

Update of Recommendations for the Use of Hematopoietic Colony-Stimulating Factors: Evidence-Based Clinical Practice Guidelines

Adopted on March 28, 1996 by the American Society of Clinical Oncology*

Summary of CSF Guidelines

Each guideline will be presented from the 1994 Summary¹ with changes for 1996.

Guideline Application

All patients as listed by condition not being treated on a clinical trial.

Review Process

The guidelines are updated by the writing panel in annual reviews; the full expert panel will provide major revisions based on new information every three years.

1. Guidelines for Primary Prophylactic CSF Administration

General Circumstances

Primary prophylactic administration of colony-stimulating factors (CSFs) was shown to reduce the incidence of febrile neutropenia by approximately 50% in the three major randomized trials in adults in which the incidence of febrile neutropenia was greater than 40% in the control group. The value of primary CSF administration has not been clearly established in less myelosuppressive regimens. It is recommended that primary administration of CSFs be reserved for patients expected to experience levels of febrile neutropenia comparable to or greater than those observed in control patients in these randomized trials, ie, an expected incidence $\geq 40\%$. Thus, in general, for previously untreated patients receiving most chemotherapy regimens, primary administration of CSFs should not be used routinely.

1996 Recommendation: No change.

Special Circumstances

Clinicians may occasionally be faced with patients who might benefit from a relatively nonmyelosuppressive chemotherapy but have potential risk factors for febrile neutropenia or infection because of bone marrow compromise or comorbidity. It is possible that primary CSF administration may be exceptionally warranted in patients at higher risk for chemotherapy-induced infectious complications even though the data supporting such use are not conclusive. Such risk factors might include preexisting neutropenia due to disease, extensive prior chemotherapy, or previous irradiation to the pelvis or other areas containing large amounts of bone marrow; a history of recurrent febrile neutropenia while receiving earlier chemotherapy of similar or lesser dose-intensity; or conditions potentially enhancing the risk of serious infection, eg, poor performance status and more advanced cancer, decreased immune function, open wounds, or already active tissue infections. This is not meant to be an all-inclusive list; it is anticipated that, depending on the unique features of the clinical situation, there will be instances when the administration of a CSF will be appropriate outside of uses recommended in other guidelines.

1996 Recommendation: No change. Note, however, that the 1994 *Special Circumstances* section was amended; specifically, "poor performance status and more advanced cancer" were added to the list of conditions potentially enhancing the risk of serious infection.

2. Guidelines for Secondary Prophylactic CSF Administration

There is evidence that CSF administration can decrease the probability of febrile neutropenia in subsequent cycles of chemotherapy after a documented occurrence in an

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earlier cycle. Even if febrile neutropenia has not occurred, the use of CSFs may be considered if prolonged neutropenia is causing excessive dose reduction or delay in chemotherapy. However, in the absence of clinical data supporting maintenance of chemotherapy dose-intensity, physicians should consider chemotherapy dose reduction as an alternative to the use of CSFs.

1996 Recommendation: No change.

3. Guidelines for CSF Therapy

Afebrile Patients

There are inadequate data to know whether patients with neutropenia but no fever will benefit clinically from the initiation of a CSF at the time neutropenia is diagnosed; intervention with a CSF in afebrile neutropenic patients is not recommended.

1996 Recommendation: No change.

Febrile Patients

For the majority of patients with febrile neutropenia, the available data do not clearly support the routine initiation of CSFs as adjuncts to antibiotic therapy. However, certain febrile, neutropenic patients may have prognostic factors that are predictive of clinical deterioration, such as pneumonia, hypotension, multiorgan dysfunction (sepsis syndrome), or fungal infection. The use of CSFs together with antibiotics may be reasonable in such high-risk patients, even though the benefits of administration under these circumstances have not been definitively proved.

1996 Recommendation: No change.

4. Guidelines for Use of CSFs to Increase Chemotherapy Dose-Intensity

Outside of clinical research trials, there is little justification for the use of CSFs to increase chemotherapy dose-intensity. In settings where clinical research demonstrates that dose-intensive therapy not requiring progenitor-cell support produces improvement in disease control, CSFs should be used when these therapies are expected to produce significant rates of febrile neutropenia (eg, in \geq 40% of patients).

1996 Recommendation: No change.

5. Guidelines for Use of CSFs as Adjuncts to Progenitor-Cell Transplantation

CSFs can successfully shorten the period of neutropenia and reduce infectious complications in patients un-

dergoing high-dose cytotoxic therapy with autologous bone marrow transplantation (BMT). Available data suggest the potential for similar benefits after allogeneic BMT, but these data remain less conclusive, and the routine use of CSFs following allogeneic transplantation cannot be strongly encouraged at the present time. Until further trials are performed to determine specifically the value of CSF administration after high-dose chemotherapy and peripheral-blood progenitor-cell (PBPC) transplantation, CSF use in this setting seems reasonable. There also may be a role for the CSFs in assisting in the recovery of patients who experience delayed or inadequate neutrophil engraftment following progenitor-cell transplantation. Available evidence indicates that the CSFs are effective in mobilizing PBPC for transplantation. The same doses, routes, and schedules of CSF administration mentioned in the Guidelines for CSF Dosing and Route of Administration and Guidelines for Initiation and Duration of CSF Administration should be used in the transplantation setting.

1996 Update: CSFs can successfully shorten the period of neutropenia and reduce infectious complications in patients undergoing high-dose cytotoxic therapy with autologous BMT. CSFs are effective in mobilizing autologous PBPC for transplantation, and autologous PBPC transplantation has been shown to lead to earlier hematopoietic recovery than autologous BMT.^{2,3} Trials have demonstrated the value of CSF administration after high-dose chemotherapy and PBPC transplantation.⁴⁻⁶ Available data suggest clinical benefits after allogeneic BMT, and routine primary CSF administration in this setting appears warranted.⁷ CSFs can also be used to mobilize donor PBPC for allogeneic transplantation.⁸⁻¹¹ There also may be a role for the CSFs in assisting in the recovery of patients who experience delayed or inadequate neutrophil engraftment following progenitor-cell transplantation.¹²

1996 Recommendation: CSFs can be routinely recommended as adjuncts to allogeneic and autologous progenitor cell transplantation, both for mobilization of PBPC and as a means to speed hematopoietic reconstitution following BMT or PBPC transplantation. Administration of a CSF in cases of engraftment failure is warranted.

6. Guidelines for Use in CSFs in Patients With Myeloid Malignancies

Acute Myeloid Leukemia

There is evidence from several studies that CSF administration can achieve modest decreases in the duration of neutropenia when begun shortly after the completion of acute myeloid leukemia (AML) induction therapy, but

beneficial CSF effects on such end points as duration of hospitalization, incidence of severe infection, complete response rates, and long-term outcome have yet to be completely determined, necessitating caution in the use of CSFs in this setting. CSFs given either before and/or concurrently with chemotherapy for “priming” effects cannot be recommended outside of the setting of a clinical trial. Potential concerns include inhibition of chemotherapeutic activity and enhancement of toxicity.

1996 Update: There is evidence from several studies, most conducted in older patients, that CSF administration can achieve modest decreases in the duration of neutropenia, accompanied in some but not all studies by an amelioration of infectious complications, when begun shortly after the completion of AML induction therapy.¹³⁻¹⁹ There has been no consistent improvement in complete response rates and long-term outcome at 2 years. There does not appear to be any harm from CSF administration when given after completion of induction chemotherapy.

1996 Recommendation: Primary administration of a CSF can be used after completion of induction chemotherapy in patients ≥ 55 years of age. Although there are fewer data, it is likely that the results showing shortening of the duration of neutropenia may apply to younger patients as well. CSFs given either before and/or concurrently with chemotherapy for priming effects still cannot be recommended outside of a clinical trial.

Myelodysplastic Syndromes

CSFs can increase the absolute neutrophil count in neutropenic patients with myelodysplastic syndromes (MDS). Data supporting the routine long-term continuous use of CSFs in these patients are lacking. Intermittent administration of CSFs may be considered in a subset of patients with severe neutropenia and recurrent infection.

1996 Recommendation: No change.

7. Guidelines for Use of CSFs in Patients Receiving Concurrent Chemotherapy and Irradiation

CSFs should be avoided in patients receiving concomitant chemotherapy and radiation therapy.

1996 Recommendation: No change.

8. Guidelines for Use of CSFs in the Pediatric Population

In the absence of conclusive pediatric data, the guidelines recommended for adults are generally applicable to

the pediatric age group. However, optimal CSF doses have yet to be determined. Further clinical research into the use of these factors in support of chemotherapy and progenitor-cell transplantation in the pediatric age group should be given high priority.

1996 Recommendation: No change.

9. Guidelines for CSF Dosing and Route of Administration

In adults, the recommended CSF doses are 5 $\mu\text{g}/\text{kg}/\text{d}$ of granulocyte CSF (G-CSF; filgrastim) or 250 $\mu\text{g}/\text{m}^2/\text{d}$ of granulocyte-macrophage CSF (GM-CSF; sargramostim). These agents can be administered subcutaneously or intravenously as clinically indicated. CSF dose escalation is not advised. The available data suggest that rounding the dose to the nearest vial size may enhance patient convenience and reduce costs without clinical detriment.

1996 Recommendation: No change.

10. Guidelines for Initiation and Duration of CSF Administration

Existing clinical data suggest that starting G-CSF or GM-CSF between 24 and 72 hours subsequent to chemotherapy may provide optimal neutrophil recovery. Continuing the CSF until the occurrence of an absolute neutrophil count (ANC) of 10,000/ μL after the neutrophil nadir, as specified in the G-CSF package insert, is known to be safe and effective. However, a shorter duration of administration that is sufficient to achieve clinically adequate neutrophil recovery is a reasonable alternative, considering issues of patient convenience and cost.

1996 Recommendation: No change.

11. Special Commentary on Comparative Clinical Activity of G-CSF and GM-CSF

Guidelines about equivalency of the available recombinant preparations of G-CSF and GM-CSF cannot be proposed because there have been no large-scale, prospective, comparative trials evaluating relative CSF efficacy. The strength of evidence to support the use of G-CSF or GM-CSF varies based on the specific indication for CSF administration, eg, support after BMT or use with non-transplantation chemotherapy regimens. The Panel strongly encourages additional clinical investigation that will guide clinical application of these biologically distinct molecules by addressing issues of comparative clinical activity, toxicity, and cost-effectiveness.

1996 Recommendation: No change.

REFERENCES

1. ASCO Ad Hoc Colony-Stimulating Factor Guidelines Expert Panel: American Society of Clinical Oncology recommendations for the use of hematopoietic colony-stimulating factors: Evidence-based, clinical practice guidelines. *J Clin Oncol* 12:2471-2508, 1994
2. Beyer J, Schwella N, Zingsem J, et al: Hematopoietic rescue after high-dose chemotherapy using autologous peripheral-blood progenitor cells or bone marrow: A randomized comparison. *J Clin Oncol* 13:1328-1335, 1995
3. Schmitz N, Linch DC, Dreger P, et al: Filgrastim-mobilised peripheral blood progenitor cell transplantation in comparison with autologous bone marrow transplantation: Results of a randomised phase III trial in lymphoma patients. *Lancet* 347:353-357, 1996
4. Nademanee A, Sniecinski I, Schmidt GM, et al: High-dose chemotherapy followed by autologous peripheral-blood stem-cell transplantation for patients with Hodgkin's disease and non-Hodgkin's lymphoma using unprimed and granulocyte colony-stimulating factor mobilized peripheral-blood stem cells. *J Clin Oncol* 12:2176-2186, 1994
5. Schmitz N, Dreger P, Zander AR, et al: Results of a randomized controlled multicenter study of recombinant human granulocyte colony stimulating factor (ilgrastim) in patients with Hodgkin's disease and non-Hodgkin's lymphoma undergoing autologous bone marrow transplantation. *Bone Marrow Transplant* 15:261-266, 1995
6. Klumpp TR, Mangan KF, Goldberg SL, et al: Granulocyte colony-stimulating factor accelerates neutrophil engraftment following peripheral-blood stem-cell transplantation: A prospective, randomized trial. *J Clin Oncol* 13:1323-1327, 1995
7. Nemunaitis J, Rosenfeld CS, Ash R, et al: Phase III randomized, double-blind placebo-controlled trial of rhGM-CSF following allogeneic bone marrow transplantation. *Bone Marrow Transplant* 15:949-954, 1995
8. Korbling M, Przepiorka D, Huh YO, et al: Allogeneic blood stem cell transplantation for refractory leukemia and lymphoma: Potential advantage of blood over marrow allografts. *Blood* 85:1659-1665, 1995
9. Dreger P, Haferlach T, Eckstein V, et al: G-CSF-mobilized peripheral blood progenitor cells for allogeneic transplantation: Safety, kinetics of mobilization, and composition of the graft. *Br J Haematol* 87:609-613, 1994
10. Schmitz N, Dreger P, Suttorp M, et al: Primary transplantation of allogeneic peripheral blood progenitor cells mobilized by filgrastim (granulocyte colony-stimulating factor). *Blood* 85:1666-1672, 1995
11. Bensinger WI, Weaver CH, Appelbaum FR, et al: Transplantation of allogeneic peripheral blood stem cells mobilized by recombinant human granulocyte colony-stimulating factor. *Blood* 85:1655-1658, 1995
12. Weisdorf DJ, Verfaillie CM, Davies SM, et al: Hematopoietic growth factors for graft failure after bone marrow graft failure: A randomized trial of granulocyte macrophage colony stimulating factor (GM-CSF) versus sequential GM-CSF plus granulocyte CSF. *Blood* 85:3452-3456, 1995
13. Rowe JM, Anderson JW, Mazza JJ, et al: A randomized placebo-controlled phase III study of granulocyte-macrophage colony-stimulating factor in adult patients (> 55 to 70 years of age) with acute myelogenous leukemia: A study of the Eastern Cooperative Oncology Group (E1490). *Blood* 86:457-462, 1995
14. Stone RM, Berg DT, George SL, et al: Granulocyte-macrophage colony-stimulating factor after initial chemotherapy for elderly patients with primary acute myelogenous leukemia. *N Engl J Med* 332:1671-1677, 1995
15. Zittoun R, Mandelli F, De Witte T, et al: Recombinant human granulocyte-macrophage colony-stimulating factor (GM-CSF) during induction treatment of acute myelogenous leukemia (AML). A randomized trial from EORTC-GIMEMA leukemia cooperative groups. *Blood* 84:231, 1994 (suppl 1; abstr)
16. Dombret H, Chastang C, Fenaux P, et al: A controlled study of recombinant human granulocyte colony-stimulating factor in elderly patients after treatment for acute myelogenous leukemia. *N Engl J Med* 332:1678-1683, 1995
17. Ohno R, Tomonaga M, Kobayashi T: Effect of granulocyte colony-stimulating factor after intensive induction therapy in relapsed or refractory acute leukemia. *N Engl J Med* 323:871-877, 1990
18. Heil G, Hoelzer D, Sanz MA, et al: Results of a randomized, double-blind placebo controlled phase III study of filgrastim in remission induction and early consolidation therapy for adults with de-novo acute myeloid leukaemia. *Blood* 86:1053, 1994 (suppl 1; abstr)
19. Godwin JE, Kopecky KJ, Head DR, et al: A double blind placebo controlled trial of G-CSF in elderly patients with previously untreated acute myeloid leukemia. A Southwest Oncology Group Study. *Blood* 86:1723, 1994 (suppl 1; abstr)