TABLE 103e-7 INDICATIONS FOR THE CLINICAL USE OF G-CSF OR GM-CSF

Preventive Uses
With the first cycle of chemotherapy (so-called *primary CSF administration*)
Not needed on a routine basis
Use if the probability of febrile neutropenia is ≥20%
Use if patient has preexisting neutropenia or active infection
Age >65 years treated for lymphoma with curative intent or other tumor treated by similar regimens
Poor performance status
Extensive prior chemotherapy
Dose-dense regimens in a clinical trial or with strong evidence of benefit
With subsequent cycles if febrile neutropenia has previously occurred (so-called *secondary CSF administration*)
Not needed after short-duration neutropenia without fever
Use if patient had febrile neutropenia in previous cycle
Use if prolonged neutropenia (even without fever) delays therapy
Therapeutic Uses
Afebrile neutropenic patients
No evidence of benefit
Febrile neutropenic patients
No evidence of benefit
May feel compelled to use in the face of clinical deterioration from sepsis, pneumonia, or fungal infection, but benefit unclear
In bone marrow or peripheral blood stem cell transplantation
Use to mobilize stem cells from marrow
Use to hasten myeloid recovery
In acute myeloid leukemia
G-CSF of minor or no benefit
GM-CSF of no benefit and may be harmful
In myelodysplastic syndromes
Not routinely beneficial
Use intermittently in subset with neutropenia and recurrent infection
What Dose and Schedule Should Be Used?
G-CSF: 5 mg/kg per day subcutaneously
GM-CSF: 250 mg/m^2 per day subcutaneously
Pegfilgrastim: one dose of 6 mg 24 h after chemotherapy
When Should Therapy Begin and End?
When indicated, start 24–72 h after chemotherapy
Continue until absolute neutrophil count is 10,000/μL
Do not use concurrently with chemotherapy or radiation therapy

Abbreviations: CSF, cerebrospinal fluid; G-CSF, granulocyte colony-stimulating factor; GM-CSF, granulocyte-macrophage colony-stimulating factor.

Source: From the American Society of Clinical Oncology: J Clin Oncol 24:3187, 2006.

regimens associated with a 20% incidence of febrile neutropenia. "Dose-dense" regimens, where cycling of chemotherapy is intended to be completed without delay of administered doses, may also benefit, but such patients should be on a clinical trial. Administration of G-CSF in these circumstances has reduced the incidence of febrile neutropenia in several studies by about 50%. Most patients, however, receive regimens that do not have such a high risk of expected febrile neutropenia, and therefore most patients initially should not receive G-CSF or GM-CSF. Special circumstances—such as a documented history of febrile neutropenia with the regimen in a particular patient or categories of patients at increased risk, such as patients older than age 65 years with aggressive lymphoma treated with curative chemotherapy regimens; extensive compromise of marrow by prior radiation or chemotherapy; or active, open wounds or deep-seated infection—may support primary treatment with G-CSF or GM-CSF. Administration of G-CSF or GM-CSF to afebrile neutropenic patients or to patients with low-risk febrile neutropenia is not recommended, and patients receiving concomitant chemoradiation treatment, particularly those with thoracic neoplasms, likewise are not generally recommended for treatment. In contrast, administration of G-CSF to high-risk patients with febrile neutropenia and evidence of organ compromise including sepsis syndrome, invasive fungal infection, concurrent hospitalization at the time fever develops, pneumonia, profound neutropenia ($<0.1 \times 10^9$/L), or age >65 years is reasonable.

Secondary prophylaxis refers to the administration of CSFs in patients who have experienced a neutropenic complication from a prior cycle of chemotherapy; dose reduction or delay may be a reasonably considered alternative. G-CSF or GM-CSF is conventionally started 24–72 h after completion of chemotherapy and continued until a PMN count of 10,000/μL is achieved, unless a "depot" preparation of G-CSF such as pegfilgrastim is used, where one dose is administered at least 14 days before the next scheduled administration of chemotherapy. Also, patients with myeloid leukemias undergoing induction therapy may have a slight reduction in the duration of neutropenia if G-CSF is commenced after completion of therapy and may be of particular value in elderly patients, but the influence on long-term outcome has not been defined. GM-CSF probably has a more restricted utility than G-CSF, with its use currently limited to patients after autologous bone marrow transplants, although proper head-to-head comparisons with G-CSF have not been conducted in most instances. GM-CSF may be associated with more systemic side effects.

Dangerous degrees of thrombocytopenia do not frequently complicate the management of patients with solid tumors receiving cytotoxic chemotherapy (with the possible exception of certain carboplatin-containing regimens), but they are frequent in patients with certain hematologic neoplasms where marrow is infiltrated with tumor. Severe bleeding related to thrombocytopenia occurs with increased frequency at platelet counts <20,000/μL and is very prevalent at counts <5000/μL.

The precise "trigger" point at which to transfuse patients has been defined as a platelet count of 10,000/μL or less in patients without medical comorbidities that may increase the risk of bleeding. This issue is important not only because of the costs of frequent transfusion, but unnecessary platelet transfusions expose the patient to the risks of allosensitization and loss of value from subsequent transfusion owing to rapid platelet clearance, as well as the infectious and hypersensitivity risks inherent in any transfusion. Prophylactic transfusions to keep platelets >20,000/μL are reasonable in patients with leukemia who are stressed by fever or concomitant medical conditions (the threshold for transfusion is 10,000/μL in patients with solid tumors and no other bleeding diathesis or physiologic stressors such as fever or hypotension, a level that might also be reasonably considered for leukemia patients who are thrombocytopenic but not stressed or bleeding). In contrast, patients with myeloproliferative states may have functionally altered platelets despite normal platelet counts, and transfusion with normal donor platelets should be considered for evidence of bleeding in these patients. Careful review of medication lists to prevent exposure to nonsteroidal anti-inflammatory agents and maintenance of clotting factor levels adequate to support near-normal prothrombin and partial thromboplastin time tests are important in minimizing the risk of bleeding in the thrombocytopenic patient.

Certain cytokines in clinical investigation have shown an ability to increase platelets (e.g., IL-6, IL-1, thrombopoietin), but clinical benefit and safety are not yet proven. IL-11 (oprelvekin) is approved for use in the setting of expected thrombocytopenia, but its effects on platelet counts are small, and it is associated with side effects such as headache, fever, malaise, syncope, cardiac arrhythmias, and fluid retention. Eltrombopag and romiplostim are thrombopoietin agonists with demonstrated efficacy in certain thrombocytopenic states, but they have not been systematically studied in chemotherapy-induced thrombocytopenia.

Anemia associated with chemotherapy can be managed by transfusion of packed RBCs. Transfusion is not undertaken until the hemoglobin falls to <80 g/L (8 g/dL), compromise of end organ function occurs, or an underlying condition (e.g., coronary artery disease) calls for maintenance of hemoglobin >90 g/L (9 g/dL). Patients who are to receive therapy for >2 months on a "stable" regimen and who are likely to require continuing transfusions are also candidates for erythropoietin (EPO). Randomized trials in certain tumors have raised the pos-