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Myeloid Growth Factors

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The NCCN

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 (FN; ≥ 38.3°C orally or ≥ 38.0°C over 1 hour) can be induced by myelosuppressive chemotherapy. FN is a major dose-limiting toxicity of chemotherapy, often necessitating hospitalization for evaluation and empiric broad-spectrum antibiotics. These complications often result in dose reductions or treatment delays, which may compromise clinical outcomes. The prophylactic use of colony-stimulating factors (CSFs) can reduce the risk, severity, and duration of FN.

Myeloid Growth Factors Clinical Practice Guidelines in Oncology

Key Words

NCCN Clinical Practice Guidelines, myeloid growth factors, neutropenia, fever, chemotherapy (*JNCCN* 2009;7:64–83)

NCCN Categories of Evidence and Consensus

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

Please Note

These 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 these 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 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 Myeloid Growth Factors Guidelines Panel

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 on-line. 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 Myeloid Growth Factors Guidelines Panel members can be found on page 82. (To view the most recent version of these guidelines and accompanying disclosures, visit the NCCN Web site at www.nccn.org.)

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

Despite these benefits, CSFs are not administered to all patients undergoing myelosuppressive chemotherapy because of the costs associated with routine use. Selective use of CSFs in patients at increased risk for neutropenic complications may, however, enhance cost-effectiveness by directing treatment toward patients most likely to benefit.

The risk for 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.[1] When reported, the rates of myelosuppression with the same and similar regimens varied greatly, making it difficult to determine the actual risk for neutropenic complications associated with common chemotherapy regimens.[1] Differences in the reported rates of neutropenic complications may relate to differences in study patient populations as well as delivered dose intensity. Treatment dose intensity was reported with even less consistency, making it very difficult to interpret differences in reported rates of toxicity or treatment efficacy.

A review by Dale[2] showed that approximately 25% to 40% of treatment-naive patients develop FN with common chemotherapy regimens.[2] Occurrence of FN may delay subsequent chemotherapy courses or result in dose reductions that may compromise treatment outcomes. Development of FN also increases diagnostic and treatment costs and often leads to longer hospital stays. Prolonged hospitalizations are

Text continues on p. 76

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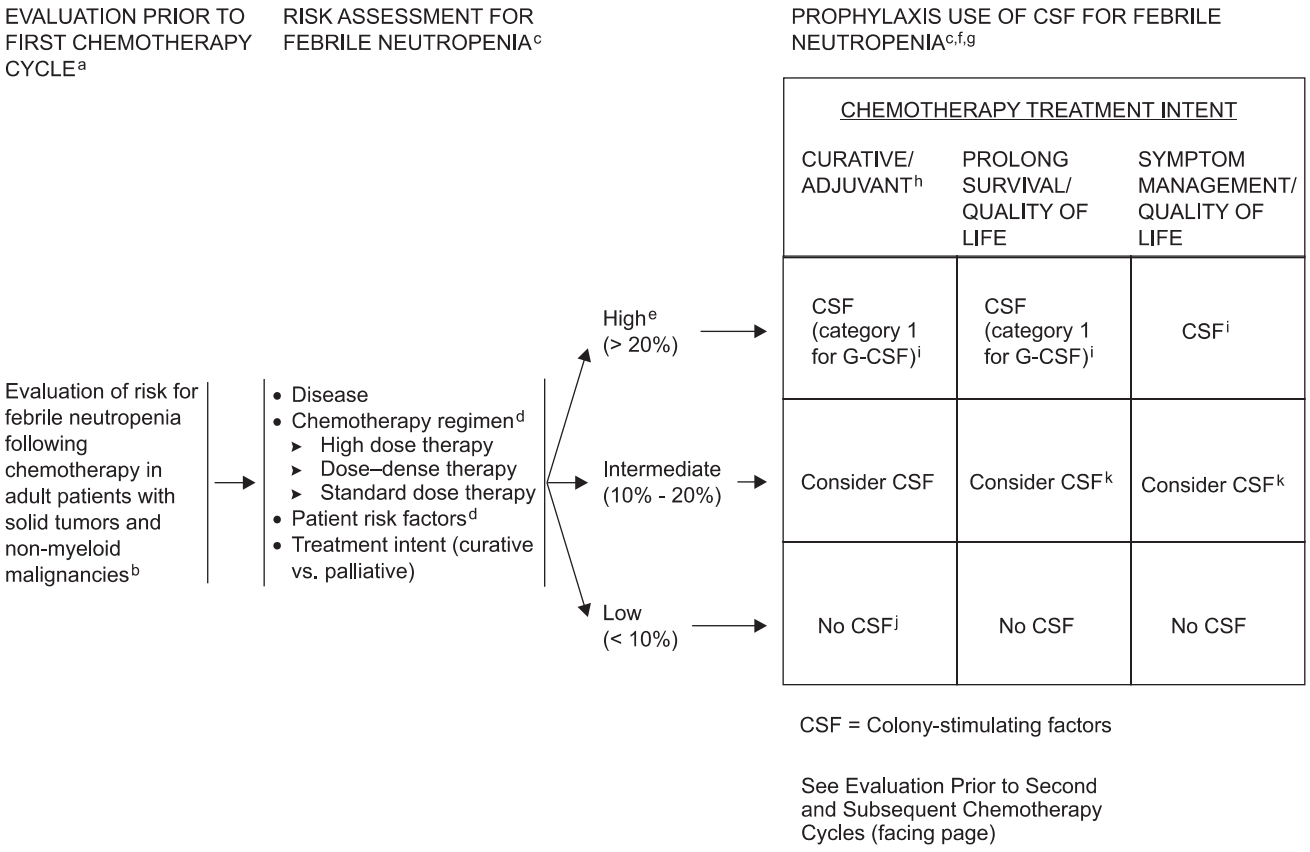

CSF = Colony-stimulating factors

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

*To view the most recent version of these guidelines, visit the NCCN Web site at www.nccn.org.

[a] The NCCN Clinical Practice Guidelines in Oncology: Myeloid Growth Factors* were formulated in reference to adult patients.

[b] For use of growth factors in myelodysplastic syndromes, see the NCCN Clinical Practice Guidelines in Oncology: Myelodysplastic Syndromes.* For use of growth factors in acute myeloid leukemia, see the NCCN Clinical Practice Guidelines in Oncology: Acute Myeloid Leukemia.*

[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 Clinical Practice Guidelines in Oncology: Prevention and Treatment of Cancer-Related Infections.*

[d] There are many factors that need to be evaluated to determine a patient's risk categorization; these include type of chemotherapy regimen (see Examples of Chemotherapy Regimens and Risk of Febrile Neutropenia, pages 69-73) and patient risk factors (see Patient Risk Factors for Developing Febrile Neutropenia, page 74).

[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 for the first and all subsequent cycles of chemotherapy for solid tumors and non-myeloid malignancies. See Myeloid Growth Factors for Prophylaxis and Treatment of Febrile Neutropenia and Maintenance of Scheduled Dose Delivery (page 74).

[g] See Toxicity Risks With Growth Factors (page 75).

[h] The confounding effects of anthracyclines and alkylating agent dose, radiation dose and field size, and CSFs 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 but has not been observed in the available prospective randomized studies.

[i] 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 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 CSF in this setting is a difficult decision and requires careful discussion between the physician and the patient. If patient and regimen risk factors determine this is the appropriate category, a CSF is reasonable. Other alternatives, such as the use of less myelosuppressive chemotherapy or chemotherapy dose reduction, if of comparable benefit, should be considered.

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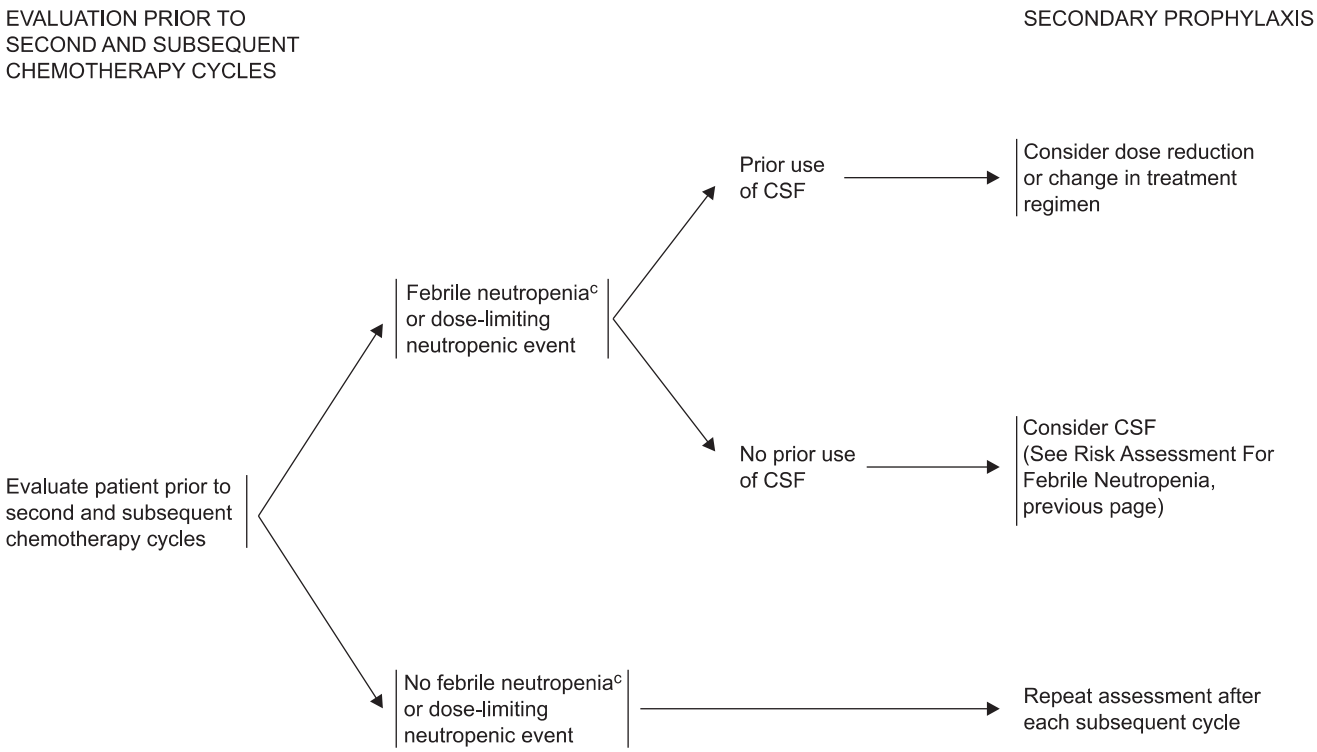

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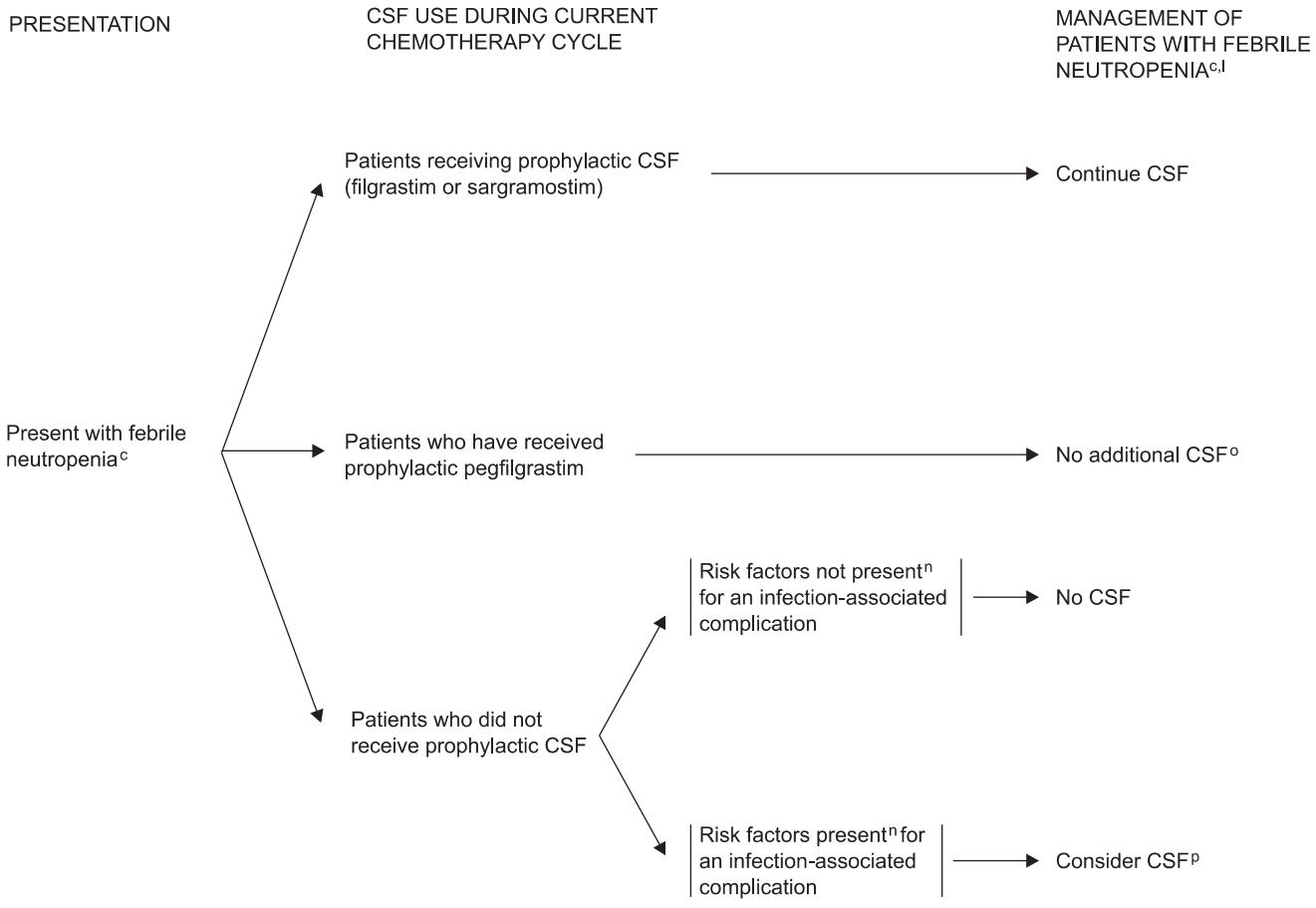
THERAPEUTIC USE OF CSF FOR FEBRILE NEUTROPENIA[c,l,m]



*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; neutropenia < 500 neutrophils/mcL or < 1000 neutrophils/mcL and a predicted decline to ≤ 500/mcL over the next 48 h. See the NCCN Prevention and Treatment of Cancer-Related Infections Guidelines.*

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

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

[n]See Patient Risk Factors for Poor Clinical Outcomes or for Developing Infection-Associated Complications (page 75).

[o]There are no studies which have addressed therapeutic use of pegfilgrastim for febrile neutropenia. However, pharmacokinetic data of pegfilgrastim demonstrated high levels during neutropenia and suggests that additional CSF will not be beneficial.

[p]See discussion for further detail. There is no data on pegfilgrastim in therapeutic setting. Either filgrastim or sargramostim should be used with initial dosing as outlined on Myeloid Growth Factors for Prophylaxis and Treatment of Febrile Neutropenia and Maintenance of Scheduled Dose Delivery (page 74) and discontinued at time of neutrophil recovery.

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

- *This list is not comprehensive;* there are other agents/regimens that have a high risk for the development of febrile neutropenia.
- The exact risk includes agent, dose, and treatment setting (i.e., treatment naive vs. heavily pretreated patients; see page 66).
- The type of chemotherapy regimen is only one component of the risk assessment (See Patient Risk Factors for Developing Febrile Neutropenia, page 74).
- Pegfilgrastim has not been documented to have benefit in regimens given for less than a 2-wk duration.
- 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)[3] (adjuvant)
- 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]

Non-Hodgkin's Lymphoma
- ICE (ifosfamide, carboplatin, etoposide) (diffuse large B-cell lymphoma, peripheral T-cell lymphomas, 2nd-line, salvage)[8]
- RICE* (rituximab, ifosfamide, carboplatin, etoposide)[9]
- CHOP-14* (cyclophosphamide, doxorubicin, vincristine, prednisone)[10]
- MINE (mesna, ifosfamide, novantrone, etoposide) (diffuse large B-cell lymphoma, peripheral T-cell lymphomas 2nd-line, refractory)[11]
- DHAP (dexamethasone, cisplatin, cytarabine) (peripheral T-cell lymphomas, diffuse large B-cell lymphoma, 2nd-line)[12]
- ESHAP (etoposide, methylprednisolone, cisplatin, cytarabine) (diffuse large B-cell lymphoma, peripheral T-cell lymphoma, 2nd-line, recurrent)[13]
- BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone)[14]
- HyperCVAD + Rituximab (cyclophosphamide, vincristine, doxorubicin, dexamethasone + rituximab) (Burkitt's Lymphoma)[15,16]

Melanoma
- Dacarbazine-based combination (dacarbazine, cisplatin, vinblastine) (advanced, metastatic, or recurrent)[17]
- Dacarbazine-based combination with IL-2, interferon alfa (dacarbazine, cisplatin, vinblastine, IL-2, interferon alfa) (advanced, metastatic, or recurrent)[17]

Myelodysplastic syndrome
- Decitabine[18]

Ovarian Cancer
- Topotecan[19]
- Paclitaxel[20]
- Docetaxel[21]

Pancreatic Cancer
- Gemcitabine/docetaxel[22]

Sarcoma
- MAID (MESNA, doxorubicin, ifosfamide, dacarbazine)[23]
- Doxorubicin[24]

Small Cell Lung Cancer
- Topotecan[25]

Testicular Cancer
- VeIP (vinblastine, ifosfamide, cisplatin)[26]
- VIP (etoposide,ifosfamide, cisplatin)
- BEP (bleomycin, etoposide, cisplatin)
- TIP (paclitaxel, ifosfamide, cisplatin)[27]

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

See Chemotherapy Regimen References (pages 71 and 72)

See Chemotherapy Regimens with an Intermediate Risk of Febrile Neutropenia (page 70)

Examples of 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 the development of febrile neutropenia.
- The exact risk includes agent, dose, and treatment setting (i.e., treatment naive vs. heavily pretreated patients; see page 66)
- The type of chemotherapy regimen is only one component of the risk assessment (See Patient Risk Factors for Developing Febrile Neutropenia, page 74).
- Pegfilgrastim has not been documented to have benefit in regimens given under a 2-week duration.
- 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[28]

Breast Cancer
- Docetaxel every 21 d[29]
- Epirubicin (adjuvant)[30]
- Epirubicin + sequential cyclophosphamide + methotrexate + 5-fluorouracil (adjuvant)[30]
- CMF classic (cyclophosphamide, methotrexate, fluorouracil) (adjuvant)[30]
- AC (doxorubicin, cyclophosphamide) + sequential docetaxel (adjuvant) (taxane portion only)[31]
- AC + sequential docetaxel + trastuzumab (adjuvant)[32]
- FEC (fluorouracil, epirubicin, cyclophosphamide) + sequential docetaxel[33]
- Paclitaxel every 21 d (metastatic or relapsed)[34]
- Vinblastine (metastatic or relapsed)[35]

Cervical Cancer
- Cisplatin + topotecan (recurrent or metastatic)[36]
- Topotecan (recurrent or metastatic)[37]
- Irinotecan (recurrent or metastatic)[38]

Colon Cancer
- FOLFOX (fluorouracil, leucovorin, oxaliplatin)[39]

Esophageal Cancer
- Irinotecan/cisplatin[40]
- Epirubicin/cisplatin/5-fluorouracil[41]
- Epirubicin/cisplatin/capecitabine[41]

Hodgkin Lymphoma*
- ABVD† (doxorubicin, bleomycin, vinblastine, dacarbazine)[42]
- Stanford V† (mechlorethamine, doxorubicin, vinblastine, bleomycin, etoposide, prednisone)[43]

†There is one retrospective review that suggests pulmonary toxicity maybe increased using G-CSF in bleomycin containing regimens. (See discussion for further detail.)

Non-Hodgkin's Lymphoma
- EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin) (AIDS-related NHL, Burkitt's, recurrent)[44]
- EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin) + IT chemotherapy (AIDS-related NHL, diffuse large B-cell lymphoma, recurrent)[44]
- Rituximab + hyperCVAD alternating with methotrexate + cytarabine (CVAD template) (cyclophosphamide, vincristine, doxorubicin, dexamethasone) regimen included IT methotrexate[45]
- ACOD (modified CHOP-doxorubicin, cyclophosphamide, vincristine, prednisone)[46]
- GDP (gemcitabine, dexamethasone, cisplatin) (peripheral T-cell lymphomas, diffuse large B-cell lymphoma, 2nd-line)[47]
- GDP (gemcitabine, dexamethasone, cisplatin) + rituximab (diffuse large B-cell lymphoma, 2nd-line)[47]
- FM (fludarabine, mitoxantrone)[48]
- CHOP + R (cyclophosphamide, doxorubicin, vincristine, prednisone, rituximab)[49,50]

Non-Small Cell Lung Cancer
- Cisplatin/paclitaxel (adjuvant, advanced/metastatic)[51]
- Cisplatin/vinorelbine (adjuvant, advanced/metastatic)[52]
- Cisplatin/docetaxel (adjuvant, advanced/metastatic)[51,53]
- Cisplatin/irinotecan (advanced/metastatic)[54]
- Cisplatin/etoposide (adjuvant, advanced/metastatic)[55]
- Carboplatin/paclitaxel (adjuvant, advanced/metastatic)[54]
- Docetaxel (advanced/metastatic)[53]

Ovarian Cancer
- Carboplatin/docetaxel[56]

Small Cell Lung Cancer
- Etoposide/carboplatin[57]

Testicular Cancer
- Etoposide/cisplatin[58]

Uterine Cancer
- Docetaxel (uterine sarcoma, advanced or metastatic)[59]

See Chemotherapy Regimen References (pages 72 and 73)

See Chemotherapy Regimens with a High Risk of Febrile Neutropenia (page 69)

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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 beast 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]. Proc Amer Soc Clin Oncol 2004;23: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]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.

[9]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.

[10]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.

[11]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.

[12]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.

[13]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.

[14]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.

[15]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.

[16]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.

[17]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.

[18]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.

[19]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.

[20]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.

[21]Verschraegen CF, Sittisomwong T, Kudelka AP, et al. Docetaxel for patients with paclitaxel-resistant Mullerian carcinoma. J Clin Oncol 2000;18:2733-2739.

[22]Lutz MP, Van Custem E, Wagener T. Docetaxel plus gemcitabine or docetaxel plus cisplatin in advanced pancreatic carcinoma: randomized phase II study 40984 of the European Organisation for Research and Treatment of Cancer Gastrointestinal Group. J Clin Oncol 2005;23:9250-9256.

References continued on page 72

CHEMOTHERAPY REGIMEN REFERENCES (cont.)

[23]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.
[24]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.
[25]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.
[26]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.
[27]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.
[28]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.
[29]Burris HA. Single-agent docetaxel (Taxotere) in randomized phase II trials. Semin Oncol 1999;26(Suppl 9):1-6.
[30]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.
[31]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 Intergroup Trial E1199 [abstract]. J Clin Oncol 2007;25(Suppl 1):Abstract 526.
[32]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.
[33]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.
[34]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.
[35]Fraschini G, Yap HY, Hortobagui G, et al. Five-day continuous-infusion vinblastine in the treatment of breast cancer. Cancer 1985;56:225-229.
[36]Long III HJ, 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.
[37]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.
[38]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.
[39]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.
[40]Ilson DH. A multicenter phase II trial of weekly irinotecan/cisplatin in advanced esophageal cancer. Oncology (Williston Park) 2004;18 (Suppl 14):22-25.
[41]Cunningham D, Starling N, Rao S, et al. Capectiabine and oxaliplatin for advanced esophagogastric cancer. N Engl J Med 2008;358:36-46.
[42]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.
[43]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.
[44]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.

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CHEMOTHERAPY REGIMEN REFERENCES

[45]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.
[46]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.
Catimel G, et al. Phase II study with docetaxel (Toxotere) in advanced soft tissue sarcomas of the adult. Ann Oncol 1994;5:539-542.
[47]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.
[48]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.
[49]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.
[50]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.
[51]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.
[52]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.
[53]Fossella F, Devore R, Kerr RN, et al. Randomized phase III trial of docetaxel versus vinorelbine or ifosfamide in patients with advanced non–small-cell lung cancer previously treated with platinum-containing chemotherapy regimens. J Clin Oncol 2000;18:2354-2362.
[54]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.
[55]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.
[56]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.
[57]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.
[58]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.
[59]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.

PATIENT RISK FACTORS FOR DEVELOPING FEBRILE NEUTROPENIA

In addition to the risk of the chemotherapy regimen and 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 y and older
- History of previous chemotherapy or radiation therapy
- Pre-existing 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 post-nadir 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.
  - Randomized phase II trials of pegfilgrastim administration the same day as chemotherapy versus administration the day after chemotherapy have shown less benefit in 2 studies of regimens associated with moderate- to high-risk neutropenia,[1,2] and comparable benefit in 1 study of a regimen with low-risk neutropenia where pegfilgrastim would not be routinely indicated.[3] Therefore, administration of growth factor on same day as chemotherapy is not recommended.
  - There is evidence to support use for chemotherapy regimens given every 3 wk (category 1).
  - Phase II studies demonstrate efficacy in chemotherapy regimens given every 2 wk.
  - There are insufficient data to support dose and schedule of weekly regimens or chemotherapy schedules < 2 wk and these cannot be recommended.
- Sargramostim[4] (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 post-nadir recovery. Administration of growth factor on same day as chemotherapy is not recommended.

- Prophylactic use of CSF 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 Prevention and Treatment of Cancer-Related Infections Guidelines. To view the most recent version of these guidelines, visit the NCCN Web site at www.nccn.org.)

[1] Lokich JJ. Same day pegfilgrastim and CHOP chemotherapy for non-Hodgkin lymphoma. Am J Clin Oncol 2006;29:361-363.
[2] Kaufman, PA, Paroly W, Rinaldi D, et al. 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]. Breast Cancer Res Treat 2004;88 (Suppl 1):Abstract 1054.
[3] 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 1):Abstract 7110.
[4] 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 following induction chemotherapy in older adult patients with AML. Studies are ongoing in other areas.

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

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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
- 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]
- 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 prior to 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, GI hemorrhage, pruritus, bone pain, eye hemorrhage, hyperglycemia, hypomagnesemia, pharyngitis, insomnia, anxiety, high BUN, high cholesterol

[1]To view filgrastim prescribing information, see http://www.fda.gov/cder/foi/label/2006/103353s5086LBL.pdf.
[2]To view pegfilgrastim prescribing information, see http://www.fda.gov/cder/foi/label/2007/125031s082lbl.pdf.
[3]To view sargramostim prescribing information, see http://berlex.bayerhealthcare.com/html/products/pi/Leukine_PI.pdf.

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

Patient risk factors include:
- Sepsis syndrome
- Age > 65 y
- Severe neutropenia (absolute neutrophil count < 100/mcL)
- Neutropenia expected to be more than 10 d in duration
- Pneumonia
- Invasive fungal infection
- Other clinically documented infections
- Hospitalization at the time of fever

[1]The decision to use or not use CSF 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. 65

the dominant factor in the high cost of cancer care. Prevention of adverse effects associated with cancer treatment, including limitation of mobility, emotional distress, and decreased energy, has a major impact on patient quality of life.[3]

Filgrastim and pegfilgrastim, both granulocyte colony-stimulating factors (G-CSF), currently have FDA approval for use in the prevention of chemotherapy-induced neutropenia. In contrast, the labeled indication for sargramostim, a granulocyte-macrophage colony-stimulating factor (GM-CSF), is limited to use after induction therapy for acute myeloid leukemia and in various stem cell transplantation settings. Recommendations are based on evidence derived mainly from studies on G-CSFs. Head-to-head comparative studies on the clinical benefits of G-CSFs and GM-CSFs are lacking.

These guidelines focus on the use of CSFs in the cancer setting; specifically they address 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: Myelodysplastic Syndromes and 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.[4–15] G-CSFs also improved delivery of full dose intensity chemotherapy at the planned schedule, although this has not been generally shown to lead to better response or higher overall survival.[4,6,8,11,13–17] However, in node-positive breast cancer[18] and NHL,[19] 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,[20,21] risk for neutropenia,[20,21] length of hospitalization,[22] and time to neutrophil recovery.[22] Clark et al.[22] found a marginal benefit of CSF in lowering infection-related mortality (odds ratio [OR], 0.51; 95% CI, 0.26–1.00; $P = .05$). In a recent meta-analysis of 17 randomized trials of prophylactic G-CSFs, including 3493 adult patients with nonmyeloid malignancies,[23] G-CSF as primary prophylaxis reduces risk for FN (relative risk [RR], 0.54; 95% CI, 0.43–0.67; $P < .001$) and improves relative dose-intensity of the chemotherapy delivered (average difference between study arms, 8.4%; $P = .001$). For the first time, this analysis also reports a substantial reduction in risk for 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; $P = .002$).

Over the past decade, costs for inpatient hospitalization have escalated, changing the risk threshold on a pure cost basis from 40% to approximately 20%.[24] Economic analyses of CSFs have yielded mixed results, depending on the context of use.[25–29] However, the policy of the NCCN Myeloid Growth Factors Panel is to look primarily at issues of therapeutic efficacy and clinical benefit, rather than cost. The indication for prophylactic CSF use depends on the risk for 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.[30] This is usually effectively controlled by nonnarcotic analgesics. The meta-analysis by Kuderer et al.[23] confirmed a heightened risk for musculoskeletal pain associated with CSF (RR, 4.03; 95% CI, 2.15–7.52; $P < .001$). In a retrospective review, a heightened rate of bleomycin pulmonary toxicity was linked to G-CSF use in patients with Hodgkin lymphoma undergoing bleomycin-containing therapy.[31]

Rare cases of splenic rupture with G-CSF use, some of which were fatal, have also been reported.[30] 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 a potentially increased risk for acute leukemia with G-CSF administration has been suggested, the Research on Adverse Drug Events and Reports (RADAR) group concluded that long-term safety data are still lacking to confirm this relationship.[32] Toxicity risks associated with G-CSFs and GM-CSF are listed on page 75.

Prophylactic Use of CSFs

Risk Assessment

The guidelines begin with an evaluation of risk for chemotherapy-induced FN before the first cycle. The risk assessment involves varied components, including

disease type, chemotherapeutic regimen (high-dose, dose–dense, or standard-dose therapy), patient risk factors, and treatment intent. The NCCN panel designated 3 categories based on the intent of chemotherapy, including curative/adjuvant therapy, treatment directed toward prolongation of survival, and symptom management therapy. Based on the chemotherapy regimen and patient-related risk factors (pages 69,70, and 74), the patient is assigned to a high-risk group (> 20% risk for FN), intermediate group (10%–20% risk), or low-risk group (< 10% risk). Notably, no consensus nomogram for risk assessment currently exists. Although the NCCN 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, along with assessing patient and treatment-related risks, the intent of cancer treatment should be considered. For example, one criterion identifying patients as high-risk is a previous neutropenic complication in the immediate previous cycle with no plan to reduce the dose intensity.

Patients at High Risk for FN

NCCN panel discussions have focused on defining a risk level for FN that would warrant routine use of prophylactic growth factors. The guidelines recommended prophylactic CSF if the risk for FN was 20% or greater. The most recent update of the ASCO guidelines and EORTC adopted the 20% threshold for considering routine prophylactic treatment.[33,34]

These consistent recommendations are based on results of several large randomized trials showing that the risk for FN can be significantly reduced with primary prophylaxis when the risk without prophylaxis is 20%. For example, Vogel et al.[7] reported on the results of a double-blind, randomized, placebo-controlled multicenter study on 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%. This is the largest randomized study of prophylactic growth factor support performed. Women with breast cancer received docetaxel at 100 mg/m^2 every 3 weeks. In this double-blind study, designed with FN as the primary end point, 465 women received a placebo injection and 463 received pegfilgrastim, each administered 24 hours after chemotherapy. The placebo group had an overall incidence of FN of 17%, whereas the pegfilgrastim group had a 1% incidence. The incidence of hospitalization decreased from 14% to 1%, and the use of intravenous antiinfectives decreased from 10% to 2%, with all of these differences statistically significant ($P < .001$). The placebo group had an 11% rate of FN in the first cycle versus less than 1% in the pegfilgrastim group. For cycles 2 through 4, the rate of FN was 6% in the placebo group and 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.[5] 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 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 applied to other cancer patients with a similar risk for FN.

The NCCN, ASCO, and EORTC guidelines all recognize various special circumstances in which patients treated with relatively nonmyelosuppressive chemotherapy regimens may nonetheless be at high risk for FN from bone marrow compromise or comorbidity (see page 74).

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 NCCN 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 individualized consideration of CSF use based on physician and patient discussion of the risk–benefit ratio of the likelihood of developing FN, potential consequences of a neutropenic event, and implications of reduced chemotherapy dose delivery. When the intent of chemotherapy is to prolong survival or for symptom management, using CSFs is a difficult decision that requires careful discussion between physician and patient. If inalterable 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, as defined by a less than 10% risk, routine use of CSFs is not considered cost-effective and alternative treatment options are appropriate.[24,34–36] 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. If the patient experienced a previous episode of FN or a dose-limiting neutropenic event during the previous cycle of treatment with the same dose and schedule planned for the current cycle, this patient is now in the high-risk group.

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 this will impact patient survival. If the patient does not develop FN or a dose-limiting neutropenic event and is believed 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-naive patients who have an incidence of FN greater than 20% undergoing chemotherapy regimens in clinical trials are considered at high risk by the panel, and CSF-prophylaxis is recommended. Some regimens, such as the RICE (cyclophosphamide, doxorubicin, vincristine, and prednisone) and CHOP-14 (mesna, ifosfamide, mitoxantrone, and etoposide) regimen for NHL, have only been tested with growth factor support. Benefits of pegfilgrastim have not been shown in regimens given over less than a 2-week duration. Pegfilgrastim should be avoided in patients undergoing weekly chemotherapy and should not be used with the FOLFOX (fluorouracil, leucovorin, and oxaliplatin) regimen. Controversy surrounds the use of G-CSFs for patients with Hodgkin lymphoma undergoing bleomycin-containing chemotherapy. An increased risk for bleomycin pulmonary toxicity has been reported with G-CSF use for this disease in a retrospective study on 141 patients.[31] In a systematic review of case reports by Azoulay et al.,[37] 70 cases of G-CSF–related pulmonary toxicity was identified in cancer patients with neutropenia. Of these, 36 patients had received bleomycin, but most were those with NHL who have also received drugs known to induce pulmonary toxicity (cyclophosphamide and/or methotrexate).

Evens et al.[38] showed that standard chemotherapy for Hodgkin lymphoma (ABVD [doxorubicin, bleomycin, vinblastine and dacarbazine]) 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 risks and benefits are discussed with the patient.

Patient Risk Factors for Developing FN

Patient risk factors are an important consideration in estimating the overall risk for FN, particularly when chemotherapy regimens are considered an intermediate risk.[39] 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 for neutropenic complications, and it is important to identify which of these patients would be considered at high risk. Higher age, notably older than 65 years, is the most important risk factor for developing severe neutropenia.[40–46] Other risk factors include poor performance status; comorbidities, including renal or liver dysfunction; and preexisting conditions, such as neutropenia and infection.[39]

Therapeutic Use of CSFs

Compared with prophylactic use, less evidence supports therapeutic use of CSFs for FN as an adjunctive to antibiotics. In a Cochrane meta-analysis including 1518 patients from 13 trials, Clark et al.[22] reported a shorter length of hospitalization (HR, 0.63; 95% CI, 0.49–0.82; $P = .0006$), 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. In an earlier meta-analysis, Berghmans et al.[47] again found no difference in

mortality but were unable to assess other clinical benefits. Notably, this analysis did not include a multicenter trial of 210 patients with solid tumors who developed chemotherapy-induced FN and had at least one high-risk factor who were randomized to treatment with G-CSF or placebo.[48] 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. As so, as there is currently a 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 for risk factors for infection-related complications or poor clinical outcome. These include 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. 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 its use after induction therapy for acute myeloid leukemia and in various stem cell transplantation settings. Therefore, when choosing among myeloid growth factors, filgrastim and pegfilgrastim are considered category 1 recommendations, while sargramostin 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 post-nadir ANC recovery is at normal or near-normal ANC levels by laboratory standards. The dose may be rounded to the nearest vial size by institution-defined weight limits. There is also evidence to support use of pegfilgrastim 24 hours after completion of chemotherapy given every 3 weeks in one dose of 6 mg per cycle of treatment.[7,50] There are insufficient data to support dose and schedule of weekly regimens or schedules less than 2 weeks and these cannot be recommended. Same day administration of pegfilgrastim is also not recommended. Randomized phase II trials of pegfilgrastim administration the same day as chemotherapy versus administration the day after have shown less benefit in 2 studies of regimens associated with moderate to high-risk neutropenia.[51,52] Same day pegfilgrastim showed comparable benefit in one study of a regimen with low risk neutropenia, but pegfilgrastim would not be routinely indicated.[53] There is insufficient evidence from randomized trials to support a category 1 recommendation for sargramostim in nonmyeloid malignancies. It is indicated for use following induction chemotherapy in older adult patients with AML.[54] Again, administration of sargramostim the same day as chemotherapy is not recommended.

The subcutaneous route is preferred for all 3 agents. There are no data to support alternative dosing schedules in intermediate- and high-risk patients. The NCCN Myeloid Growth Factors 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 guidelines focus on chemotherapy-induced neutropenia in the cancer setting. Severe chronic neutropenia requiring 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 on a randomized control trial involving 123 patients.[55] 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 with severe congenital neutropenia, but not all patients with chronic neutropenia, are at risk for developing myelodysplasia and leukemia, with or without G-CSF treatment. More severely affected patients, as reflected by the requirement of higher doses of G-CSF, seem to be at greater risk. These considerations emphasize the importance of making a correct diagnosis and following up 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. Dale DC, McCarter GC, Crawford J. Myelotoxicity and dose intensity of chemotherapy: reporting practices from randomized clinical trials. J Natl Compr Canc Netw 2003;1:440–454.
2. Dale DC. Colony-stimulating factors for the management of neutropenia in cancer patients. Drugs 2002;62(Suppl 1):1–15.
3. Lyman GH, Kuderer NM. Filgrastim in patients with neutropenia: potential effects on quality of life. Drugs 2002;62(Suppl 1):65–78.
4. 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.
5. 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.
6. 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.
7. 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.
8. 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.
9. 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.
10. 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.
11. 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.
12. 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.
13. 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.
14. 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.
15. 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.
16. 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.
17. 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.
18. 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.
19. 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.
20. 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.
21. 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.
22. 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.
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, 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.
25. 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.
26. 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.

27. 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.
28. 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.
29. 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.
30. U.S. Food and Drug Administration. FDA filgrastim and pegfilgrastim labels. Available at: http://www.fda.gov/cder/foi/label/2006/103353s5086LBL.pdf and http://www.fda.gov/cder/foi/label/2007/125031s082lbl.pdf. Accessed October 29, 2008.
31. 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.
32. 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.
33. 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.
34. 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.
35. Crawford J, Dale DC, Lyman GH. Chemotherapy-induced neutropenia: risks, consequences, and new directions for its management. Cancer 2004;100:228–237.
36. Lyman GH. Risk assessment in oncology clinical practice. From risk factors to risk models. Oncology (Williston Park) 2003;17:8–13.
37. 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.
38. 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.
39. Lyman GH, Lyman CH, Agboola O. Risk models for predicting chemotherapy-induced neutropenia. Oncologist 2005;10:427–437.
40. Aslani A, Smith RC, Allen BJ, et al. The predictive value of body protein for chemotherapy-induced toxicity. Cancer 2000;88:796–803.
41. 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.
42. 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.
43. 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.
44. 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.
45. Lyman GH, Dale DC, Crawford J. Incidence and predictors of low dose-intensity in adjuvant breast cancer chemotherapy: a nationwide study of community practices. J Clin Oncol 2003;21: 4524–4531.
46. 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.
47. 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.
48. 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.
49. 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.
50. Crawford J. Once-per-cycle pegfilgrastim (Neulasta) for the management of chemotherapy-induced neutropenia. Semin Oncol 2003;30:24–30.
51. Lokich JJ. Same day pegfilgrastim and CHOP chemotherapy for non-Hodgkin lymphoma. Am J Clin Oncol 2006;29:361–363.
52. 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 SABCS [abstract]. Breast Cancer Res Treat 2004;88:Abstract 1054.
53. 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 1):Abstract 7110.
54. 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.
55. 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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