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Myeloid Growth Factors

Clinical Practice Guidelines in Oncology

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Overview

Neutropenia (< 500 neutrophils/mcL or < 1000 neutrophils/mcL and a predicted decline to ≤ 500/mcL over the next 48 hours) and resulting febrile neutropenia (≥ 38.3°C orally or ≥ 38.0°C over 1 hour) can be induced by myelosuppressive chemotherapy. Febrile neutropenia (FN) in turn is a major dose-limiting toxicity of chemotherapy, often requiring prolonged hospitalization and broad-spectrum antibiotic use.[1] These can prompt dose reductions or treatment delays in subsequent chemotherapy cycles and compromise clinical outcome. Studies have shown that prophylactic use of colony-stimulating factors (CSFs) can reduce the risk, severity, and duration of FN, but its cost has prevented its routine use for all patients undergoing myelosuppressive

NCCN Clinical Practice Guidelines in Oncology for Myeloid Growth Factors

Key Words

NCCN Clinical Practice Guidelines, NCCN Guidelines, myeloid growth factors, neutropenia, fever, chemotherapy *(JNCCN* 2011;9:914–932)

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Category 1: The recommendation is based on high-level evidence (e.g., randomized controlled trials) and there is uniform NCCN consensus.

Category 2A: The recommendation is based on lower-level evidence and there is uniform NCCN consensus.

Category 2B: The recommendation is based on lower-level evidence and there is nonuniform NCCN consensus (but no major disagreement).

Category 3: The recommendation is based on any level of evidence but reflects major disagreement.

All recommendations are category 2A unless otherwise noted.

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

Please Note

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines™) are a statement of consensus of the authors regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult the NCCN Guidelines™ is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care or treatment. The National Comprehensive Cancer Network® (NCCN®) makes no representation or warranties of any kind regarding their content, use, or application and disclaims any responsibility for their applications or use in any way.

Disclosures for the NCCN Guidelines Panel for Myeloid Growth Factors

At the beginning of each NCCN Guidelines panel meeting, panel members disclosed any financial support they have received from industry. Through 2008, this information was published in an aggregate statement in *JNCCN* and online. Furthering NCCN's commitment to public transparency, this disclosure process has now been expanded by listing all potential conflicts of interest respective to each individual expert panel member.

Individual disclosures for the NCCN Guidelines for Myeloid Growth Factors panel members can be found on page 932. (The most recent version of these guidelines and accompanying disclosures, including levels of compensation, are available on the NCCN Web site at www.NCCN.org.)

These guidelines are also available on the Internet. For the latest update, visit www.NCCN.org.

chemotherapy. Selective use of CSFs in patients at increased risk for neutropenic complications may, however, enhance the cost-effectiveness.

The risk of FN is usually based on the treatment regimen and delivered dose intensity. A survey of the literature on randomized clinical trials of chemotherapy in patients with early-stage breast cancer and non-Hodgkin's lymphoma (NHL) has shown, however, that the rates of myelosuppression and delivered dose intensity are underreported.[2] When reported, the rates of myelosuppression with the same and similar regimens varied greatly, making the actual risk for neutropenic complications associated with common chemotherapy regimens difficult to determine.[2] Differences in the reported rates of neutropenic complications may relate to differences in study patient populations and the delivered dose intensity. Treatment dose intensity was reported with even less consistency, making differences in reported rates of toxicity or treatment efficacy very difficult to interpret.

A review by Dale[3] showed that 25% to 40% of treatment-naïve patients develop FN with common chemotherapy regimens. Occurrence of FN may delay subsequent chemotherapy courses or result in dose reduction that may compromise treatment outcomes. Development of FN also increases diagnostic and treatment costs and often leads to longer hospital stays. In addition, correlations have been reported between changes in neutrophil counts and quality of life, as measured by physical functioning, vitality, and mental health.[4]

Filgrastim and pegfilgrastim, both granulocyte-colony stimulating factors (G-CSFs), are currently FDA approved for use in preventing chemotherapy-

Text continues on p. 925

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EVALUATION PRIOR TO FIRST CHEMOTHERAPY CYCLE[a]

RISK ASSESSMENT FOR FEBRILE NEUTROPENIA[c]

PROPHYLACTIC USE OF CSF FOR FEBRILE NEUTROPENIA[c,f,g]

Evaluation of risk for febrile neutropenia after chemotherapy in adult patients with solid tumors and nonmyeloid malignancies[b]

- Disease
- Chemotherapy regimen[d]
  - High-dose therapy
  - Dose-dense therapy
  - Standard-dose therapy
- Patient risk factors[d]
- Treatment intent (curative vs. palliative)

	Chemotherapy Treatment Intent		
	Curative/ Adjuvant[h]	Prolong Survival/ Quality of LIfe	Symptom Management/ Quality of Life
High[e] (> 20%)	CSF (category 1 for G-CSF)[i]	CSF (category 1 for G-CSF)[i]	CSF[k]
Intermediate (10%-20%)	Consider CSF	Consider CSF[k]	Consider CSF[k]
Low (< 10%)	No CSF[j]	No CSF	No CSF

CSF = colony stimulating factors

See Evaluation Prior to Second and Subsequent Chemotherapy Cycles (facing page)

[a] These NCCN Guidelines were formulated in reference to adult patients.

[b] For use of growth factors in myelodysplastic syndromes, see the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Myelodysplastic Syndromes. For use of growth factors in acute myeloid leukemia, see the NCCN Guidelines for Acute Myeloid Leukemia. To view the most recent version of these guidelines, visit the NCCN Web site at www.NCCN.org.

[c] Febrile neutropenia is defined as single temperature: ≥ 38.3°C orally or ≥ 38.0°C over 1 h and neutropenia: < 500 neutrophils/mcL or < 1000 neutrophils/mcL and a predicted decline to ≤ 500/mcL over the next 48 h. See the NCCN Guidelines for Prevention and Treatment of Cancer-Related Infections (to view the most recent version of these guidelines, visit the NCCN Web site at www.NCCN.org).

[d] Many factors must be evaluated to determine a patient's risk categorization, including type of chemotherapy regimen (see pages 919-922) and patient risk factors (see page 923).

[e] One criterion that places a patient at high risk is a previous neutropenic complication in the immediate previous cycle with no plan to reduce dose intensity.

[f] This table applies to prophylaxis beginning with the first cycle of chemotherapy for solid tumors and nonmyeloid malignancies (see page 923).

[g] See Toxicity Risks With Growth Factors (page 924).

[h] The confounding effects of anthracycline and alkylating agent dose, radiation dose and field size, and CSF use on the slight excess risk of leukemia and MDS in patients treated with these agents and modalities are currently unquantified. The associated risk of leukemia and MDS has been suggested by epidemiologic studies. A systematic review of randomized clinical trials of patients receiving chemotherapy with or without primary G-CSF support with at least 2 years of follow-up reported increases in relative and absolute risk of AML/MDS of 1.92% and 0.41%, respectively. The relative risk and absolute risk reduction for all-cause mortality with an average follow-up of 5 years were 0.897% and 3.40%, respectively, and correlated with chemotherapy relative dose intensity with G-CSF support (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).

[i] There is category 1 evidence for G-CSF for a reduction of: risk of febrile neutropenia, hospitalization, and need for 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 further detail.)

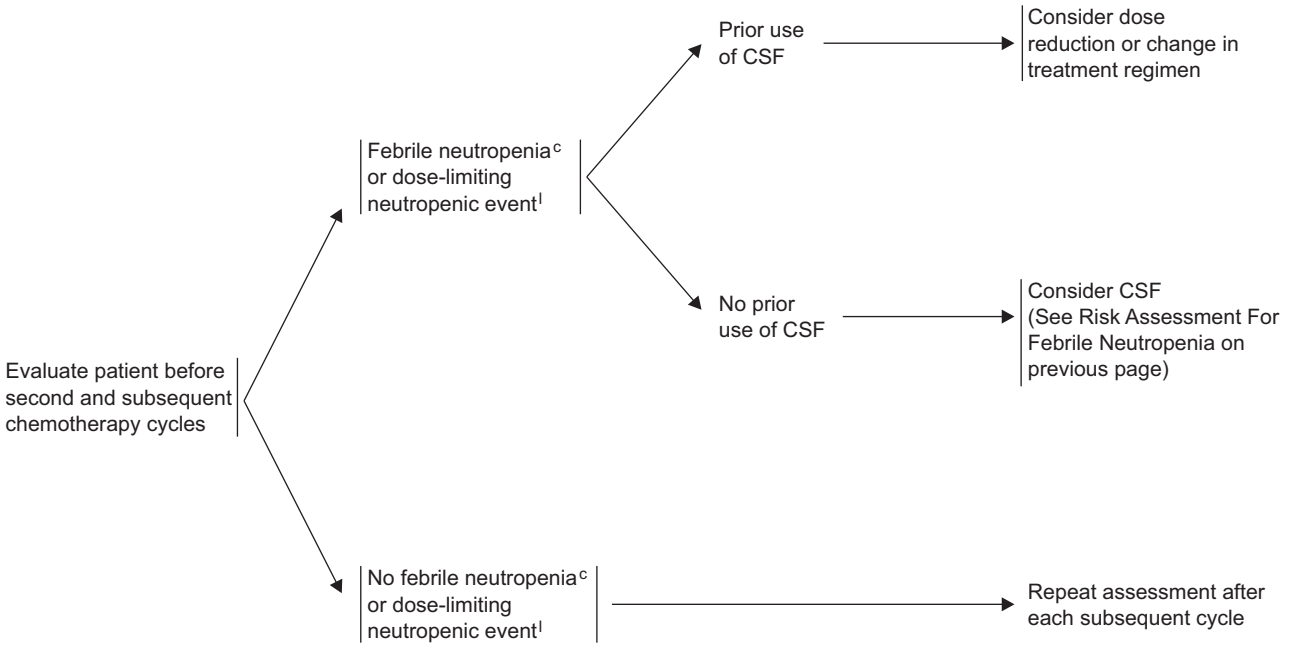
[j] Only consider CSF if patients are at significant risk for serious medical consequences of febrile neutropenia, including death.

[k] The use of CSFs in this setting is a difficult decision and requires careful discussion between the physician and the patient. If patient risk factors determine the risk is 10%-20%, CSF is reasonable. However, if the risk is from the chemotherapy regimen, other alternatives, such as the use of less myelosuppressive chemotherapy or dose reduction, if of comparable benefit, should be explored.

Myeloid Growth Factors Version 1:2011

EVALUATION PRIOR TO SECOND AND SUBSEQUENT CHEMOTHERAPY CYCLES

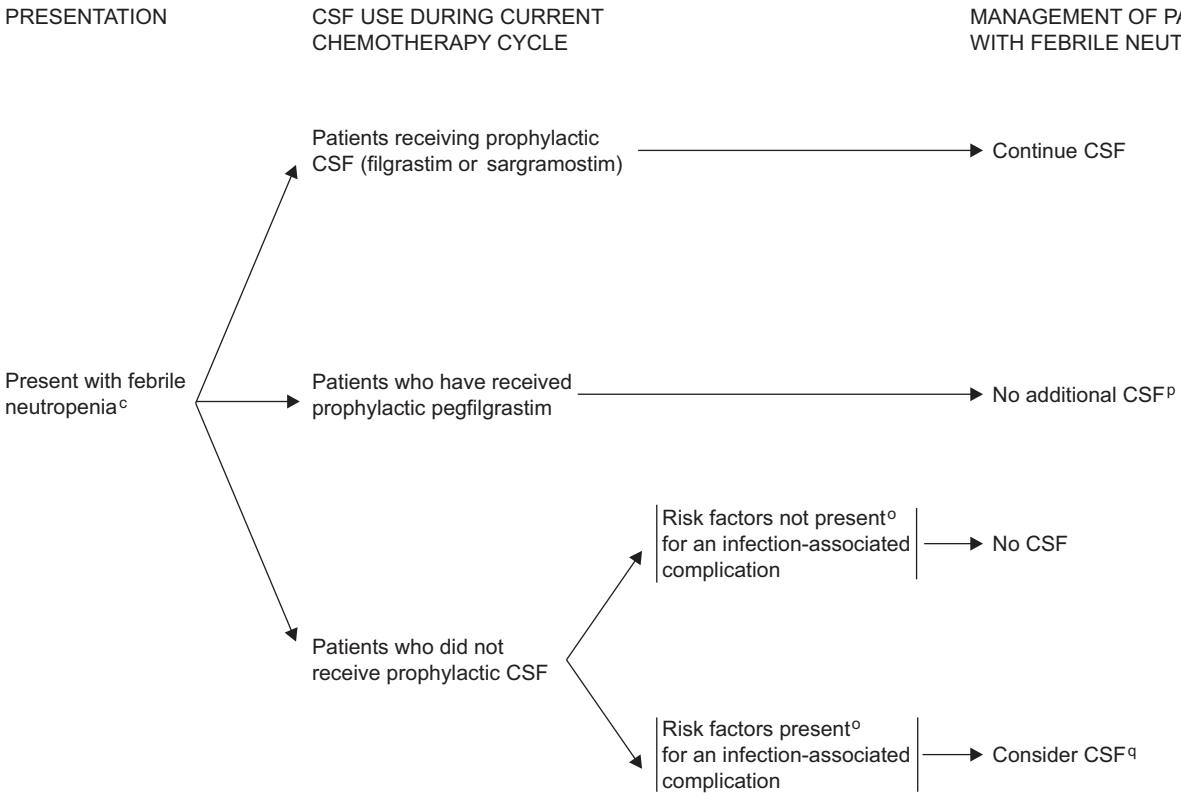
SECONDARY PROPHYLAXIS



[c]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/mcL over the next 48 h. See NCCN Guidelines for Prevention and Treatment of Cancer-Related Infections (to view the most recent version of these guidelines, visit the NCCN Web site at www.NCCN.org).

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

THERAPEUTIC USE OF CSF FOR FEBRILE NEUTROPENIA[c,m,n]



[c] Febrile neutropenia is defined as single temperature: ≥ 38.3°C orally or ≥ 38.0°C over 1 h; neutropenia: < 500 neutrophils/mcL or < 1000 neutrophils/mcL and a predicted decline to ≤ 500/mcL over the next 48 h. See the NCCN Guidelines for Prevention and Treatment of Cancer-Related Infections (to view the most recent version of these guidelines, visit the NCCN Web site at www.NCCN.org).

[m] For antibiotic therapy recommendations for fever and neutropenia, see the NCCN Guidelines for Prevention and Treatment of Cancer-Related Infections (to view the most recent version of these guidelines, visit the NCCN Web site at www.NCCN.org).

[n] The decision to use CSF in the therapeutic setting is controversial. See discussion for further detail.

[o] See Patient Risk Factors for Poor Clinical Outcomes or for Developing Infection-Associated Complications (page 924).

[p] No studies 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 CSF will not be beneficial.

[q] See discussion for further detail. No data are available on pegfilgrastim in the therapeutic setting. Either filgrastim or sargramostim should be used with initial dosing, as outlined in Myeloid Growth Factors for Prophylaxis and Treatment of Febrile Neutropenia and Maintenance of Scheduled Dose Delivery (page 923) and discontinued at time of neutrophil recovery.

Myeloid Growth Factors Version 1:2011

Examples of Disease Settings and Chemotherapy Regimens with a High Risk of Febrile Neutropenia (> 20%)

- *This list is not comprehensive;* other agents/regimens have a high risk for development of febrile neutropenia.
- The exact risk includes agent, dose, and treatment setting (i.e., treatment-naive vs. heavily pretreated patients; see page 916).
- The type of chemotherapy regimen is only one component of the risk assessment (See Patient Risk Factors for Developing Febrile Neutropenia, page 923)
- Pegfilgrastim has not been documented to have benefit in regimens given for < 2 weeks.
- 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.

Bladder Cancer
- MVAC (methotrexate, vinblastine, doxorubicin, cisplatin) (neoadjuvant, adjuvant, metastatic)[1]

Breast Cancer
- Docetaxel + trastuzumab (metastatic or relapsed)[2]
- Dose dense AC→T* (doxorubicin, cyclophosphamide, paclitaxel) (adjuvant)[3]
- AT (doxorubicin, paclitaxel) (metastatic or relapsed)[4]
- AT (doxorubicin, docetaxel) (metastatic or relapsed)[5]
- TAC (docetaxel, doxorubicin, cyclophosphamide) (adjuvant)[6]

Esophageal and Gastric Cancer
- Docetaxel/cisplatin/fluorouracil[7]

Hodgkin Lymphoma
- BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone)[8]

Kidney Cancer
- Doxorubicin/gemcitabine[9]

Non-Hodgkin's Lymphomas
- CFAR (cyclophosphamide, fludarabine, alemtuzumab, rituximab) (CLL with del(17p), relapsed/refractory)[10,11]
- ICE (ifosfamide, carboplatin, etoposide) (diffuse large B-cell lymphoma, peripheral T-cell lymphoma, second-line, salvage)[12]
- RICE* (rituximab, ifosfamide, carboplatin, etoposide)[13]
- CHOP-14* (cyclophosphamide, doxorubicin, vincristine, prednisone)[14]
- MINE (mesna, ifosfamide, novantrone, etoposide) (diffuse large B-cell lymphoma, peripheral T-cell lymphoma, second-line, refractory)[15]
- DHAP (dexamethasone, cisplatin, cytarabine) (peripheral T-cell lymphoma, diffuse large B-cell lymphoma, second-line)[16]
- ESHAP (etoposide, methylprednisolone, cisplatin, cytarabine) (diffuse large B-cell lymphoma, peripheral T-cell lymphoma, second-line, recurrent)[17]
- HyperCVAD + rituximab (cyclophosphamide, vincristine, doxorubicin, dexamethasone + rituximab)[18,19]

Melanoma
- Dacarbazine-based combination (dacarbazine, cisplatin, vinblastine) (advanced, metastatic, or recurrent)[20]
- Dacarbazine-based combination with IL-2, interferon-alfa (dacarbazine, cisplatin, vinblastine, IL-2, interferon-alfa) (advanced, metastatic, or recurrent)[20]

Multiple Myeloma
- Modified HyperCVAD[21]

Myelodysplastic Syndromes
- Antithymocyte globulin, rabbit/cyclosporine[22]
- Decitabine[23]

Ovarian Cancer
- Topotecan[24]
- Paclitaxel[25]
- Docetaxel[26]

Sarcoma
- MAID (mesna, doxorubicin, ifosfamide, dacarbazine)[27]
- Doxorubicin[28]

Small Cell Lung Cancer
- Topotecan[29]

Testicular Cancer
- VeIP (vinblastine, ifosfamide, cisplatin)[30]
- VIP (etoposide, ifosfamide, cisplatin)
- BEP (bleomycin, etoposide, cisplatin)
- TIP (paclitaxel, ifosfamide, cisplatin)[31]

*In general, dose-dense regimens require growth factor support for chemotherapy administration.

See Disease Settings and Chemotherapy Regimens with an Intermediate Risk of Febrile Neutropenia (page 920)

See Chemotherapy Regimen References (pages 921 and 922)

Examples of Disease Settings and Chemotherapy Regimens with an Intermediate Risk of Febrile Neutropenia (10%-20%)

- *This list is not comprehensive;* there are other agents/regimens that have an intermediate risk for development of febrile neutropenia.
- The exact risk includes agent, dose, and treatment setting (i.e., treatment naive vs. heavily pretreated patients; see page 916).
- The type of chemotherapy regimen is only one component of the risk assessment. (See Patient Risk Factors for Developing Febrile Neutropenia, page 923)
- Pegfilgrastim has not been documented to have benefit in regimens given for < 2 weeks.
- 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.

Occult Primary-Adenocarcinoma
- Gemcitabine, docetaxel[32]

Breast Cancer
- Docetaxel every 21 days [33]
- Epirubicin (adjuvant)[34]
- Epirubicin + sequential cyclophosphamide + methotrexate + 5-fluorouracil (adjuvant)[34]
- CMF classic (cyclophosphamide, methotrexate, fluorouracil) (adjuvant)[34]
- AC (doxorubicin, cyclophosphamide)+ sequential docetaxel (adjuvant) (taxane portion only)[35]
- AC + sequential docetaxel + trastuzumab (adjuvant)[36]
- FEC (fluorouracil, epirubicin, cyclophosphamide) + sequential docetaxel [37]
- Paclitaxel every 21 days (metastatic or relapsed)[38]
- Vinblastine (metastatic or relapsed)[39]

Cervical Cancer
- Cisplatin + topotecan (recurrent or metastatic)[40]
- Topotecan (recurrent or metastatic)[41]
- Irinotecan (recurrent or metastatic)[42]

Colorectal Cancer
- FOLFOX (fluorouracil, leucovorin, oxaliplatin)[43]

Esophageal and Gastric Cancer
- Irinotecan/cisplatin[44]
- Epirubicin/cisplatin/5-fluorouracil[45]
- Epirubicin/cisplatin/capecitabine[45]

Hodgkin Lymphoma
- ABVD* (doxorubicin, bleomycin, vinblastine, dacarbazine)[46]
- Stanford V* (mechlorethamine, doxorubicin, vinblastine, bleomycin, etoposide, prednisone)[47]

Non-Hodgkin's Lymphomas
- EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin) (AIDS-related NHL, Burkitt's lymphoma, recurrent)[48]
- EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin) + IT chemotherapy (AIDS-related NHL, diffuse large B-cell lymphoma, recurrent)[48]
- ACOD (modified CHOP-doxorubicin, cyclophosphamide, vincristine, prednisone)[49]
- GDP (gemcitabine, dexamethasone, cisplatin) (peripheral T-cell lymphoma, diffuse large B-cell lymphoma, second-line)[50]
- GDP (gemcitabine, dexamethasone, cisplatin) + rituximab (diffuse large B-cell lymphoma, second-line)[50]
- FM (fludarabine, mitoxantrone)[51]
- CHOP + rituximab (cyclophosphamide, doxorubicin, vincristine, prednisone, rituximab)[52,53] including regimens with pegylated liposomal doxorubicin[54,55] or mitoxantrone[56] substituted for doxorubicin

Non-Small Cell Lung Cancer
- Cisplatin/paclitaxel (adjuvant, advanced/metastatic)[57]
- Cisplatin/vinorelbine (adjuvant, advanced/metastatic)[58]
- Cisplatin/docetaxel (adjuvant, advanced/metastatic)[57,59]
- Cisplatin/irinotecan (advanced/metastatic)[60]
- Cisplatin/etoposide (adjuvant, advanced/metastatic)[61]
- Carboplatin/paclitaxel (adjuvant, advanced/metastatic)[60]
- Docetaxel (advanced/metastatic)[59]

Ovarian Cancer
- Carboplatin/docetaxel[62]

Prostate†
- Cabazitaxel[63]

Small Cell Lung Cancer
- Etoposide/carboplatin[64]

Testicular Cancer
- Etoposide/cisplatin[65]

Uterine Cancer
- Docetaxel (uterine sarcoma, advanced or metastatic)[66]

* One retrospective review suggests pulmonary toxicity may be increased using G-CSF in bleomycin-containing regimens. (See discussion for further detail.)

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

See Disease Settings and Chemotherapy Regimens with a High Risk of Febrile Neutropenia (page 919)

See Chemotherapy Regimen References (pages 921 and 922)

CHEMOTHERAPY REGIMEN REFERENCES

[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 20924. J Clin Oncol 2001;19:2638-2646.
[2]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.
[3]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.
[4]Gianni L, Munzone E, Capri G, et al. Paclitaxel by 3-hour infusion in combination with bolus doxorubicin in women with untreated metastatic breast cancer: high antitumor efficacy and cardiac effects in a dose-finding and sequence-finding study. J Clin Oncol 1995;13:2688-2699.
[5]Nabholtz JM, Falkson C, Campos D, et al. Docetaxel and doxorubicin compared with doxorubicin and cyclophosphamide as first-line chemotherapy for metastatic breast cancer: results of a randomized, multicenter, phase III trial. J Clin Oncol 2003;21:968-975.
[6]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]. J Clin Oncol 2004;22(Suppl 1): 22: Abstract 620.
[7]Van Custem E, Moiseyenko VM, Tjulandin S, et al. Phase III study of docetaxel and cisplatin plus fluorouracil compared with cisplatin and fluorouracil as first-line therapy for advanced gastric cancer: a report of the V325 Study Group. J Clin Oncol 2006;24:4991-4997.
[8]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.
[9]Nanus DM, Garino A, Milowsky MI, et al. Active chemotherapy for sarcomatoid and rapidly progressing renal cell carcinoma. Cancer 2004;101:1545-1551.
[10]Wierda W, Faderl S, O'Brien S, et al. Combined cyclophosphamide, fludarabine, alemtuzumab, and rituximab (CFAR) is active for relapsed and refractory patients with CLL [abstract]. Blood 2004;104:Abstract 340.
[11]Wierda W, O'Brien S, Ferrajoli A, et al. Combined cyclophosphamide, fludarabine, alemtuzumab, and rituximab (CFAR), an active frontline regimen for high-risk patients with CLL [abstract]. Blood 2007;110:Abstract 628.
[12]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;17(Suppl 4):25-30.
[13]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.
[14]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.
[15]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.
[16]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.
[17]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.
[18]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.
[19]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.
[20]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.
[21]Dimopoulos MA, et al. HyperCVAD for VAD-resistant multiple myeloma. Am J Hematol 1996;52:77-81.
[22]Garg R, Faderl S, Garcia-Manero G, et al. Phase II study of rabbit anti-thymocyte globulin, cyclosporine and granulocyte colony-stimulating factor in patients with aplastic anemia and myelodysplastic syndrome. Leukemia 2009;23:1297-1302.
[23]Kantarjian H, Issa JJ, Rosenfeld CS, et al. Decitabine improves patient outcomes in myelodysplastic syndromes: result of a phase III randomized study. Cancer 2006;106:1794-1803.
[24]Spannuth WA, Leath CA III, Huh WK, et al. A phase II trial of weekly topotecan for patients with secondary platinum-resistant recurrent epithelial ovarian carcinoma following the failure of second-line therapy. Gynecol Oncol 2007;104:591-595.
[25]Trimble EL, Adams JD, Vena D, et al. Paclitaxel for platinum-refractory ovarian cancer: results from the first 1,000 patients registered to National Cancer Institute Treatment Referral Center 9103. J Clin Oncol 1993;11:2405-2410.
[26]Verschraegen CF, Sittisomwong T, Kudelka AP, et al. Docetaxel for patients with paclitaxel-resistant Mullerian carcinoma. J Clin Oncol 2000;18:2733-2739.
[27]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.
[28]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.
[29]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.
[30]Miller KD, Loehrer PJ, Gonin R, et al. Salvage chemotherapy with vinblastine, ifosfamide, and cisplatin in recurrent seminoma. J Clin Oncol 1997;15:1427-1431.
[31]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.

CHEMOTHERAPY REGIMEN REFERENCES

[32]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.
[33]Burris HA III. Single-agent docetaxel (Taxotere) in randomized phase II trials. Semin Oncol 1999;26:1-6.
[34]Poole CJ, Earl HM, Dunn JA, et al. NEAT (National Epirubicin Adjuvant Trial) and SCTBG BR9601 (Scottish Cancer Trials Breast Group) phase III adjuvant breast trials show a significant relapse-free and overall survival advantage for sequential ECMF [abstract]. Proc Am Soc Clin Oncol 2003;22:Abstract 13.
[35]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 [abstract]. Presented at the San Antonio Breast Cancer Symposium; December 8-11, 2005; San Antonio, Texas. Abstract 48.
[36]Slamon D, Leyland-Jones B, Shak S, et al. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. N Engl J Med 2001;344:783-792.
[37]Roché H, Fumoleau P, Spielmann M, et al. Sequential adjuvant epirubicin-based and docetaxel chemotherapy for node-positive breast cancer patients: the FNCLCC PACS 01 Trial. J Clin Oncol 2006;24:1-8.
[38]Seidman 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.
[39]Fraschini G, Yap HY, Hortobagui G, et al. Five-day continuous-infusion vinblastine in the treatment of breast cancer. Cancer 1985;56:225-229.
[40]Long HJ III, 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.
[41]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.
[42]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.
[43]Goldberg RM, Sargent DJ, Morton, 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.
[44]Ilson DH. A multicenter phase II trial of weekly irinotecan/cisplatin in advanced esophageal cancer. Oncology (Williston Park) 2004;18(14 Suppl 14):22-25.
[45]Cunningham D, Starling N, Rao S, et al. Capectiabine and oxaliplatin for advanced esophagogastric cancer. N Eng J Med 2008;358:36-46.
[46]Younes, A, Fayad L, Romaguera J, et al. ABVD with pegfilgrastim (Neulasta) support in newly diagnosed Hodgkin lymphoma: long-term safety and efficacy results of a phase-II study [abstract]. Blood 2005;106:Abstract 4790.
[47]Horning SJ, Hoppe RT, Breslin S, et al. Stanford V and radiotherapy for locally extensive and advanced Hodgkin's disease: mature results of a prospective clinical trial. J Clin Oncol 2002;20:630-637.
[48]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.
[49]Martinelli G, Ferrucci PF, Mingrone W, et al. ACOD, a modified CHOP regimen for elderly patients with aggressive non-Hodgkin's lymphoma. Leuk Lymphoma 2003;44:801-806.
[50]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. Cancer 2004;101:1835-1842.
[51]Dimopoulos MA, Fountzilas G, Papageorgiou E, et al. Primary treatment of low-grade non-Hodgkin's lymphoma with the combination of fludarabine and mitoxantrone: a phase II study of the Hellenic Cooperative Oncology Group. Leuk Lymphoma 2002;43:111-114.
[52]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.
[53]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.
[54]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.
[55]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.
[56]Economopoulos T, Fountzilas G, Pavlidis N, et al. Rituximab in combination with CNOP chemotherapy in patients with previously untreated indolent non-Hodgkin's lymphoma. Hematol J 2003;4:110-115.
[57]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.
[58]Pujol JL, Breton JL, 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.
[59]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.
[60]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.
[61]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.
[62]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 Natl Cancer Inst 2004;96:1682-1691.
[63]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.
[64]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.
[65]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.
[66]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.

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

Myeloid Growth Factors Version 1:2011

PATIENT RISK FACTORS FOR DEVELOPING FEBRILE NEUTROPENIA

In addition to the risk of the chemotherapy regimen and the specific malignancy being treated, these factors need to be considered when evaluating a patient's overall risk for febrile neutropenia:

- Older patient, notably patients aged 65 and older (see NCCN Guidelines for Senior Adult Oncology; to view the most recent version of these guidelines, visit the NCCN Web site at www.NCCN.org)
- Previous chemotherapy or radiation therapy
- Preexisting neutropenia or bone marrow involvement with tumor
- Preexisting conditions
  - Neutropenia
  - Infection/open wounds
  - Recent surgery
- Poor performance status
- Poor renal function
- Liver dysfunction, most notably elevated bilirubin

MYELOID GROWTH FACTORS FOR PROPHYLAXIS AND TREATMENT OF FEBRILE NEUTROPENIA AND MAINTENANCE OF SCHEDULED DOSE DELIVERY

- Filgrastim (category 1)
  - Daily dose of 5 mcg/kg (rounding to the nearest vial size by institution-defined weight limits) until postnadir ANC recovery to normal or near-normal levels by laboratory standards.
  - Start 24-72 h after completion of chemotherapy and treat through post-nadir recovery. Administration of growth factor on same day as chemotherapy is not recommended.
- Pegfilgrastim (category 1) (For prophylactic use only)
  - One dose of 6 mg per cycle of treatment.
  - Start 24-72 h after completion of chemotherapy. Administration of growth factor on same day as chemotherapy is not recommended.[1]
  - Evidence supports use for chemotherapy regimens given every 3 weeks (category 1).
  - Phase II studies demonstrate efficacy in chemotherapy regimens given every 2 weeks.
  - Data are insufficient to support dose and schedule of weekly regimens or chemotherapy schedules less than 2 weeks, and therefore these cannot be recommended.
- Sargramostim[2] (category 2B)
  - Used in clinical trials at a dose of 250 mcg/m^2/d (rounding to the nearest vial size by institution-defined weight limits).
  - Start 24-72 h after completion of chemotherapy and treat through postnadir recovery. Administration of growth factor on same day as chemotherapy is not recommended.

- Prophylactic use of CSFs in patients given concurrent chemotherapy and radiation is not recommended.
- Subcutaneous route is preferred for all 3 agents.
- No data support alternative dosing schedules in intermediate- and high-risk patients.
- The safety data appear to be similar between filgrastim and pegfilgrastim.
- Prophylactic antibiotics are not routinely recommended for standard-dose chemotherapy, see NCCN Guidelines for Prevention and Treatment of Cancer-Related Infections (to view the most recent version of these guidelines, visit the NCCN Web site at www.NCCN.org).

[1] Randomized phase II trials of pegfilgrastim administration the same day as chemotherapy versus administration the day after chemotherapy have shown an increase in febrile neutropenia and/or other adverse events. See discussion for details.

[2] There is category 1 evidence to support filgrastim or pegfilgrastim for the prevention of febrile neutropenia. There is insufficient evidence for a category 1 recommendation for sargramostim in this setting. Sargramostim is indicated for use after induction chemotherapy in older adult patients with AML. Studies are ongoing in other areas.

TOXICITY RISKS WITH GROWTH FACTORS

Filgrastim[1]
- Warnings
  - Allergic reactions
    - Skin: rash, urticaria, facial edema
    - Respiratory: wheezing, dyspnea
    - Cardiovascular: hypotension, tachycardia
  - Splenic rupture
  - Adult respiratory distress syndrome
  - Precipitate sickle cell disease crisis
  - MDS and AML (see discussion for details)
- Adverse reactions
  - Medullary bone pain (> 10%)
- Precautions
  - Cutaneous vasculitis

Pegfilgrastim[2]
- Warnings
  - Splenic rupture
  - Adult respiratory distress syndrome
  - Allergic reactions
    - Skin: rash, urticaria
    - Respiratory: anaphylaxis
  - Precipitate sickle cell disease crisis
- Adverse reactions
  - Bone pain

Sargramostim[3,4]
- Warnings
  - Fluid retention: edema, capillary leak syndrome, pleural and/or pericardial effusion
  - Respiratory symptoms: sequestration of granulocytes in pulmonary circulation dyspnea
  - Cardiovascular symptoms: occasional transient supraventricular arrhythmia. Use with caution in patients with preexisting cardiac disease
  - Renal and hepatic dysfunction: elevation of serum creatinine or bilirubin and hepatic enzymes. Monitor patients who display renal or hepatic dysfunction before initiation of treatment
- Adverse reactions with autologous bone marrow transplant or peripheral blood progenitor cell transplant
  - Asthenia, diarrhea, rash
- Adverse reactions with allogeneic bone marrow transplant or peripheral blood progenitor cell transplant
  - Abdominal pain, chest pain, diarrhea, nausea, vomiting, gastrointestinal hemorrhage, pruritus, bone pain, eye hemorrhage, hyperglycemia, hypomagnesemia, pharyngitis, insomnia, anxiety, high BUN, high cholesterol

[1] View filgrastim prescribing information.
[2] View pegfilgrastim prescribing information.
[3] View sargramostim prescribing information.
[4] Toxicity data are based primarily on studies from leukemia and transplant patients.

PATIENT RISK FACTORS FOR POOR CLINICAL OUTCOMES OR FOR DEVELOPING INFECTION-ASSOCIATED COMPLICATIONS[1,2]

Patient risk factors include:
- Sepsis syndrome
- Age > 65 years
- Severe neutropenia (absolute neutrophil count < 100/mcL)
- Neutropenia expected to last more than 10 days
- Pneumonia
- Invasive fungal infection
- Other clinically documented infections
- Hospitalization at the time of fever
- Prior episode of febrile neutropenia

[1] The decision to use or not use CSFs in the treatment of febrile neutropenia is controversial. See discussion for further detail.
[2] Smith TJ, Khatcheressian J, Lyman G, et al. 2006 update of recommendations for the use of white blood cell growth factors: an evidence-based clinical practice guideline. J Clin Oncol 2006;24:1-11.

Text continued from p. 915

induced neutropenia. In contrast, the labeled indication for sargramostim, a granulocyte-macrophage CSF (GM-CSFs), is limited to use after induction therapy for acute myeloid leukemia (AML) and in various stem cell transplantation settings. Recommendations are based on evidence derived mainly from studies on G-CSFs; head-to-head comparative studies are lacking on the clinical benefits of G-CSFs and GM-CSFs.

These NCCN Guidelines focus on the use of CSFs in the cancer setting, specifically in adult patients with solid tumors and nonmyeloid malignancies. Growth factors in the treatment of myeloid malignancies are discussed in the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Myelodysplastic Syndromes (in this issue; also available at www.NCCN.org) and the NCCN Guidelines for Acute Myeloid Leukemia (to view the most recent version of these guidelines, visit the NCCN Web site at www.NCCN.org).

Benefits and Risks of CSFs

The prophylactic use of G-CSFs has been shown to reduce the incidence, length, and severity of chemotherapy-related neutropenia in small cell lung cancer, breast cancer, sarcoma, and NHL.[5–16] G-CSFs also improved delivery of full dose intensity of chemotherapy at the planned schedule, although this has not been generally shown to lead to better response or higher overall survival.[5,7,9,12–15,17,18] However, in node-positive breast cancer[19] and aggressive lymphoma,[20] dose-dense regimens supported by G-CSFs improved disease-free and/or overall survival compared with conventional chemotherapy.

Meta-analyses have confirmed the efficacy of prophylactic CSFs in decreasing rates of infection[21,22] and risk of neutropenia.[21,22] In a meta-analysis of 17 randomized trials of prophylactic G-CSFs, including 3493 adult patients with solid tumors and lymphoma,[23] G-CSF as primary prophylaxis reduced the risk of FN (relative risk [RR], 0.54; 95% CI, 0.43–0.67; $P < .001$) and improved relative dose intensity of the chemotherapy delivered (average difference between study arms, 8.4%; $P = .001$). For the first time, this analysis also reported a substantial reduction in risk of infection-related mortality (RR, 0.55; 95% CI, 0.33–0.90; $P = .018$) and all early deaths during chemotherapy (RR, 0.60; 95% CI, 0.43–0.83; $P = .002$). The survival advantage is confirmed in a recent systematic review by Lyman et al.[24] of 25 randomized controlled trials involving more than 12,000 patients undergoing chemotherapy with or without G-CSF support. With an average follow-up of 5 years, G-CSF was associated with 0.897% and 3.40% reductions in relative and absolute risks for all-cause mortality, respectively, although this is associated with an increased risk for AML and myelodysplastic syndromes (MDS; see later discussion). The degree of benefit correlated with chemotherapy dose intensity.

Over the past decade, the costs of inpatient hospitalization have escalated, changing the risk threshold on a pure cost basis from 40% to approximately 20%.[25] Economic analyses of CSFs have yielded mixed results, depending on the context of use.[26–30] However, the policy of the panel is to primarily examine issues of therapeutic efficacy and clinical benefit, rather than cost. The indication for prophylactic CSF use depends on the risk of FN or other neutropenic events that can potentially compromise treatment.

To date, the main consistently observed toxicity associated with G-CSF therapy was mild to moderate bone pain.[31,32] This is usually effectively controlled by nonnarcotic analgesics. The meta-analysis by Kuderer et al.[23] confirmed a heightened risk of musculoskeletal pain associated with CSFs (RR, 4.03; 95% CI, 2.15–7.52; $P < .001$). In a retrospective review, a heightened rate of bleomycin pulmonary toxicity has been linked to G-CSF use in patients with Hodgkin lymphoma undergoing bleomycin-containing therapy.[33] This has not been seen with G-CSF use in bleomycin-containing testicular cancer chemotherapy regimens.[18]

Rare cases of splenic rupture with G-CSF use have also been reported, some of which were fatal.[31,32] These cases occurred in patients and healthy donors in the stem cell transplantation setting. Some patients develop allergic reactions in the skin, respiratory system, or cardiovascular system (filgrastim only).

Although some epidemiologic studies have suggested a potentially increased risk of AML/MDS with G-CSF administration, this was not observed in individual randomized trials.[34] The recent analysis by Lyman et al.[24] reported an increase in relative and absolute risk of AML/MDS of 1.92% and 0.41%, respectively, related to G-CSF. Whether the risk of AML/MDS is secondary to G-CSFs or related to the

higher total doses of chemotherapy cannot be determined from this meta-analysis. Overall mortality was nevertheless decreased.

Prophylactic Use of CSFs

Risk Assessment

The NCCN Guidelines begin with an evaluation of risk for chemotherapy-induced FN before the first cycle. The risk assessment involves varied components, including the disease type, chemotherapeutic regimen (high-dose, dose-dense, or standard-dose therapy), patient risk factors, and treatment intent. Three categories based on the intent of chemotherapy have been designated by the panel, including curative/adjuvant therapy, treatment directed toward prolongation of survival, and symptom management therapy. Based on the chemotherapy regimen and patient-related risk factors, the patient is assigned to a high-risk group (> 20% risk of FN), an intermediate-risk group (10%–20% risk), and low-risk group (< 10% risk). No consensus nomogram exists for risk assessment. Although the panel outlines criteria to aid in assessment, independent clinical judgment should be exercised based on the patient's situation. When determining the appropriate use of CSFs, in addition to assessing patient and treatment-related risk, consideration should be given to the intent of cancer treatment. For example, one criterion that identifies a high-risk patient is a previous neutropenic complication in the immediate previous cycle with no plan to reduce the dose intensity.

Patients at High Risk for FN

Panel discussions have focused on defining a risk level of FN that would warrant routine use of prophylactic growth factors. The NCCN Guidelines recommended prophylactic CSFs if the risk of FN was 20% or greater. The most recent update of the ASCO and EORTC guidelines both adopted the 20% threshold for considering routine prophylactic treatment.[35,36]

These consistent recommendations are based on the results of several large randomized trials that have documented that the risk of FN can be significantly reduced by primary prophylaxis when the risk of FN without prophylaxis is 20%. For example, Vogel et al.[8] reported on the results of a double-blind, randomized, placebo-controlled multicenter study to show whether first and subsequent cycle prophylactic CSF support with pegfilgrastim would significantly reduce FN in a regimen that had previously been associated with an expected FN incidence of 20%.[8] This is the largest randomized study of prophylactic growth factor support performed to date. Among women with breast cancer who received docetaxel at 100 mg/m^2 every 3 weeks, 465 received a placebo injection and 463 pegfilgrastim, each administered 24 hours after chemotherapy in a double-blind study designed with FN as the primary end point. The overall incidence of FN was 17% in the placebo group, compared with 1% in the pegfilgrastim group. The incidence of hospitalization was reduced from 14% to 1%, and the use of intravenous anti-infectives was reduced from 10% to 2%, with all of these differences statistically significant ($P < .001$). In cycle 1, the rate of FN in the first cycle was 11% in the placebo group versus less than 1% in the pegfilgrastim group. For cycles 2 through 4, the placebo group had a 6% rate of FN compared with less than 1% in the pegfilgrastim group.

A second trial reported the results of 175 patients with small cell lung cancer who were randomized to receive prophylactic antibiotics with or without prophylactic G-CSF.[6] In cycle 1, 20 patients (24%) in the antibiotics-only group developed FN compared with 9 patients (10%) in the antibiotics plus FN group ($P = .01$). In cycles 2 to 5, the incidences of FN were similar in both groups (17% vs. 11%). The authors concluded that primary FN prophylaxis added to primary antibiotic prophylaxis is effective in reducing FN and infections in patients with small cell lung cancer with the first cycle of chemotherapy. Furthermore, this strategy could be considered for other patients with cancer who have a similar risk for developing FN.

The NCCN, ASCO, and EORTC guidelines all recognize a variety of special circumstances in which patients treated with relatively nonmyelosuppressive chemotherapy regimens may nonetheless be at high risk of FN because of bone marrow compromise or comorbidity.

Prophylactic CSF is recommended for any patient considered at high risk, regardless of whether the treatment is intended to be curative, prolong survival, or manage symptoms.

Patients at Intermediate Risk for FN

The panel defines intermediate risk as a 10% to 20% probability of developing FN or a neutropenic event that would compromise treatment. In all 3 categories

of treatment intent, the panel recommends CSFs be considered on an individualized basis after discussion between the physician and patient regarding the risk/benefit ratio of 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 to prolong survival or manage symptoms, the use of CSF is a difficult decision and requires careful discussion between the physician and patient. If patient risk factors determine the risk, CSF is reasonable. If the risk is from the chemotherapy regimen, other alternatives, such as the use of less myelosuppressive chemotherapy or dose reduction, if of comparable benefit, should be explored.

Patients at Low Risk for FN

For low-risk patients, defined as those with a less than 10% risk, routine use of CSFs is not considered cost-effective, and alternative treatment options are appropriate.[25,36–38] However, CSFs may be considered if the patient is undergoing curative or adjuvant treatment and is at significant risk for serious medical consequences of FN, including death.

Evaluation of Subsequent Chemotherapy Cycles

After the first cycle, patient evaluation should be performed before each subsequent cycle to determine the risk categorization and treatment intent. Patients who experience a previous episode of FN or a dose-limiting neutropenic event (a nadir or a day-of-treatment count impacting the planned dose of chemotherapy) during the previous cycle of treatment with the same dose and schedule planned for the current cycle are now considered high-risk.

If the patient experiences an episode such as this despite receiving CSF, the panel recommends a chemotherapy dose reduction or change in treatment regimen unless it has an impact on patient survival. If the patient does not develop FN or a dose-limiting neutropenic event and is thought to be benefiting from chemotherapy, the previous assessment should be repeated after each subsequent cycle.

Chemotherapy Regimens and Risk for FN

The development of FN is a common dose-limiting toxicity of many single agents and combination chemotherapy regimens. This risk is directly related to the intensity of the chemotherapy regimen. Chemotherapy regimens that have an incidence of FN greater than 20% in clinical trials in chemotherapy-naïve patients are considered high risk by the panel, and CSF prophylaxis is recommended. Notably, some regimens, such as RICE and CHOP-14 for NHL, have only been tested with growth factor support. Benefits of pegfilgrastim have not been shown in regimens given for fewer than 2 weeks. Pegfilgrastim should be avoided in patients undergoing weekly chemotherapy.

Controversy has surrounded the use of G-CSFs for patients with Hodgkin lymphoma undergoing bleomycin-containing chemotherapy. A retrospective study of 141 patients reported an increased risk of bleomycin-related pulmonary toxicity associated with G-CSF use in patients with Hodgkin lymphoma.[33] A systematic review of case reports by Azoulay et al.[39] identified 70 cases of G-CSF–related pulmonary toxicity in patients with cancer and neutropenia. Of these patients, 36 received bleomycin, but most had NHL and had also received drugs known to induce pulmonary toxicity (cyclophosphamide and/or methotrexate). Notably, this possible risk of increased pulmonary toxicity was not seen with bleomycin-containing testicular cancer chemotherapy.[18]

Evens et al.[40] showed that standard chemotherapy for Hodgkin lymphoma (doxorubicin, bleomycin, vinblastine, and dacarbazine [ABVD]) can be safely administered at full dose without G-CSF support. However, this requires treatment with ABVD in some patients at the time of neutropenia. Until further evidence from larger prospective studies becomes available, prophylactic G-CSF use with ABVD can be considered after discussion of risks and benefits with the patient.

Patient Risk Factors for Developing FN

As previously mentioned, patient risk factors are an important consideration in estimating the overall risk of FN, particularly when chemotherapy regimens are considered an intermediate risk.[41] Patient factors may elevate the overall risk to a high-risk category, where prophylactic CSFs are more routinely recommended. For example, many regimens for breast and lung cancer are associated with an intermediate risk of neutropenic complications, and identifying which of these patients would be considered at high risk is important. Even a low-risk regimen does not necessarily preclude the use of CSFs in a patient with high-risk factors.

Higher age, notably over 65 years, is the most important risk factor for developing severe neutropenia

(see NCCN Clinical Practice Guidelines in Oncology [NCCN Guidelines] for Senior Adult Oncology; to view the most recent version of these guidelines, visit the NCCN Web site at www.NCCN.org).[42–47] Other risk factors include previous chemotherapy or radiotherapy; preexisting neutropenia or tumor involvement in the bone marrow; poor performance status; comorbidities, including renal or liver dysfunction; and preexisting conditions, such as neutropenia and infection.

Therapeutic Use of CSFs

Compared with prophylactic use, less evidence supports therapeutic use of CSFs for FN as an adjunct to antibiotics. In a Cochrane meta-analysis involving 1518 patients from 13 trials, Clark et al.[48] reported a shorter length of hospitalization (hazard ratio [HR], 0.63; 95% CI, 0.49–0.82; $P = .0006$) and shorter time to neutrophil recovery (HR, 0.32; 95% CI, 0.23–0.46; $P < .00001$), but no improvement in overall survival associated with therapeutic CSF. An earlier meta-analysis by Berghmans et al.[49] again found no difference in mortality, but they were unable to assess other clinical benefits. Notably, this analysis did not include a multicenter trial that randomized 210 patients with solid tumors who developed chemotherapy-induced FN and had at least one high-risk factor to therapeutic G-CSF or placebo.[50] The G-CSF arm showed a significantly shorter duration of grade 4 neutropenia (median 2 vs. 3 days; $P = .0004$), antibiotic therapy (median 5 vs. 6 days; $P = .013$), and hospital stay (median 5 vs. 7 days; $P = .015$).

Patients with FN who are receiving prophylactic filgrastim or sargramostim should continue with CSF therapy. However, because pegfilgrastim is long-acting, those who have received prophylactic pegfilgrastim should not be treated with additional CSFs.[51] Also, because of the current lack of evidence for therapeutic use of pegfilgrastim, only filgrastim or sargramostim should be administered in the therapeutic setting. For patients who have not received prophylactic CSFs, the panel recommends an evaluation of risk factors for infection-related complications or poor clinical outcome, including old age (> 65 years), sepsis syndrome, severe (absolute neutrophil count [ANC] < 100/mcL) or anticipated prolonged (> 10 days) neutropenia, pneumonia, invasive fungal infection or other clinically documented infections, hospitalization, and prior episode of FN. If risk factors are present, CSFs should be considered.

Dosing and Administration

Currently used myeloid growth factors for the prophylaxis of FN and maintenance of scheduled dose delivery include filgrastim, pegfilgrastim, and sargramostim. Although data from randomized studies support the use of filgrastim and pegfilgrastim in patients with solid malignancies, randomized studies of sargramostim have focused on their use after induction therapy for AML and in various stem cell transplantation settings. Therefore, when choosing among myeloid growth factors, filgrastim and pegfilgrastim are considered category 1 recommendations, whereas sargramostim is considered a category 2B recommendation.

Initial doses of filgrastim are initiated beginning within 1 to 3 days after completion of chemotherapy in a daily dose of 5 mcg/kg until postnadir ANC recovery is to normal or near-normal ANC levels according to laboratory standards. The dose may be rounded to the nearest vial size according to institution-defined weight limits. Evidence also supports the use of pegfilgrastim 24 hours after completion of chemotherapy given every 3 weeks in 1 dose of 6 mg per cycle of treatment.[8,52] Data are insufficient to support dose and schedule of weekly regimens or schedules less than 2 weeks, and these cannot be recommended. Same day administration of filgrastim or pegfilgrastim (within 24 hours of chemotherapy) is not recommended. Phase II studies of pegfilgrastim administration the same day as chemotherapy versus the day after chemotherapy have shown increased incidence of FN and/or adverse events in breast cancer and lymphoma.[53–55] Same day administration of pegfilgrastim showed comparable benefit in one study of a regimen with low risk for neutropenia, but in this setting pegfilgrastim would not be routinely indicated.[56]

Evidence from randomized trials is insufficient to support a category 1 recommendation for sargramostim in nonmyeloid malignancies. Sargramostim is indicated for use after induction chemotherapy in older adult patients with AML.[57] Again, administration of sargramostim on the same day as chemotherapy is not recommended. The subcutaneous route is preferred for all 3 agents. No data are available to

support alternative dosing schedules in intermediate- and high-risk patients. The panel members do not routinely recommend use of prophylactic antibiotics in these settings. In addition, prophylactic use of CSFs in patients given concurrent chemotherapy and radiation is not recommended.

Severe Chronic Neutropenia

These NCCN Guidelines focus on chemotherapy-induced neutropenia in the cancer setting. Severe chronic neutropenia that requires G-CSF therapy is briefly discussed in this section. G-CSF is established as an effective treatment for cyclic, congenital, and idiopathic neutropenia (types of severe chronic neutropenia) based a randomized controlled trial involving 123 patients.[58] In this study, daily treatment with subcutaneously administered G-CSF normalized neutrophils in most patients and prevented fever, mouth ulcers, and infections. Subsequent observation studies show that patients with idiopathic and cyclic neutropenia generally respond to low-dose daily, alternate-day, or thrice-per-week subcutaneous G-CSF (1–3 mcg/kg/d). Patients with congenital neutropenia generally require somewhat higher doses (3–10 mcg/kg/d). 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 diagnosed with severe congenital neutropenia, but not all patients with chronic neutropenia, are at risk of having their condition evolve to myelodysplasia and leukemia, with or without G-CSF treatment. More severely affected patients, which are those requiring higher doses of G-CSF, seem to be at greater risk. These considerations emphasize the importance of making a correct diagnosis and following up with these patients carefully. Currently, the only alternative therapy is hematopoietic stem cell transplantation. For further reading on chronic neutropenia, refer to the Web site developed by The Severe Chronic Neutropenia International Registry (http://depts.washington.edu/registry/index.html).

References

1. Lyman GH, Kuderer NM. Epidemiology of febrile neutropenia. Support Cancer Ther 2003;1:23–35.
2. Dale DC, McCarter GC, Crawford J, Lyman GH. Myelotoxicity and dose intensity of chemotherapy: reporting practices from randomized clinical trials. J Natl Compr Canc Netw 2003;1:440–454.
3. Dale DC. Colony-stimulating factors for the management of neutropenia in cancer patients. Drugs 2002;62(Suppl 1):1–15.
4. 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.
5. 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.
6. 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.
7. 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.
8. 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.
9. 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.
10. 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.
11. 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.
12. 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.
13. 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.
14. 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.
15. 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.
16. 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.

17. 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.
18. 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.
19. 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.
20. Pfreundschuh M, Trumper L, Kloess M, et al. Two-weekly or 3-weekly CHOP chemotherapy with or without etoposide for the treatment of elderly patients with aggressive lymphomas: results of the NHL-B2 trial of the DSHNHL. Blood 2004;104:634–641.
21. Bohlius J, Reiser M, Schwarzer G, Engert A. Granulopoiesis-stimulating factors to prevent adverse effects in the treatment of malignant lymphoma. Cochrane Database Syst Rev 2004:CD003189.
22. 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.
23. 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.
24. 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.
25. 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.
26. 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.
27. 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.
28. 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.
29. 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.
30. 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.
31. Food and Drug Administration. Filgrastim label. Available at: http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?id=16952. Accessed May 3, 2011.
32. Food and Drug Administration. Pegfilgrastim label. Available at: http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?id=16131. Accessed May 3, 2011.
33. 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.
34. 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.
35. Aapro MS, Cameron DA, Pettengell R, et al. EORTC guidelines for the use of granulocyte-colony stimulating factor to reduce the incidence of chemotherapy-induced febrile neutropenia in adult patients with lymphomas and solid tumours. Eur J Cancer 2006;42:2433–2453.
36. Smith TJ, Khatcheressian J, Lyman GH, et al. 2006 update of recommendations for the use of white blood cell growth factors: an evidence-based clinical practice guideline. J Clin Oncol 2006;24:3187–3205.
37. Crawford J, Dale DC, Lyman GH. Chemotherapy-induced neutropenia: risks, consequences, and new directions for its management. Cancer 2004;100:228–237.
38. Lyman GH. Risk assessment in oncology clinical practice. From risk factors to risk models. Oncology (Williston Park) 2003;17:8–13.
39. Azoulay E, Attalah H, Harf A, et al. Granulocyte colony-stimulating factor or neutrophil-induced pulmonary toxicity: myth or reality? Systematic review of clinical case reports and experimental data. Chest 2001;120:1695–1701.
40. 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.
41. Lyman GH, Lyman CH, Agboola O. Risk models for predicting chemotherapy-induced neutropenia. Oncologist 2005;10:427–437.
42. Aslani A, Smith RC, Allen BJ, et al. The predictive value of body protein for chemotherapy-induced toxicity. Cancer 2000;88:796–803.
43. 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.
44. 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.
45. 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.
46. 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.
47. 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.

48. 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.
49. Berghmans T, Paesmans M, Lafitte JJ, et al. Therapeutic use of granulocyte and granulocyte-macrophage colony-stimulating factors in febrile neutropenic cancer patients. A systematic review of the literature with meta-analysis. Support Care Cancer 2002;10:181–188.
50. Garcia-Carbonero R, Mayordomo JI, Tornamira MV, et al. Granulocyte colony-stimulating factor in the treatment of high-risk febrile neutropenia: a multicenter randomized trial. J Natl Cancer Inst 2001;93:31–38.
51. 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.
52. 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.
53. 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 [abstract]. Presented at the SABCS. Abstract 1054.
54. 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 [abstract]. J Clin Oncol 2006;24(Suppl 18):Abstract 7570.
55. Yardley DA, Burris HA III, Farley CP, et al. A phase II feasibility trial of dose-dense docetaxel followed by doxorubicin/cyclophosphamide as adjuvant or neoadjuvant treatment for women with node-positive or high-risk node-negative breast cancer. Clin Breast Cancer 2008;8:242–248.
56. Belani CP, Ramalingam S, Al-Janadi A, et al. A randomized double-blind phase II study to evaluate same-day vs next-day administration of pegfilgrastim with carboplatin and docetaxel in patients with NSCLC [abstract]. J Clin Oncol 2006;24(Suppl 18):Abstract 7110.
57. Stull DM, Bilmes R, Kim H, Fichtl R. Comparison of sargramostim and filgrastim in the treatment of chemotherapy-induced neutropenia. Am J Health Syst Pharm 2005;62:83–87.
58. 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.

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