Review

Controversies Regarding Use of Myeloid Growth Factors in Leukemia

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Abstract

This review focuses on the data supporting the use of myeloid growth factors (MGFs) in patients being treated for acute myeloid leukemia, acute lymphoblastic leukemia, chronic myeloid leukemia, and hairy cell leukemia, for which neutropenia is a common complication of treatment. However, due to the lack of randomized trial data or conflicting results of clinical studies, comprehensive guidelines have been difficult to formulate. Moreover, to date, these diagnoses have not been addressed in the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for MGFs. However, in most cases, the general principles have been included in the applicable NCCN Guidelines for each individual cancer site.

J Natl Compr Canc Netw 2017;15(12):1551–1557
doi: 10.6004/jnccn.2017.7044

Acute Myeloid Leukemia

The 2 key goals of myeloid growth factor (MGF) use in the management of acute myeloid leukemia (AML) have been (1) a theoretical benefit for "priming" to improve efficacy of chemotherapy, and (2) reduction of neutropenia duration with the potential to reduce days of hospitalization and incidence of life-threatening infections. MGFs have been shown to drive growth of AML blasts[1–4] and initiate cell cycle progression.[5] A slight increase in cells entering S-phase was observed in patients who received granulocyte-macrophage colony-stimulating factor (GM-CSF) between days 4 and 8 of induction chemotherapy compared with a decline in cells in S-phase for those receiving placebo.[5] Enhancing entry into S-phase theoretically promotes an increased response to S-phase–specific drugs, such as cytarabine (ara-C), which is the cornerstone of treatment for AML. Ara-C is metabolized intracellularly by deoxycytidine kinase to the active metabolite, cytosine arabinoside triphosphate (ie, ara-cytidine-5′-triphosphate [ara-CTP]), which competes with deoxycytidine triphosphate for incorporation into DNA, and leads to chain termination and block of DNA synthesis. Increases in intracellular ara-CTP levels are seen with MGFs, as well as increased rates of ara-CTP incorporation into DNA.[6–8]

Attempts were made to directly determine whether there was an increase in S-phase for patients receiving clinical growth factor on study and to determine whether there was a correlation with response. Additionally, more recent preclinical studies highlight various potential applications of growth factor strategies in the treatment of leukemia. For example, Padron et al[9] identified a hypersensitivity to GM-CSF in patients with chronic myelomonocytic leukemia, with signal transduction through the STAT-5 pathway. They suggest that a combination of growth factor plus JAK2 inhibitor may have clinical utility.

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Submitted August 7, 2017; accepted for publication September 29, 2017.

The authors have disclosed that they have no financial interests, arrangements, affiliations, or commercial interests with the manufacturers of any products discussed in this article or their competitors. Dr. Poston receives support from an institutional training grant from the National Heart, Lung, and Blood Institute (T32 HL007093). Dr. Becker has disclosed that she has received support from the NCI of the NIH (P01CA077852). The content is solely the responsibility of the authors, and does not necessarily represent the official views of the NIH.

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Another potential rationale for priming with growth factors is that they may mobilize cells out of the protected marrow microenvironment, rendering them more susceptible to chemotherapy. One preclinical study found that granulocyte colony-stimulating factor (G-CSF) reduced the viability of AML cells in vitro when cocultured with HS-5 stroma cells, and that reduced clonogenic capacity after G-CSF treatment correlated with patients who achieved remission compared with those who were refractory.[10] In another study, a preclinical model of the marrow niche constructed of osteoblast and stroma coated 3-dimensional (3D) scaffold demonstrated that "mobilization" of a leukemia cell line with the CXCR4 inhibitor plerixafor and G-CSF led to enhanced ara-C–induced cytotoxicity.[11]

G-CSF has an FDA-approved indication "for reducing the time to neutrophil recovery and the duration of fever, following induction or consolidation chemotherapy treatment of patients with AML."[12] The listed side effects, with at least 2% difference in incidence, compared with placebo include epistaxis, back pain, pain in extremity, erythema, maculopapular rash, diarrhea, constipation, and transfusion reaction. Although the biosimilar filgrastim-sndz shares all indications granted to filgrastim, pegfilgrastim and tbo-filgrastim do not have an indication in AML. However, one trial that randomized patients to pegfilgrastim or filgrastim showed the drugs to be equivalent in terms of days to neutrophil count recovery after induction or consolidation and in terms of adverse events.[13] GM-CSF also has an FDA-approved indication "for use following induction chemotherapy in older adult patients with acute myelogenous leukemia to shorten time to neutrophil recovery and to reduce the incidence of severe and life-threatening infections and infections resulting in death," and is applicable to patients aged ≥55 years.[14]

One of the initial concerns regarding the use of MGFs in AML was the potential for driving proliferation of the blasts in patients undergoing treatment. For this reason, several of the clinical trials did not permit patients with high circulating blast counts to enroll. Although there are individual case reports of life-threatening increases in blast count with MGF administration, such as in a patient treated with pegfilgrastim[15] in whom the blast count increased to 283 x 10^9/L, in general, clinical trials with long-term follow-up that combined growth factor and chemotherapy have not shown an increase in mortality or relapse rate (RR) with use of MGFs.[16] To summarize, MGFs may be safely used in patients with AML, but the question remains whether they are beneficial.

One of the largest trials designed to address the impact of priming randomized 917 patients with AML to receive G-CSF versus no G-CSF during induction chemotherapy.[17] A benefit in overall survival (OS; *P*=.003) and event-free survival (EFS; *P*=.01) was only seen in patients who received G-CSF with a dose escalation of ara-C, suggesting that priming with G-CSF is particularly effective with higher doses of ara-C. A multicenter randomized controlled trial of 640 patients with newly diagnosed AML undergoing induction with G-CSF versus placebo showed a similar response rate after induction in both groups; however, the G-CSF group showed a reduced probability of relapse (RR, 0.77; 95% CI, 0.61–0.99; *P*=.04).[18] Within the group of patients who achieved a complete response after induction, those who received G-CSF had improved disease-free survival (DFS; 4-year DFS , 42% vs 33%; *P*=.02). Notably, patients with an unfavorable prognosis did not receive a benefit from the use of G-CSF in the subgroup analysis.

Table 1 lists the details of a number of randomized trials that used G-CSF or GM-CSF in combination with chemotherapy for AML.[19–31] Individual trials have shown a reduction in the duration of neutropenia for trials that continued growth factor treatment until neutrophil recovery, without any adverse effects on remission rate, EFS, or OS.

G-CSF has also been used to manage neutropenia and infectious complications in AML. The most extensive data analysis regarding the use of G-CSF is a Cochrane meta-analysis of 19 randomized controlled trials.[32] This showed no benefit with the use of G-CSF, including no difference in mortality, OS, remission, DFS, and incidence of bacteremia and invasive fungal infections. Furthermore, there was a marginal increase in adverse events with growth factors, leading to discontinuation of CSFs, compared with the control arm (RR, 1.33; 95% CI, 1.00–1.56).

One pediatric trial that assigned 258 patients with AML to induction therapy without G-CSF and then 254 patients to therapy with G-CSF[33] reported earlier time to neutrophil recovery and shorter hospitalization without a difference in severe adverse events, remission rate, EFS, or OS. Another pedi-

Table 1. Randomized Trials of Myeloid Growth Factors in Acute Myeloid Leukemia

Study	Treatment Phase	Age Range, y	GF Type	GF Dose	CR With vs Without GF	DFS (or RFS or EFS) With vs Without GF	OS With vs Without GF[a]	Days of Fever	Days to ANC Recovery ($0.5x10^9$/L) With vs Without GF
Ohno et al,[19] 1994	Induction	16–66	G-CSF	200 mcg/m^2 2 days pretreatment to d35	50% vs 37% (*P*=.3)	*P*=.54	ND	11.3 vs 9.6	24 vs 29
Rowe et al,[20] 1995	Induction	55–70	GM-CSF	d11 until recovery if d10 marrow is without leukemia	60% vs 44% (*P*=.08)	Median DFS: 8.5 vs 9.6 mo (*P*=.95)	Median OS: 10.6 vs 4.8 (*P*=.048)	ND	13 vs 17 (*P*=.001)
Zittoun et al,[21] 1996	Induction	17–59	GM-CSF	5 mcg/kg/d, d0–7 or d8–28 or d0–28	72% d0–7, 48% d8–28, 46% d0–28 vs 77% (*P*=.008 with vs without GF)	*P*=.02 for d8–28 group vs not; *P*=.16 for GF d0–7 group vs not	ND	7, 7, 10.5 vs 5.5 (same 4 groups as for CR)	22.2, 22.0, 19.5 vs 24.5 (same 4 groups as for CR)
Löwenberg et al,[22] 1997	Induction	≥61	GM-CSF	5 mcg/kg/d, d0–28	56% vs 55% (*P*=.98)	2-y: 14% vs 19% (*P*=.69)	2-y 22% both groups (*P*=.55)	10 vs 6 (*P*<.001)	23 vs 25 (*P*=.0002)
Witz et al,[23] 1998	Induction	55–75	GM-CSF	5 mcg/kg/d, d1–28	63% vs 60.5% (*P*=.79)	2-y: 48% vs 21% (*P*=.003)	Longer OS with GF: 39% vs 27% (*P*=.082)	8 vs 10 (*P*=.5)	24 vs 29 (*P*=.0001)
Godwin et al,[24] 1998	Induction	56–88	G-CSF	400 mcg/m^2/d, d11–recovery	41% vs 50% (*P*=.89)	Median RFS: 8 vs 9 mo	6 vs 9 mo (*P*=.71)	8 vs 10 (*P*=.091)	Median: 24 vs 27 (*P*=.014)
Thomas et al,[5] 1999	Salvage	16–65	GM-CSF	5 mcg/kg/d, d4–8	65% vs 59%	Median DFS: 251 vs 240 d	Median OS: 303 vs 254 d	ND	38 vs 37
Estey et al,[25] 1999	Induction	≥71	G-CSF	200 mcg/m^2/d d0 until recovery	55% FAI+G-CSF vs 40% FAI (*P*=.087)	EFS: *P*=.95 FAI+G-CSF vs FAI	ND	ND	ND
Harousseau et al,[26] 2000	Consolidation	15–60	G-CSF	5 mcg/kg/d from day after chemo until recovery	ND	2-y DFS: 47% vs 43%	2-y actuarial OS: 64% vs 63%	5 vs 6 (*P*=.35)	12 vs 19 first consolidation
Löwenberg et al,[18] 2003	Induction	18–60	G-CSF	150 mcg/m^2/d, d0–8 first cycle, d0–6 second cycle	79% vs 83% (*P*=.24)	4-y EFS: 33% vs 28% (*P*=.17) Standard-risk subset: 39% vs 29% (*P*=.01)	4-y OS: 40% vs 35% (*P*=.16) Standard-risk subset: 45% vs 35% (*P*=.02)	ND	Cycle 1: 30 vs 30 Cycle 2: 26 vs 25
Rowe et al,[27] 2004	Induction	56–86	GM-CSF	250 mcg/m^2/d 48 hours prechemo until d10 marrow negative then both GF and placebo group received GF until ANC recovery	38% vs 40% with or with GF priming	Median DFS: 6.9 vs 5.1 mo (*P*=.73)	Median OS: 5.3 vs 8.5 mo (*P*=.11)	ND	ND
Amadori et al,[28] 2005	Induction	61–80	G-CSF	150 mcg/m^2/d, d1–7 or d1 or d8 until ANC recovery	58.3% for GF during chemo vs 48.6% for no GF or GF after chemo (*P*=.009)	3-y DFS: 14.5%–18.6% vs 21.5 %	3-y OS: 7.6%–18.3% vs 15.2%	8 for groups with GF until recovery vs 8.8 for no GF or just d1–7	20 for groups with GF until recovery vs 25 for no GF or just d1–7 (*P*<.001)
Heil et al,[29] 1997 Heil et al,[16] 2006	Induction	16–89	G-CSF	5 mcg/kg/d, d6 until recovery	69% vs 68% (*P*=.77)	Median DFS: 0.86 vs 0.79 y	Median OS: 1.04 vs 1.13 y	7 vs 8.5 (*P*=.009)	Median 20 vs 25 (*P*=.0001)
Thomas et al,[30] 2007	Induction	15–49	GM-CSF	5 mcg/kg/d, d1–10	88% vs 77% (*P*<.04)	3-y EFS: 42% vs 34% (*P*=.06) Median EFS: 22.5 vs 15.5 mo	3-y OS: 54% vs 46% Median OS: 40.4 vs 29 mo	ND	31 vs 31
Pabst et al,[17] 2012	Induction	17–60	G-CSF	5 mcg/kg/d, d0–7	81% vs 77% (*P*=.11)	5-y DFS: 37% vs 31% (*P*=.29) Escalated-dose cytarabine subset: 43% vs 28% (*P*=.012)	5-y OS: 43% vs 40% (*P*=.88) Escalated-dose cytarabine subset: 50% vs 30% (*P*=.003)	ND	Cycle 1: 29 vs 29 Cycle 2: 31 vs 28 (*P*=.007)
Stone et al[31] 1995	Induction	>60	GM-CSF	5 mcg/kg/d, d8 until recovery	51% vs 54% (*P*=.61)	ND	0.7 vs 0.9 y	ND	15 vs 17

Abbreviations: ANC, absolute neutrophil count; chemo, chemotherapy; CR, complete response; d0, day before chemotherapy begins; DFS, disease-free survival; EFS, event-free survival; FAI, fludarabine/cytarabine/idarubicin; G-CSF, granulocyte colony-stimulating factor; GF, growth factor; GM-CSF, granulocyte-macrophage colony-stimulating factor; ND, not determined; OS, overall survival; RFS, relapse-free survival.
[a]Order of comparison is GF vs placebo.

atric trial showed a reduction in days of neutropenia (18.0 vs 23.0 days; *P*=.02 after AIE [cytarabine, idarubicin, etoposide] for newly diagnosed AML), but no impact on the incidence of grade 3 and 4 infections.[34] One retrospective trial focusing on G-CSF dosing found that patients who received <5 mcg/kg of G-CSF had a significantly increased risk of developing neutropenic fever compared with those who received G-CSF at ≥5 mcg/kg (87% for <5 mcg/kg; 68% for 5 mcg/kg; and 54% for >5 mcg/kg).[35]

Although G-CSF does not appear to change overall outcomes, individual trials have shown a reduction in the duration of neutropenia, hospitalization, and antibiotic use.[26,36] In a retrospective study, there was benefit to preemptive initiation of G-CSF after chemotherapy but before development of fever, with a shorter duration (*P*<.001) and trend toward reduced mortality (*P*=.076).[36] In older patients (age >55 years), G-CSF has been shown to reduce the number of days spent febrile (thus leading to less antibiotic use) even though there was no difference in the total documented infections or number of fatal infections with G-CSF versus placebo.[24] Even if G-CSF does not equate to a survival benefit, there may be cases in which the use of G-CSF still provides a benefit; it is difficult to extrapolate the data to each particular patient or underlying infection.

Perhaps with better modern supportive care, including more options for antifungal prophylaxis and treatment, simply reducing days of neutropenia does not improve survival. Has the meta-analysis[32] that did not show improved survival in patients with AML who received growth factor affected recommendations in the guidelines for growth factor use? In the current NCCN Guidelines for AML,[37] the supportive care section states that "Growth factors may be considered as a part of supportive care for postremission therapy" (AML-C; to view the most recent version of these guidelines, visit NCCN.org). Note that such use may confound interpretation of the bone marrow evaluation. Patients should be off GM-CSF or G-CSF for a minimum of 7 days before bone marrow collection to document remission. For supportive care of acute promyelocytic leukemia, the guidelines state that MGFs should not be used in induction (AML-C). They may be considered during consolidation in selected cases (eg, life-threatening infections, signs/symptoms of sepsis); however, there are no outcomes data regarding the prophylactic use of MGFs in consolidation.[37] The guidelines also note that "some regimens such as FLAG incorporate G-CSF into the regimen" (MS-53, available online at NCCN.org). G-CSF and its dosing are included in the description in the publications on the regimens that include it. They also stated that, "Growth factors are not routinely recommended in postremission therapy, except in life-threatening infections or when signs and symptoms of sepsis are present and the leukemia is believed to be in remission" (MS-53).[37]

An alternative to the use of growth factors in the setting of life-threatening infection would be to use granulocyte transfusions, but a recent randomized multicenter trial did not show superiority of this treatment.[38] There has not been a randomized trial of growth factors versus no growth factors in patients with AML who are neutropenic after chemotherapy and have a life-threatening infection; growth factors are simply empirically used based on the finding derived from the randomized studies that they might hasten neutrophil recovery.

Acute Lymphoblastic Leukemia

The current NCCN Guidelines for Acute Lymphoblastic Leukemia (ALL) recommend that G-CSF be used "for myelosuppressive blocks of therapy or as directed by treatment protocol" (ALL-C; to view the most recent version of these guidelines, visit NCCN.org).[39] The individual clinical trials of pediatric/young adult versus adult chemotherapy differed regarding the incorporation of G-CSF; for example, the CALGB 10403 regimen[40] discouraged the routine use of MGFs and permitted them only in life-threatening occurrences such as pneumonia, sepsis syndrome, or fungal infection, whereas HyperCVAD included G-CSF prophylaxis.[41] There are few trials evaluating G-CSF use in HyperCVAD, although one trial evaluated the timing of its use, showing that G-CSF initiation could be moved safely from day 5 to day 10 with no significant difference in infection rate.[42]

The largest study of G-CSF use in ALL treatment was a joint analysis of 5 randomized trials regarding its use during induction chemotherapy in adolescent and adult patients.[43] In the multivariate analysis, prophylactic use of G-CSF was associated with a reduced risk of relapse (hazard ratio [HR], 0.64;

P=.007) and treatment failure (HR, 0.67; *P*=.02). There was an improved OS in the T-cell ALL subgroup at a median follow-up of 5 years (51%±8% vs 29%±9%; *P*=.01) and among patients aged 21 to 40 years (44%±6% vs 27%±6%; *P*=.03).

Other trials specifically testing the role of G-CSF and induction chemotherapy in ALL have shown a reduction in the duration of neutropenia.[44–48] However, whether this results in a clinically meaningful reduction in the rate of infections is unclear, and another trial showed no benefit in DFS or OS.[49] It is likely that outcomes with MGFs will vary depending on the depth and duration of neutropenia associated with the particular regimen, leading to the NCCN recommendation that use of MGFs be confined to regimens associated with more pronounced myelosuppression.

Chronic Myeloid Leukemia

Development of neutropenia during treatment for chronic myeloid leukemia (CML) with tyrosine kinase inhibitors (TKIs) or omacetaxine is not infrequent, although no randomized trials have explored this issue. Heim et al[50] described the use of G-CSF given 3 times weekly in 6 patients with neutropenia on imatinib. Akard et al[51] described frequent grade 3/4 myelosuppression for patients with CML on omacetaxine, and the need to use G-CSF in 25% of patients with chronic-phase and 10% of patients with accelerated-phase disease. Studies initially focused on the use of growth factor to prevent neutropenia, and later to see if concurrent administration of TKI and growth factor could improve response. One study on the use of filgrastim in patients with CML on imatinib who developed grade ≥3 neutropenia found that all patients had an improvement in absolute neutrophil count (ANC)—64% of them to ANC >2x10^9/L within 21 days—and that the total time spent off imatinib declined from 21% to 6% (*P*=.0008), with the number of patients experiencing major cytogenetic responses increasing from 1 to 5 of 11 patients.[52] The doses were 5 mcg/kg either daily or 1 to 3 times weekly, titrated to maintain ANC >1x10^9/L.

A second study examined the use of filgrastim in 130 patients treated with dasatinib.[53] Grade ≥3 neutropenia or thrombocytopenia occurred in 52% of patients; management included interruption of dasatinib in 37% and filgrastim administration in 14% at a dose of 300 or 480 mcg daily for 2 to 7 days per week, titrated to maintain ANC >1x10^9/L. After initiation of filgrastim, 5 of 9 patients experienced an improved cytogenetic response.

The concept of finding a mechanism to eradicate leukemia stem cells led to the study of concomitant growth factor with TKI in an effort to sensitize the leukemia stem cells by inducing cell cycle. One randomized phase II trial compared continuous versus pulsed imatinib in patients with chronic-phase CML who had at least a complete cytogenetic response while on imatinib.[54] Findings showed no difference in progression rates between the arms, and that the growth factor itself was not associated with a benefit in terms of reduction in BCR-ABL1 transcript levels. Moreover, a mathematical model predicted no therapeutic benefit of adding filgrastim to imatinib.[55]

The NCCN Guidelines for CML recommend that growth factors, in combination with imatinib, dasatinib, nilotinib, bosutinib, or ponatinib, can be used to manage neutropenia and thrombocytopenia (to view the most recent version of these guidelines, visit NCCN.org).[56]

Hairy Cell Leukemia

Recommendations vary regarding the role of G-CSF in hairy cell leukemia (HCL). In general, the recommendation is to consider MGFs on a case-by-case basis in patients with active infections.[57,58] However, the rate of neutropenia is high, ranging from 30% to 50%,[59] which meets the threshold for recommended use of growth factors in the NCCN Guidelines for MGFs. These guidelines suggest the use of growth factors for regimens that are associated with a high risk of febrile neutropenia (>20%) or an with intermediate risk (10%–20%) in patients who have additional risk factors, such as age >65 years, hepatic or renal dysfunction, prior chemoradiotherapy, tumor involvement of the bone marrow, or recent surgery.[60]

A phase II trial compared the use of filgrastim prophylaxis with a cladribine-based regimen versus historical controls who did not receive G-CSF.[61] Patients received filgrastim priming on days –3 through –1, then continued it through chemotherapy and until the ANC was >2x10^9/L for 2 consecutive days. A reduction in the duration of neutropenia was seen compared with historical controls (9 vs 22 days;

$P<10^{-5}$), but no difference was seen in the rate of neutropenic fever, days with fever, or frequency of admissions for antibiotics. These findings support the consideration of MGFs on an individual basis rather than for routine prophylaxis.

Conclusions

One meta-analysis[31] of 19 clinical trials of G-CSF in AML did not show any meaningful advantage favoring growth factor use. However, individual randomized large studies did find specific circumstances that led to an advantage with G-CSF use in patients with standard-risk AML[18] or in those treated with a higher dose of ara-C.[17] GM-CSF may also benefit selected patients with AML, but on a practical level, GM-CSF use has become infrequent. G-CSF may be helpful in ALL with selected regimens when there is appreciable risk of prolonged and profound neutropenia. G-CSF has permitted the continuation of treatment for patients with CML who sustain neutropenia with the use of TKIs or omacetaxine, and is recommended to be considered in individual cases of HCL with higher risk of developing neutropenia, such in patients aged >65 years. For these leukemias, guidelines for the use of MGFs are addressed in the individual disease-specific NCCN Guidelines rather than in the "Supportive Care" section of the NCCN Guidelines for MGF (to view the most recent version of all guidelines, visit NCCN.org).

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