: results of the randomized placebo-controlled GHSG HD15EPO trial. J Clin Oncol 2010;28:2239-2245. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20368566.

369. Moebus V, Jackisch C, Lueck HJ, et al. Intense dose-dense sequential chemotherapy with epirubicin, paclitaxel, and cyclophosphamide compared with conventionally scheduled chemotherapy in high-risk primary breast cancer: mature results of an AGO phase III study. J Clin Oncol 2010;28:2874-2880. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20458045.

370. Nitz U, Gluz O, Zuna I, et al. Final results from the prospective phase III WSG-ARA trial: impact of adjuvant darbepoetin alfa on event-free survival in early breast cancer. Ann Oncol 2014;25:75-80. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24356620.

371. Moebus V, Jackisch C, Schneeweiss A, et al. Adding epoetin alfa to intense dose-dense adjuvant chemotherapy for breast cancer: randomized

clinical trial. J Natl Cancer Inst 2013;105:1018-1026. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23860204.

372. Pirker R, Ramlau RA, Schuette W, et al. Safety and efficacy of darbepoetin alpha in previously untreated extensive-stage small-cell lung cancer treated with platinum plus etoposide. J Clin Oncol 2008;26:2342-2349. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18467726.

373. Grote T, Yeilding AL, Castillo R, et al. Efficacy and safety analysis of epoetin alfa in patients with small-cell lung cancer: a randomized, double-blind, placebo-controlled trial. J Clin Oncol 2005;23:9377-9386. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16361638.

374. Nagel S, Kellner O, Engel-Riedel W, et al. Addition of darbepoetin alfa to dose-dense chemotherapy: results from a randomized phase II trial in small-cell lung cancer patients receiving carboplatin plus etoposide. Clin Lung Cancer 2011;12:62-69. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21273182.

375. Heit JA, Silverstein MD, Mohr DN, et al. Risk factors for deep vein thrombosis and pulmonary embolism: a population-based case-control study. Arch Intern Med 2000;160:809-815. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10737280.

376. Khorana AA, Francis CW, Culakova E, et al. Thromboembolism is a leading cause of death in cancer patients receiving outpatient chemotherapy. J Thromb Haemost 2007;5:632-634. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17319909.

377. Levine MN, Gent M, Hirsh J, et al. The thrombogenic effect of anticancer drug therapy in women with stage II breast cancer. N Engl J Med 1988;318:404-407. Available at: http://www.ncbi.nlm.nih.gov/pubmed/3340118.

378. Saphner T, Tormey DC, Gray R. Venous and arterial thrombosis in patients who received adjuvant therapy for breast cancer. J Clin Oncol 1991;9:286-294. Available at: http://www.ncbi.nlm.nih.gov/pubmed/1988575.

379. Lyman GH, Khorana AA, Falanga A, et al. American Society of Clinical Oncology guideline: recommendations for venous thromboembolism prophylaxis and treatment in patients with cancer. J Clin Oncol 2007;25:5490-5505. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17968019.

380. Pfeffer MA, Burdmann EA, Chen CY, et al. A trial of darbepoetin alfa in type 2 diabetes and chronic kidney disease. N Engl J Med 2009;361:2019-2032. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19880844.

381. Seliger SL, Zhang AD, Weir MR, et al. Erythropoiesis-stimulating agents increase the risk of acute stroke in patients with chronic kidney disease. Kidney Int 2011;80:288-294. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21389972.

382. Singh AK, Szczech L, Tang KL, et al. Correction of anemia with epoetin alfa in chronic kidney disease. N Engl J Med 2006;355:2085-2098. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17108343.

383. Bennett CL, Cournoyer D, Carson KR, et al. Long-term outcome of individuals with pure red cell aplasia and antierythropoietin antibodies in patients treated with recombinant epoetin: a follow-up report from the Research on Adverse Drug Events and Reports (RADAR) Project. Blood 2005;106:3343-3347. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16099877.

384. Bennett CL, Luminari S, Nissenson AR, et al. Pure red-cell aplasia and epoetin therapy. N Engl J Med 2004;351:1403-1408. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15459301.

385. McKoy JM, Stonecash RE, Cournoyer D, et al. Epoetin-associated pure red cell aplasia: past, present, and future considerations. Transfusion 2008;48:1754-1762. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18482185.

386. Food and Drug Administration. Information on Erythropoiesis-Stimulating Agents (ESA) Epoetin alfa (marketed as Procrit, Epogen), Darbepoetin alfa (marketed as Aranesp). 2017. Available at:

https://www.fda.gov/Drugs/DrugSafety/ucm109375.htm. Accessed December 16, 2019.

387. Imai E, Yamamoto R, Suzuki H, Watanabe T. Incidence of symptomatic stroke and cancer in chronic kidney disease patients treated with epoetins. Clin Exp Nephrol 2010;14:445-452. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20589407.

388. Besarab A, Bolton WK, Browne JK, et al. The effects of normal as compared with low hematocrit values in patients with cardiac disease who are receiving hemodialysis and epoetin. N Engl J Med 1998;339:584-590. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9718377.

389. Besarab A, Goodkin DA, Nissenson AR. The normal hematocrit study--follow-up. N Engl J Med 2008;358:433-434. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18216370.

390. Bennett CL, Becker PS, Kraut EH, et al. Intersecting guidelines: administering erythropoiesis-stimulating agents to chronic kidney disease patients with cancer. Semin Dial 2009;22:1-4. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19175532.

391. Schwartzberg LS, Yee LK, Senecal FM, et al. A randomized comparison of every-2-week darbepoetin alfa and weekly epoetin alfa for the treatment of chemotherapy-induced anemia in patients with breast, lung, or gynecologic cancer. Oncologist 2004;9:696-707. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15561813.

392. Waltzman R, Croot C, Justice GR, et al. Randomized comparison of epoetin alfa (40,000 U weekly) and darbepoetin alfa (200 microg every 2 weeks) in anemic patients with cancer receiving chemotherapy. Oncologist 2005;10:642-650. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16177289.

393. Glaspy J, Bukowski R, Steinberg D, et al. Impact of therapy with epoetin alfa on clinical outcomes in patients with nonmyeloid malignancies during cancer chemotherapy in community oncology practice. Procrit Study Group. J Clin Oncol 1997;15:1218-1234. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9060566.

394. Gabrilove JL, Cleeland CS, Livingston RB, et al. Clinical evaluation of once-weekly dosing of epoetin alfa in chemotherapy patients: improvements in hemoglobin and quality of life are similar to three-times-weekly dosing. J Clin Oncol 2001;19:2875-2882. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11387360.

395. Henry DH, Gordan LN, Charu V, et al. Randomized, open-label comparison of epoetin alfa extended dosing (80,000 U Q2W) vs weekly dosing (40,000 U QW) in patients with chemotherapy-induced anemia. Curr Med Res Opin 2006;22:1403-1413. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16834839.

396. Steensma DP, Molina R, Sloan JA, et al. Phase III study of two different dosing schedules of erythropoietin in anemic patients with cancer. J Clin Oncol 2006;24:1079-1089. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16505427.

397. Canon JL, Vansteenkiste J, Bodoky G, et al. Randomized, double-blind, active-controlled trial of every-3-week darbepoetin alfa for the treatment of chemotherapy-induced anemia. J Natl Cancer Inst 2006;98:273-284. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16478746.

398. Boccia R, Malik IA, Raja V, et al. Darbepoetin alfa administered every three weeks is effective for the treatment of chemotherapy-induced anemia. Oncologist 2006;11:409-417. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16614237.

399. Auerbach M, Silberstein PT, Webb RT, et al. Darbepoetin alfa 300 or 500 mug once every 3 weeks with or without intravenous iron in patients with chemotherapy-induced anemia. Am J Hematol 2010;85:655-663. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20661916.

400. Thames WA, Smith SL, Scheifele AC, et al. Evaluation of the US Oncology Network's recommended guidelines for therapeutic substitution with darbepoetin alfa 200 microg every 2 weeks in both naive patients and patients switched from epoetin alfa. Pharmacotherapy 2004;24:313-323. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15040644.

401. Mhaskar R, Wao H, Miladinovic B, et al. The role of iron in the management of chemotherapy-induced anemia in cancer patients receiving erythropoiesis-stimulating agents. Cochrane Database Syst Rev 2016;2:CD009624. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26845108.

402. Petrelli F, Borgonovo K, Cabiddu M, et al. Addition of iron to erythropoiesis-stimulating agents in cancer patients: a meta-analysis of randomized trials. J Cancer Res Clin Oncol 2012;138:179-187. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21972052.

403. Aapro M, Osterborg A, Gascon P, et al. Prevalence and management of cancer-related anaemia, iron deficiency and the specific role of i.v. iron. Ann Oncol 2012;23:1954-1962. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22575608.

404. Collings R, Harvey LJ, Hooper L, et al. The absorption of iron from whole diets: a systematic review. Am J Clin Nutr 2013;98:65-81. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23719560.

405. Lapointe M. Iron supplementation in the intensive care unit: when, how much, and by what route? Crit Care 2004;8 Suppl 2:S37-41. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15196322.

406. Henry DH. Supplemental iron: a key to optimizing the response of cancer-related anemia to rHuEPO? Oncologist 1998;3:275-278. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10388116.

407. Weiss G, Goodnough LT. Anemia of chronic disease. N Engl J Med 2005;352:1011-1023. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15758012.

408. Silverstein SB, Gilreath JA, Rodgers GM. Intravenous iron therapy: a summary of treatment options and review of guidelines. J Pharm Pract 2008;21:431-443. Available at: http://journals.sagepub.com/doi/abs/10.1177/0897190008318916.

409. Auerbach M, Ballard H, Trout JR, et al. Intravenous iron optimizes the response to recombinant human erythropoietin in cancer patients with chemotherapy-related anemia: a multicenter, open-label, randomized trial. J Clin Oncol 2004;22:1301-1307. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15051778.

410. Bastit L, Vandebroek A, Altintas S, et al. Randomized, multicenter, controlled trial comparing the efficacy and safety of darbepoetin alpha administered every 3 weeks with or without intravenous iron in patients with chemotherapy-induced anemia. J Clin Oncol 2008;26:1611-1618. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18375890.

411. Hedenus M, Birgegard G, Nasman P, et al. Addition of intravenous iron to epoetin beta increases hemoglobin response and decreases epoetin dose requirement in anemic patients with lymphoproliferative malignancies: a randomized multicenter study. Leukemia 2007;21:627-632. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17252006.

412. Henry DH, Dahl NV, Auerbach M, et al. Intravenous ferric gluconate significantly improves response to epoetin alfa versus oral iron or no iron in anemic patients with cancer receiving chemotherapy. Oncologist 2007;12:231-242. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17296819.

413. Pedrazzoli P, Farris A, Del Prete S, et al. Randomized trial of intravenous iron supplementation in patients with chemotherapy-related anemia without iron deficiency treated with darbepoetin alpha. J Clin Oncol 2008;26:1619-1625. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18375891.

414. Mhaskar R, Djulbegovic B. Iron supplementation for chemotherapy-induced anemia in patients receiving erythropoiesis-stimulating agents. JAMA Oncol 2016;2:1499-1500. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27387766.

415. Steensma DP, Sloan JA, Dakhil SR, et al. Phase III, randomized study of the effects of parenteral iron, oral iron, or no iron supplementation on the erythropoietic response to darbepoetin alfa for patients with chemotherapy-associated anemia. J Clin Oncol 2011;29:97-105. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21098317.

416. Aapro M, Beguin Y, Birgegård G, et al. Too-low iron doses and too many dropouts in negative iron trial? J Clin Oncol 2011;29:e525-e526. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21537041.

417. Steensma DP, Sloan JA, Loprinzi CL. Reply to M. Aapro et al. J Clin Oncol 2011;29:e527-e528. Available at: http://ascopubs.org/doi/abs/10.1200/JCO.2011.35.4597.

418. Verschraegen CF, Levy T, Kudelka AP, et al. Phase II study of irinotecan in prior chemotherapy-treated squamous cell carcinoma of the cervix. J Clin Oncol 1997;15:625-631. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9053486.

419. Goldberg RM, Sargent DJ, Morton RF, et al. Randomized controlled trial of reduced-dose bolus fluorouracil plus leucovorin and irinotecan or infused fluorouracil plus leucovorin and oxaliplatin in patients with previously untreated metastatic colorectal cancer: a North American Intergroup Trial. J Clin Oncol 2006;24:3347-3353. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16849748.

420. Silverstein SB, Rodgers GM. Parenteral iron therapy options. Am J Hematol 2004;76:74-78. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15114602.

421. Chertow GM, Mason PD, Vaage-Nilsen O, Ahlmen J. Update on adverse drug events associated with parenteral iron. Nephrol Dial Transplant 2006;21:378-382. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16286429.

422. Auerbach M, Ballard H, Glaspy J. Clinical update: intravenous iron for anaemia. Lancet 2007;369:1502-1504. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17482969.

423. Perez-Lopez O, Martin-Sanchez J, Parody-Porras R, et al. Lenograstim compared to filgrastim for the mobilization of hematopoietic stem cells in healthy donors. Transfusion 2013;53:3240-3242. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23489237.

424. Athibovonsuk P, Manchana T, Sirisabya N. Prevention of blood transfusion with intravenous iron in gynecologic cancer patients receiving platinum-based chemotherapy. Gynecol Oncol 2013;131:679-682. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24099839.

425. Steinmetz T, Tschechne B, Harlin O, et al. Clinical experience with ferric carboxymaltose in the treatment of cancer- and chemotherapy-associated anaemia. Ann Oncol 2013;24:475-482. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23071262.

426. Toledano A, Luporsi E, Morere JF, et al. Clinical use of ferric carboxymaltose in patients with solid tumours or haematological malignancies in France. Support Care Cancer 2016;24:67-75. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25921449.

427. Verhaeghe L, Bruyneel L, Stragier E, et al. The effectiveness of intravenous iron for iron deficiency anemia in gastrointestinal cancer patients: a retrospective study. Ann Gastroenterol 2017;30:654-663. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29118560.

428. Keeler BD, Simpson JA, Ng O, et al. Randomized clinical trial of preoperative oral versus intravenous iron in anaemic patients with colorectal cancer. Br J Surg 2017;104:214-221. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28092401.

429. Keeler BD, Dickson EA, Simpson JA, et al. The impact of pre-operative intravenous iron on quality of life after colorectal cancer surgery: outcomes from the intravenous iron in colorectal cancer-associated anaemia (IVICA) trial. Anaesthesia 2019;74:714-725. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30963552.

430. Calleja JL, Delgado S, del Val A, et al. Ferric carboxymaltose reduces transfusions and hospital stay in patients with colon cancer and anemia. Int J Colorectal Dis 2016;31:543-551. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26694926.

431. Klein K, Asaad S, Econs M, Rubin JE. Severe FGF23-based hypophosphataemic osteomalacia due to ferric carboxymaltose

administration. BMJ Case Rep 2018;2018. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29298794.

432. Schaefer B, Wurtinger P, Finkenstedt A, et al. Choice of high-dose intravenous iron preparation determines hypophosphatemia risk. PLoS One 2016;11:e0167146. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27907058.

433. Zoller H, Schaefer B, Glodny B. Iron-induced hypophosphatemia: an emerging complication. Curr Opin Nephrol Hypertens 2017;26:266-275. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28399017.

434. Hardy S, Vandemergel X. Intravenous iron administration and hypophosphatemia in clinical practice. Int J Rheumatol 2015;2015. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26000018.

435. Blazevic A, Hunze J, Boots JM. Severe hypophosphataemia after intravenous iron administration. Neth J Med 2014;72:49-53. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24457442.

436. Adkinson NF, Strauss WE, Macdougall IC, et al. Comparative safety of intravenous ferumoxytol versus ferric carboxymaltose in iron deficiency anemia: a randomized trial. Am J Hematol 2018;93:683-690. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29417614.

437. Hetzel D, Strauss W, Bernard K, et al. A phase III, randomized, open-label trial of ferumoxytol compared with iron sucrose for the treatment of iron deficiency anemia in patients with a history of unsatisfactory oral iron therapy. Am J Hematol 2014;89:646-650. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24639149.

438. Vadhan-Raj S, Strauss W, Ford D, et al. Efficacy and safety of IV ferumoxytol for adults with iron deficiency anemia previously unresponsive to or unable to tolerate oral iron. Am J Hematol 2014;89:7-12. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23983177.

439. Vadhan-Raj S, Dahl NV, Bernard K, et al. Efficacy and safety of IV ferumoxytol for iron deficiency anemia in patients with cancer. J Blood Med 2017;8:199-209. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29263710.

440. Schieda N. Parenteral ferumoxytol interaction with magnetic resonance imaging: a case report, review of the literature and advisory warning. Insights Imaging 2013;4:509-512. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23756996.