Original Article

Long-Term Outcomes of Myeloid Growth Factor Treatment

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Key Words

G-CSF, chronic neutropenia, leukemia, myeloid growth factors, survival

Abstract

Myeloid growth factors are used to reduce myelotoxicity and the risk of infection after cancer chemotherapy and in patients with chronic neutropenia. This article addresses the long-term benefits and risks associated with granulocyte colony-stimulating factor (G-CSF) therapy in both settings. A systematic review of randomized controlled trials recently reported long-term outcomes regarding the risk of second malignancies and overall survival. Based on these studies, the risk for acute myeloid leukemia (AML) associated with known carcinogenic agents, such as chemotherapy, could not be distinguished from any risk associated with growth factor support. However, the enhanced delivery of chemotherapy dose intensity enabled by the use of G-CSF in these studies was associated with a significant reduction in all-cause mortality. Although some reduction in treatment-related mortality with G-CSF support may occur, the observed improvement in long-term survival likely relates to better disease control with more-intense G-CSF–supported chemotherapy. Myeloid growth factors have also been shown to benefit patients with severe chronic neutropenia. Almost all patients with cyclic, congenital, or idiopathic neutropenia experience response to G-CSFs. Treatment is titrated to determine a dose that provides a safe elevation in neutrophil counts. Reports have shown that patients can be maintained for years at the same dose after adjusting for growth and development. In congenital neutropenia, the inherent risk of developing myelodysplastic syndromes or AML requires careful monitoring, including routine blood counts and annual bone marrow examinations. (*JNCCN* 2011;9:945-952)

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Myeloid growth factors have been used for more than 20 years to ameliorate myelotoxicity after cancer chemotherapy and to prevent infections in patients with chronic neutropenia. Almost all data on long-term outcomes come from studies of granulocyte colony-stimulating factor (G-CSF). This article focuses on the long-term benefits and risks associated with G-CSF therapy, including data for other myeloid factors, as available.

Chemotherapy-Induced Neutropenia

G-CSF reduces neutropenic complications, including febrile neutropenia, infection, and infection-related mortality, in patients undergoing cancer chemotherapy, while enabling an increase in delivered chemotherapy dose intensity.[1,2] Clinical practice guidelines from NCCN, ASCO, and EORTC recommend myeloid growth factors be considered for patients undergoing chemotherapy who have a 20% or greater risk of febrile neutropenia.[3–5] G-CSF support is closely correlated with the delivery of systemic chemotherapy and, therefore, both the long-term efficacy and harm of chemotherapy. This article summarizes the effects of G-CSF support on disease recurrence, toxicity, and overall survival.

Many pivotal randomized controlled trials of myeloid growth factors assessed early outcomes, particularly neutropenia, febrile neutropenia, infections, and short-term side effects. A meta-analysis of studies of primary G-CSF prophylaxis, in which G-CSF was initiated in the first cycle of chemotherapy, showed a significant reduction in early mortality for patients receiving G-CSFs.[1] The adverse event observed was transient mild to moderate bone pain. Importantly, patients randomized to treatment with primary G-CSF prophylaxis received significantly greater chemotherapy relative dose intensity (RDI) than control patients who did not receive prophylaxis.

Cancer chemotherapeutic agents are associated with an increased risk of acute myeloid leukemia (AML).[6,7] Several common chemotherapeutic agents are considered to be leukemogenic[8–13] (Table 1). Retrospective registry studies have suggested increased risk of AML and myelodysplastic syndromes (MDS) in patients undergoing chemotherapy with myeloid growth factor support.[14,15] An individual patient data meta-analysis of 19 randomized controlled trials of adjuvant chemotherapy in 7110 patients with early breast cancer treated with epirubicin, most of whom also received cyclophosphamide, reported a cumulative probability of AML/MDS out to 8 years of 0.55% (95% CI, 0.33%–0.78%).[13] The risk of AML/MDS increased significantly with the cumulative dose of epirubicin. In multivariate regression analysis, the cumulative doses of epirubicin and cyclophosphamide, but not of G-CSF, were independent risk factors for AML/MDS. Because G-CSF enables the delivery of more dose-intense and dose-escalated chemotherapy, clearly separating any leukemogenic effects of the myeloid growth factors from those of greater doses or dose intensity of chemotherapy is difficult, if not impossible.

Randomized Controlled Trials of Long-Term Outcomes

A systematic review recently reported on randomized controlled trials in adult patients with solid tumors or lymphoma undergoing systemic chemotherapy with or without primary G-CSF support with a follow-up of at least 2 years.[16] The occurrence of AML or MDS and all-cause mortality represented the primary outcomes for analysis. A priori planned exploratory analyses included subgroup comparisons based on the type of cancer, the type of chemotherapy regimen, and chemotherapy RDI in the study arms. The search identified 25 eligible randomized controlled trials, including 23 reporting AML and/or MDS,[16] comprising 6058 patients who were randomized to G-CSF and 6746 controls. Mean and median follow-ups of 60 and 53 months were observed, respectively. The studies included 2 forms of G-CSF: filgrastim (n = 20) and lenograstim (n = 5). Sixteen randomized controlled trials reported RDIs according to treatment group assignment. The median RDI in the G-CSF–supported patients was 98.1% compared with 93.5% in controls. Estimated chemotherapy RDI with G-CSF support versus controls in studies with the same drugs and doses, dose-dense schedules, and dose-escalation regimens were 1.18, 1.46, and 1.23, respectively.

Table 1 Medical Risk Factors for Treatment-Associated Leukemia and Myelodysplastic Syndromes

Chemotherapy
- Alkylating agents: nitrogen mustard, chlorambucil, cyclosphosphamide, nitrosoureas
- Topoisomerase II inhibitors:
  - Anthracyclines: doxorubicin, daunorubicin, epirubicin
  - Mitoxantrone
  - Epipodopyllotoxins: etoposide, tenisposide
- Topoisomerase I inhibitors: topotecan, irinotecan
- Combinations: mechlorethamine, vincristine, procarbazine, prednisone
- Dose and schedule dependency

Radiation therapy: particularly total nodal radiation

Combined chemotherapy and radiation therapy

Others: splenectomy, increasing age, thrombocytopenia

Over the observation period, G-CSF support was associated with a significant reduction in all-cause mortality (relative risk [RR], 0.897; 95% CI, 0.857–0.938; $P < .001$).[16] The estimated absolute reduction in all-cause mortality was 3.40% (95% CI, 2.01%–4.80%; $P < .001$) across studies. The RR in studies that randomized patients either to receive G-CSF to support dose-dense chemotherapy regimens or to a control group was 0.841 ($P < .001$), and for dose-escalated schedules was 0.785 ($P = .097$). For studies in which the dose and schedule were the same in both groups, the RR was 0.942 ($P = .088$; Figure 1). A meta-regression analysis showed a significant association between RR reduction for all-cause mortality and the planned RDI with G-CSF support compared with controls ($P = .0159$; Figure 2). Meta-regression analysis also showed a significant association between reduced mortality and both relative ($P = .0148$) and absolute increases ($P = .0266$) in delivered RDI in patients receiving G-CSF support compared to controls.

Second malignancies were reported in 115 patients undergoing G-CSF–supported chemotherapy (3.28%) and in 114 controls (3.25%). AML or MDS was reported in 65 patients, including 43 in the G-CSF arms and 22 in the control arms. Although no significant increase was seen in all sec-

ond malignancies in patients randomized to primary G-CSF–supported chemotherapy (RR, 1.01; 95% CI, 0.78–1.3; P = .941), the risk of AML or MDS was significantly greater in these patients (RR, 1.92; 95% CI, 1.19–3.07; P = .007). The risk of AML/MDS did not vary significantly according to tumor type (Table 2). The absolute increase in AML/MDS in patients randomized to G-CSF compared with controls was 0.41% (95% CI, 0.11%–0.73%; P = .009; Figure 3). The absolute risk difference of AML/MDS was greatest in patients treated with chemotherapy regimens associated with dose escalation and was least among patients on dose-dense schedules. The risk of AML/MDS was significantly greater in studies in which G-CSF support was associated with greater total dose of chemotherapy (RR, 2.334; 95% CI, 1.237–4.403; P = .009), but not when the planned total dose of chemotherapy was the same in each arm. Furthermore, no significant association was seen between the duration of follow-up and the RR of AML/MDS among patients receiving G-CSF support (P = .941).

In this study with a median follow-up of nearly 5 years, the RR for AML/MDS in patients randomized to G-CSF was 1.92 compared with controls, with an absolute increased risk of 0.4%.[16] Alternatively, the RR for all-cause mortality with G-CSF–supported chemotherapy was 0.897, with an absolute decrease in mortality of 3.4%. Some randomized controlled trials were designed to administer greater-dose or dose-intensity chemotherapy in the G-CSF–supported arm. However, even in studies in which patients were scheduled to receive the same dose, schedule, duration, and dose intensity of chemotherapy, those randomized to receive G-CSF often received greater RDI and/or total doses of chemotherapy by virtue of fewer dose reductions and treatment delays, resulting in an imbalance in chemotherapy drug exposure.

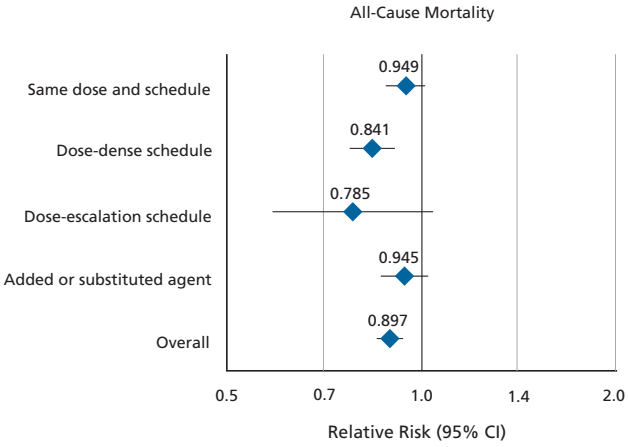

Figure 1 Diagram illustrating the relative risk and 95% CIs for all-cause mortality across randomized controlled trials stratified by type of regimen, including same dose and schedule, dose-dense schedule, dose-escalation schedule, and single drug added or substituted.

Myeloid Growth Factors, Chemotherapy-Induced Neutropenia, and AML

Based on this analysis, it is difficult, if not impossible, to separate the risk of AML associated with known

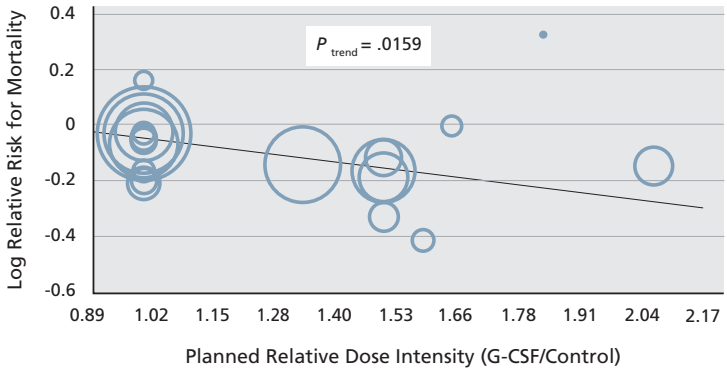

Figure 2 Graphic display of meta-regression of planned relative dose intensity on the natural logarithm of the relative risk for mortality in granulocyte colony-stimulating factor (G-CSF)–supported chemotherapy compared with control. Each study is represented by a circle, the area of which is proportional to the weight provided by each study to overall estimate.
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Table 2 Relative and Absolute Risk Reduction in AML and MDS and All-Cause Mortality With Granulocyte Colony-Stimulating Factor Versus Control by Cancer Type and Regimen

Group		AML/MDS					All-Cause Mortality			
			Relative Risk		Absolute Risk Difference (%)			Relative Risk		Absolute Risk Difference (%)	
	Subgroup	N	(95% CLs)		(95% CLs)		N	(95% CLs)		(95% CLs)	
Overall	-	23	1.915*	1.195, 3.070	0.41*	0.11, 0.73	25	0.897†	0.857, 0.938	-3.40†	-4.80, -2.01
Cancer type	Breast	7	1.811	0.897, 3.656	0.30	-0.06, 0.67	7	0.902‡	0.815, 0.998	-1.89‡	-3.72, -0.06
	Endometrial	2	2.916	0.305, 27.872	0.68	-0.66, 2.02	2	0.945	0.874, 1.021	-4.64	-10.89, 1.61
	Germ cell	1	0.336	0.014, 8.170	-0.77	-2.90, 1.36	1	0.849	0.568, 1.269	-4.42	-15.23, 6.38
	Hodgkin	1	2.013	0.820, 4.942	1.51	-0.39, 3.41	1	0.660‡	0.452, 0.963	-4.42‡	-8.39, -0.46
	Non-Hodgkin's	8	2.732	0.804, 9.280	0.45	-0.13, 1.03	10	0.895*	0.832, 0.963	-4.66*	-7.57, -1.75
	Lung	3	0.956	0.101, 9.072	0.00	-1.66, 1.66	3	0.945	0.875, 1.021	-4.88	-11.46, 1.71
	Urothelial	1	0.963	0.061, 15.229	-0.03	-2.13, 2.07	1	0.868‡	0.772, 0.977	-11.45‡	-20.79, -2.11
Regimen category	Same drugs, dose, and schedule	9	1.947	0.487, 7.779	0.35	-0.51, 1.21	11	0.942	0.881, 1.009	-2.90	-6.22, 0.42
	Dose-dense schedule	6	1.288	0.577, 2.875	0.11	-0.25, 0.48	6	0.841†	0.776, 0.912	-4.79†	-7.01, -2.57
	Dose escalation	3	2.211	0.940, 5.203	1.34	-0.09, 2.78	3	0.785	0.598, 1.045	-2.97	-6.46, 0.52
	Added or substituted agent	5	2.827‡	1.013, 7.885	0.56‡	0.01, 1.12	5	0.945	0.868, 1.029	-1.65	-4.08, 0.78

Abbreviations: AML, acute myeloid leukemia; CLs, confidence limits; MDS, myelodysplastic syndromes; N, number of trials.
*$P < .01$
†$P < .001$
‡$P < .05$
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carcinogenic agents, such as the alkylating agents and topoisomerase II inhibitors, from that associated with G-CSF. This systematic review, however, did show a significant association between planned and actually delivered RDI and reduced mortality, presumably from a reduced risk of disease-specific mortality, consistent with previously reported meta-analyses of G-CSF prophylaxis and treatment.[1,17] Although some reduction in treatment-related mortality with G-CSF support may occur, the observed improvement in long-term survival likely relates to better disease control with more-intense G-CSF–supported chemotherapy.[16]

Severe Chronic Neutropenia

Severe chronic neutropenia (SCN) is an immunodeficiency disorder in which neutropenia, generally in the absence of other host-defense defects, predisposes patients to severe and recurrent bacterial infections.[18,19] Patients with SCN usually have blood neutrophil counts that are chronically or intermittently less than 0.5×10^9/L for several years or their lifetime. SCN can be inherited or acquired and is usually categorized as cyclic, congenital, or idiopathic based on clinical and genetic information.[20] Development of the myeloid growth factors,

particularly G-CSF, has provided major long-term benefits to these patients.

Causes of SCN

The responses to myeloid growth factors are distinctive for each type of SCN. The SCN disease categories are cyclic neutropenia, severe congenital neutropenia, and chronic idiopathic neutropenia.

Cyclic neutropenia is a rare autosomal dominant hematologic disorder, usually attributable to mutations in the gene for neutrophil elastase (*ELANE*).[21,22] Patients with cyclic neutropenia have oscillations in blood neutrophils usually at 3-week intervals, measured from nadir to nadir. During the period of most severe neutropenia, fever, severe mouth ulcers, pharyngitis, sinusitis, anal ulcers, and abdominal pain frequently occur, and some patients develop bacteremia, often clostridial bacteremia, leading to septic shock and death. Thus, before the availability of the myeloid growth factors, these patients faced the risk of a sudden septic event every 3 weeks from childhood onward.

Severe congenital neutropenia is also a rare inherited hematologic disorder. It occurs both as an autosomal dominant disorder attributable to mutations in the *ELANE* gene[23] and as an autosomal recessive disorder attributable to mutations in the *HAX1* gene (Kostmann syndrome).[24] Fever and deep tissue infections are severe and frequent. Several other inherited diseases with chronic neutropenia exist that vary in severity as part of the clinical phenotype.[25]

Chronic idiopathic neutropenia is an acquired hematologic disorder affecting children and adults. In children, it is often diagnosed as autoimmune neutropenia, but diseases defining immunologic tests are not generally available. In adults, it predominantly occurs in women.[18,26] Characteristically, adult patients have both neutropenia and lymphocytopenia, with stable reductions in both populations. If neutrophils are less than 0.5×10^9/L, recurrent fevers, sinusitis, pharyngitis, and other respiratory tract infections occur frequently.

Clinical Trials

Clinical trials of myeloid growth factors for treating SCN began nearly 25 years ago.[27–31] A randomized trial established the benefits of G-CSF treatment[32] and was followed by a long-term observational study.[33,34] The multicenter randomized controlled trial established the effectiveness of G-CSF for long-term treatment for cyclic, congenital, and idiopathic neutropenia.[33] G-CSF doses were gradually increased to

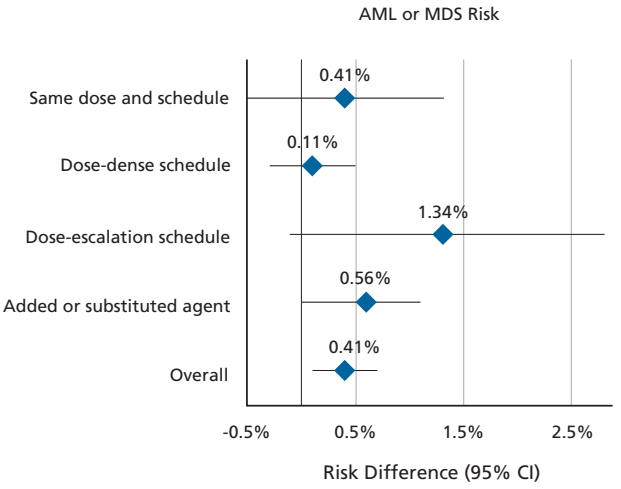

Figure 3 Diagram illustrating the absolute risk difference and 95% CIs for all acute myeloid leukemia (AML) or myelodysplastic syndromes (MDS) across randomized controlled trials stratified by type of regimen, including same dose and schedule, dose-dense schedule, dose-escalation schedule, and single drug added or substituted.

achieve a blood neutrophil count of 2.0×10^9/L in the first month, and patients were treated for 4 months on study, with continuing therapy offered to those who showed a response. The study end points were blood neutrophil counts, infections, and infection-related events for similar periods with and without G-CSF treatment. This trial clearly established the benefits of G-CSF in increasing blood neutrophils and decreasing the occurrence of fever and infection-related events. It was not long enough to determine the long-term consequences of this new therapy.

Clinical Trials of Granulocyte-Macrophage Colony-Stimulating Factor for Treatment of SCN

Several reports exist of patients receiving granulocyte-macrophage colony-stimulating factor (GM-CSF) for weeks to months for the treatment of cyclic, congenital, and idiopathic neutropenia.[30,35,36] Most, but not all, of these reports indicate that GM-CSF is effective, with increases in blood neutrophils, but the studies are small and no randomized controlled trials have been conducted.

Long-Term G-CSF Therapy

In 1994, regulatory authorities in the United States and Europe approved marketing of recombinant human G-CSF for treatment of SCN. These authorities, however, required follow-up of patients to determine long-term benefits and risks. A team of investigators established the Severe Chronic Neutropenia Inter-

national Registry (SCNIR) to determine the natural history and treatment risks and benefits of long-term myeloid growth factor therapy.

Hematologic Effects

SCNIR data established that more than 90% of patients with SCN experience response to G-CSF with increased neutrophils and decreased infection-related events.[34,35] Responses are disease- and patient-specific. Most patients with idiopathic and cyclic neutropenia experience response to G-CSF in low doses (1–4 mcg/kg administered subcutaneously daily or every other day), titrating the dose, starting low to avoid bone pain and other acute adverse effects. Patients with idiopathic neutropenia usually experience response in 1 to 3 days. In cyclic neutropenia, the timing for increase in blood neutrophils depends on the phase of the patient's cycle when therapy begins. Blood neutrophils will continue to oscillate, with greater amplitude of oscillation and a shorter periodicity than before treatment (i.e., 14- instead of 21-day cycle length).

Shortening the duration of neutropenia seems to provide clinical benefits. Severe congenital neutropenia has more variable responses, with required doses ranging from 1 to more than 100 mcg/kg/d, and a delay of up to 10 days before blood neutrophils increase. The delay is probably attributable to the absence of neutrophils in the proliferative and storage pools in the bone marrow before therapy. Clinical improvement is predictable if blood neutrophils are increased to approximately 1.0×10^9/L.[34,35]

Infection-Related Events

A randomized controlled trial established the effectiveness of G-CSF to prevent infections.[32] Subsequent observational data confirm this finding. In general, the blood neutrophil response is a satisfactory surrogate for establishing benefit. Patients for whom G-CSF failed (~ 3%–5% of congenital patients) continue to have problems with recurrent infections.

Oral Health

Neutrophils are essential for oral health, and patients with SCN have many oral problems, including mouth ulcers, gingivitis, periodontal inflammation, and loss of deciduous and permanent teeth. Most of these problems are attributable to neutropenia, although functional defects of neutrophils may also contribute. G-CSF therapy decreases mouth ulcers and gingivitis, but does not reverse more severe periodontal problems. For this reason, experts advise treatment from early childhood, but the clinical benefits of starting treatment to prevent periodontal disease have not been established.

Quality of Life

Retrospective studies and observational research indicate that G-CSF treatment improves the quality of life for patients with SCN and their families.[37] Treatment reduces symptoms associated with acute and chronic inflammation, including fatigue and anorexia, with major secondary benefits to the family.

G-CSF for Other Causes of SCN

Observational studies indicate that most patients with SCN will increase blood neutrophils in response to G-CSF. These include Barth syndrome, Shwachman-Diamond syndrome, glycogen storage disease type 1B, HIV infections, and several other conditions.

Adverse Events

Hematopoietic Effects

Administration of G-CSF causes acute bone pain and other musculoskeletal symptoms, usually attributed to expansion of myeloid cells in the bone marrow. Bone pain usually abates, and most patients do not require analgesic medications.

Long-term G-CSF therapy is usually associated with an increase in hemoglobin and hematocrit. Pretreatment platelet counts are often elevated secondary to chronic inflammation and revert to normal on treatment. Hematopoietic exhaustion and cytopenias are not expected consequences of treatment. If they occur, other causes or complications should be investigated.

Splenomegaly occurs on chronic therapy with G-CSF; the degree of increase in the spleen size varies substantially. In children, the increase in size may be detected during physical examination. In adults, it is infrequently noted except on imaging studies. Management rests largely on careful observation and using the minimal G-CSF dose necessary to maintain blood neutrophils greater than 1.0×10^9/L.

Leukemia and Other Malignancies

Several cases of MDS/AML were reported in severe congenital neutropenia before the availability of G-CSFs and other myeloid growth factors.[38] Data from the SCNIR for a population of 374 patients with severe congenital neutropenia and 29 with Shwachman-Diamond syndrome were reported in 2006 to show a hazard ratio of MDS/AML that increased significantly over time, from 2.9% per year after 6 years to 8.0% per year after 12 years on G-CSF. After 10 years, the cumulative incidence was estimated to be 8% for sepsis mortality and 21% for MDS/AML. Subgroup analysis indicated that patients who received more than the median dose of G-CSF (≥ 8 mcg/kg/d) but achieved less than the median absolute neutrophil count (ANC) response (ANC < 2.188×10^9/L at 6–18 months) were at greater risk. In the group requiring more G-CSF, the cumulative incidence of AML/MDS was estimated to be 40% after 10 years. With longer follow-up, the estimated annual risk of MDS/AML in this population of 374 patients was adjusted downward from 2.9% to a plateau of 2.3% per year after 10 years.[39] Other analyses have indicated that patients with and without the ELANE mutation are at similar risk, and cases of AML/MDS also have been observed in patients with HAX1 mutations and other causes of SCN, both with and without G-CSF therapy.[40] Patients with cyclic and idiopathic neutropenia have no or, at most, a very low risk of MDS/AML. The biologic basis for the difference in the risk of AML among patients with cyclic versus congenital neutropenia is unknown.

Other Long-Term Observations

Decreased bone mineral density may occur in patients on long-term G-CSF. A recent report on 128 patients (40 children and 88 adults) indicated that decreased bone mineral density is relatively common in this population, particularly in children with congenital neutropenia and patients who have received G-CSF for longer periods.[41] Fractures, however, are very uncommon, and the cause-and-effect relationships between the decreased bone mineral density and treatment are not yet clear.

Pregnant patients with SCN tend to have frequent spontaneous abortions. Observational data indicate that G-CSF treatment during pregnancy is protective of maternal health and reduces fetal loss, without increasing fetal malformations.[42]

Alternative to Myeloid Growth Factors

Hematopoietic stem cell transplantation is the only effective alternative to myeloid growth factors for the treatment of SCN.[43,44] Transplantation is limited by the availability of suitably matched donors and the risk of early posttransplant mortality. Experts agree that unless a donor who is an excellent match is available, G-CSF is the recommended initial therapy with careful follow-up, especially for patients with severe congenital neutropenia.

Summary of Long-Term Outcomes in SCN

The development of the myeloid growth factors greatly benefited patients with SCN. Almost all patients with cyclic, congenital, or idiopathic neutropenia experience response, including patients with severe neutropenia as part of numerous rare congenital disorders. Treatment is usually titrated upward, starting at 1 to 2 mcg/kg/d, to determine a dose that will give mean neutrophil counts of 1.0 to 2.0×10^9/L. Patients achieving this neutrophil level can be maintained for years at the same dose, adjusting for growth and development. In congenital neutropenia, the risk of AML/MDS requires careful follow-up of blood counts, usually at least quarterly, and annual bone marrow examinations.

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