Clinical Use of Subcutaneous G-CSF or GM-CSF in Malignancy

Guest Editor
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Colon-stimulating factors are glycoproteins that act on hematopoietic cells by binding to specific cell surface receptors and stimulating proliferation, differentiation commitment, and a degree of end-cell functional activation. Granulocyte colony-stimulating factor (G-CSF), produced by monocytes, fibroblasts, and endothelial cells, regulates the production of neutrophils within the bone marrow and affects neutrophil progenitor proliferation.[1,2] While the precise mechanism by which G-CSF is able to induce leukemia remission is unknown. Among hypotheses are a direct effect of G-CSF on AML blast cells, partial commitment, regulating the expansion and maturation of primitive hematopoietic progenitors.[3] The GM-CSF cell receptor is expressed on granulocyte, erythroid, megakaryocyte, and macrophage progenitor cells. GM-CSF principally affects proliferation, differentiation, and activation of granulocytes and macrophages by inducing partially committed progenitor cells to divide and differentiate in the granulocyte-macrophage pathways. GM-CSF also plays a vital role in hematopoiesis by enhancing numerous functional activities of mature effector cells (eg, neutrophils, monocytes, macrophages, dendritic cells) involved in antigen presentation and cell-mediated immunity.[4-7] G-CSF regulates both basal and neutrophil production and increased production and release of neutrophils from the marrow in response to infection. GM-CSF mediates its action on the neutrophil lineage through its effects on phagocytic accessory cells and its synergy with G-CSF.[8] G-CSF and GM-CSF differ somewhat in the number and composition of peripheral blood progenitor cells (PBPCs) and effectors cells mobilized to the peripheral blood.[9] Filgrastim, Pegfilgrastim, and Sargramostim

Filgrastim (Neupogen) is a human G-CSF produced by recombinant DNA technology. It is indicated for the treatment of patients with severe, chronic neutropenia; receiving myelosuppressive chemotherapy or bone marrow transplant; undergoing PBPC collection and therapy; and for acute myelogenous leukemia (AML) patients receiving induction or consolidation chemotherapy.[10] Pegfilgrastim (Neulasta) is a crossed-linked form of G-CSF (lenograstim) in which bone fibrin and polyethylene glycol indicated for decreasing the incidence of infection in patients receiving myelosuppressive chemotherapy for nonmyeloid malignancies.[11] Sargramostim (Leukine), a human GM-CSF produced by recombinant DNA technology in a yeast (Saccharomyces cerevisiae) expression system, was initially approved in the setting of bone marrow transplant. Although not labeled for chemotherapy-induced neutropenia, its potential is being demonstrated to increase the rate of neutrophil recovery following chemotherapy.[12,13] and is included in the American Society of Clinical Oncology’s (ASCO) evidence-based clinical practice guidelines for this use.[14] Among current clinical indications, sargramostim is given to shorten the duration of neutropenia following induction chemotherapy in older adults with AML; for myeloid reconstitution after autologous or allogeneic bone marrow transplantation (BMT); and for BMT failure or engraftment delay, to mobilize autologous PBPCs following transplantation.[15]

Emerging Data From Colony-Stimulating Factor Trials G-CSF facilitates adherence to full dose intensity in both standard and dose-reintensified regimens.[16] G-CSF support during combination chemotherapy (cisplatin, doxorubicin, cyclophosphamide [Cytoxan, Neosar]) to treat advanced or recurrent endometrial cancer allowed patients to remain on therapy for an average of 7 months, with no dose-limiting neutropenia.[17] Once-per-cycle dosing of pegfilgrastim (pegylated recombinant filgrastim), a longer-acting version of G-CSF, has been evaluated in clinical trials using myelosuppressive chemotherapy in breast cancer, and has been demonstrated comparable in safety and efficacy for filgrastim for decreasing the duration of severe neutropenia after chemotherapy in patients with nonmyeloid malignancy.[18,19] An additional beneficial action of adjuvant G-CSF in premenopausal, node-negative breast cancer patients has recently been proposed. In this setting, in addition to stimulating blood stem cells, may activate and repopulate dormant breast cancer stem cells (personal communication, K. Altundag, 2004). The activated breast cancer stem cells may then become chemosensitive to various cell cycle-specific chemotherapy agents.[20] Both G-CSF and GM-CSF play important roles in modern cancer treatment, and new data regarding their uses have the potential to impact the practice of oncology. Researchers are exploring new avenues of investigation to determine the antitumor potential of both of these agents. Data supporting the use of G-CSF as an antitumor agent have been largely anecdotal or retrospective. G-CSF may be useful in selected AML patients who are not candidates for traditional treatments, and complete remissions have been reported with G-CSF alone in treatment of AML. A short course of G-CSF (300 mg/d for 13 days) resulted in complete hematologic remission in a patient with acute undifferentiated leukemia. Two further relapses in this patient were also successfully treated with G-CSF. The patient died 50 months after starting G-CSF therapy from progressive neutropenia, anemia, thrombocytopenia, and acute leukemia, despite reinstitution of G-CSF therapy.[21] Leukemic cells from AML patients with the t(8;21) translocation undergop neutrophil differentiation following in vitro exposure to G-CSF.[22] A second patient with t(8;21) (q22;q22) karyotype achieved a complete remission when treated with G-CSF (10 µg/kg for 14 days), in the absence of cytotoxic chemotherapy.[23] A third case report describes a patient who achieved cytogenic remission with G-CSF (lenograstim 3 mg/kg/d). Peripheral blood and bone marrow aspirate were normal in this patient following treatment, and the t(9;11) + 8 clone was no longer detectable.[24] No serious adverse events have been observed in the approximately 16 case reports of complete response achieved with G-CSF treatment of patients with AML.[24] The mechanism by which G-CSF is able to induce leukemia remission is unknown. Among hypotheses are a direct effect of G-CSF on AML blasts, degradation of AML1-ETO (an oncprotein that blocks G-CSF-mediated cell differentiation in t(8;21) AML), the activation of STAT (signal transducers and activators of transcription) pathways on myeloid leukemic cells, and induction of leukemic cell apoptosis.[25,26] The role of G-CSF and GM-CSF in hematopoietic recovery and control of disease in patients with chemosensitive gynecologic cancer has been assessed in one trial. Thirty-seven patients with ovarian cancer patients and 24 breast cancer patients were treated with high-dose chemotherapy (carboplatin [Paraplatin], etoposide, and melphalan [Alkeran]), and then randomly assigned to receive either 5 mg/kg of G-CSF or GM-CSF until day 13 after PBPC transplantation. Significantly higher T-cell counts were observed in G-CSF-treated patients during early and late posttransplant follow-up, and patients who received G-CSF showed a significantly longer median time to progression.[29] Data supporting the use of GM-CSF (sargramostim), either alone or in combination with chemotherapy, continue to emerge. The articles in this supplement examine the role of this key cytokine in a variety of clinical settings, based on presentations from the ASCO 40th Annual Meeting, held June 5-8, 2004, in New Orleans. GM-CSF Use in AML Successful treatment of AML requires the control of bone marrow and systemic disease and specific treatment of central nervous system disease, if present. The cornerstone of this strategy includes systemically administered combination chemotherapy, which poses a particular problem for some patient populations (for example, the induction mortality rate is especially high among older adults with AML).[30,31] Extending survival in this group of patients is therefore an area of active clinical research, and cytokines continue to be used to prime AML blasts to the cytotoxic actions of chemotherapy. Response rate, overall survival, and relapsefree survival are improved in elderly, high-risk patients with AML and myelodysplastic syndrome when G-CSF is used to support intensive chemotherapy.[32] In this supplement, we report a trial of GM-CSF used to enhance the cytoreductive effects of low-dose cytarabine in elderly patients with AML and myelodysplastic syndrome who were intolerant of conventional induction chemotherapy.

Colony-Stimulating Factors in Melanoma
The outcome of therapy for metastasized melanoma remains poor. Biochemotherapy- combination chemotherapy and biotherapy-appears to have a higher response rate than single-agent or combination regimens.[33-36] Patients with metastatic melanoma have been treated with paclitaxel and dacarbazine, with G-CSF added to allow escalated doses while limiting toxicity.[37,38] A recent phase II trial demonstrated that initial starting doses of paclitaxel and dacarbazine, in combination, could be escalated from 135 and 800 mg/m², respectively, to 250, and 1,000 mg/m² when G-CSF was included to limit myelosuppression in patients with advanced malignant melanoma.[39] One of the most potentially important activities of GM-CSF in the treatment of melanoma is its ability to activate macrophages, causing them to become cytotoxic for human melanoma cells at doses low enough to avoid the toxicity associated with interleukin-2 (IL-2), a cytokine commonly used in treatment.[40-42] GM-CSF may provide an antitumor effect that prolongs disease-free and overall survival in patients with stage III/IV melanoma who are clinically disease-free,[40] and investigation of GM-CSF in patients with metastatic melanoma undergoing chemotherapy shows promising results.[41] To take advantage of the different functions but complementary actions of GM-CSF and IL-2, E. George Elias et al conducted a phase II trial of this combination as adjuvant treatment of cutaneous melanoma in high-risk patients. Continuing this theme, John Fruehauf and colleagues performed a pilot study of the DVS regimen (docetaxel [Taxotere], vinorelbine [Navelbine], sargramostim) for the treatment of patients with stage IV melanoma, either following initial biochemotherapy or as first-line treatment.

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Results of both of these trials are reported within. **GM-CSF in Breast and Female Genital Tract Cancer**

Reported in this supplement, Christian Kurzchiner and colleagues conducted a trial in which the safety and efficacy of chronic, low-dose, salvage GM-CSF were evaluated in heavily pretreated patients with chemotherapy-refractory carcinomas of the breast or female genital tract cancer. Their findings imply that GM-CSF has a pleiotropic effect in these tumors by both activating the dendritic cell-mediated antitumor response and directly inducing growth arrest by stimulating intratumoral GM-CSF receptors. **Conclusion**

Both G-CSF and GM-CSF are cytokines with a crucial role as a component of different combination regimens used for the immunotherapy or biochemotherapy of malignancies. As results from the clinical trials reported in this supplement suggest, GM-CSF may well have clinical benefits beyond enhancing neutrophil recovery. While encouraging, these results must be augmented by further study of the immunologic function of GM-CSF and its therapeutic potential in the treatment of cancer. Many recent investigations remain relevant regarding specific immune modulation with this agent, including an optimal dosing schedule and its combination with other agents and the specific mechanism of effect. Future clinical trials exploring the extent to which the addition of GM-CSF to current anticancer therapies can improve outcomes and produce less toxicity will help to answer these questions.

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