The Role of Myeloid Growth Factors in Acute Leukemia

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Key Words
Myeloid growth factors, acute myeloid leukemia, acute lymphoblastic leukemia, priming

Abstract
Myeloid growth factors granulocyte-colony stimulating and granulocyte macrophage colony-stimulating factors have been extensively studied in acute leukemias. Whether administered before, during, or after chemotherapy for acute myeloid leukemia and acute lymphoblastic leukemia, these agents reduce the duration of neutropenia and seem to be safe and well tolerated. Despite consistently showing a shorter duration of neutropenia, multiple, prospective, randomized trials have documented only modest benefits in terms of reduction in the incidence and severity of infections, without substantial gains or impact in complete remission, overall survival, and disease-free survival rates. Growth factors have also been used to recruit quiescent leukemia cells into the S-phase of the cell cycle to increase their susceptibility to chemotherapy with the goal to reduce relapse and resistance. Randomized trials evaluating this priming strategy have consistently shown improvement in disease- or event-free survival in the intermediate-risk group of patients with acute myeloid leukemia, but no overall survival benefit. This article focuses on the clinical experience with these agents as adjuncts to the treatment of acute leukemias. (JNCCN 2009;7:84–91)

Over the past 2 decades, considerable efforts have been made to determine if the benefits of human granulocyte colony-stimulating factors (G-CSFs) and human granulocyte macrophage colony-stimulating factors (GM-CSFs) can be extended to the treatment of acute leukemias. Experts postulated that growth factors could be beneficial in the treatment of leukemia as either supportive agents or a means to enhance the effects of chemotherapy. Through reducing the duration of neutropenia, these agents could decrease the morbidity and mortality caused by bacterial and fungal infections in patients with acute leukemia undergoing chemotherapy, and thus improve remission and survival rates. Furthermore, because myeloid leukemia cells express colony-stimulating factor (CSF) receptors on their surface, experts hypothesized that administering G-CSF and GM-CSF before and during chemotherapy, in a strategy called priming, would enhance the susceptibility of leukemia cells to cell-cycle-specific chemotherapeutic agents. Concern for the potential to stimulate residual leukemia cell proliferation or extend the duration of pancytopenia by affecting normal hematopoietic precursors that are usually dormant delayed development of growth factors in leukemia management. This article focuses on the clinical evidence showing that G-CSF or GM-CSF has no clear role in the treatment of acute myeloid leukemia (AML), either as part of supportive care or in a priming strategy. However, their use has some benefit in the supportive treatment of patients with acute lymphoblastic leukemia (ALL) undergoing chemotherapy.

AML
G-CSF and GM-CSF
The treatment of AML during induction and consolidation results in prolonged periods of marrow aplasia with resultant grade 4 neutropenia. Bacterial and fungal infections account for most morbidity and, to a certain extent, mortality in patients with AML undergoing treatment. FEVERS and infection are the norm and occur in most patients with AML undergoing chemotherapy. In patients younger than 60, the induction death rate from sepsis and infection is roughly 10%, but this number can...
increase to 20% or more in patients older than 60.7 If growth factors could decrease the incidence of bacterial and fungal infections, then perhaps treatment outcomes would improve with less induction deaths and more complete remissions (CRs).

Multiple prospective, randomized, placebo-controlled trials have been conducted with GM-CSF and G-CSF administered after chemotherapy in patients with newly diagnosed AML to test this hypothesis (Table 1). Comparison among these studies is difficult, owing to design variability, especially because some clinicians used growth factors only after chemotherapy to evaluate their effectiveness in attenuating neutropenia, whereas others used them before, during, and after chemotherapy to evaluate any additional benefits of a priming strategy.

Of 13 randomized trials, all but one small study showed a statistically significant reduction in the duration of neutropenia by 2 to 7 days with growth factor support either during or after chemotherapy. This shortened period of neutropenia modestly decreased duration of infection and antibiotic and antifungal use, and in some trials decreased hospitalization.

Despite a consistent reduction in duration of neutropenia in these studies, only the ECOG trial showed that accelerated neutrophil recovery lowered the rate of documented infection. In this trial, GM-CSF in patients older than 55 years was associated with fewer grade 4/5 documented infections (P = .02) and deaths from grade 3/4 pneumonia. This led to the approval of GM-CSF in patients with AML. Cost-effective analyses have yielded mixed results, with 2 studies showing a cost savings of up to $2000 and 2 showing a cost increase.

Disappointingly, a shorter duration of neutropenia had no effect on the end points of CR, overall survival (OS), or disease-free survival (DFS) in most of these studies. A few studies showed a statistically greater CR rate for patients in the growth factor arms, but this did not translate into improvement in OS or DFS. The aforementioned ECOG study by Rowe et al. was the only one to show a survival benefit for the GM-CSF-treated group over placebo (median survival, 10.6 vs. 4.8 months; P = .021). However, the median survival in the placebo arm was substantially lower than that reported in other studies for the same age group.

Growth factor support did not have a favorable impact on OS or DFS in older patients, for whom there was the greatest hope for impact.

Initially, when growth factors were introduced and contemplated for use in AML, experts were concerned that they would have detrimental effects based on substantial in vitro evidence that growth factors would stimulate persistent leukemia cells. Therefore, some studies delayed the administration of growth factor until a bone marrow aspirate/biopsy performed on day 10 showed marrow aplasia. However, the reproducibility of the results (Table 1) shows that this may be unnecessary. Only the study by Zittoun et al. showed a nonsignificant decrease in CR rate in patients randomized to GM-CSF.

Collectively, the data suggest that either G-CSF or GM-CSF can be given during or after chemotherapy without compromising CR, OS, or DFS rates. These agents seem safe and well tolerated during not only induction therapy but also consolidation therapy. Because of the heterogeneity of studies, no clear consensus exists for their use, nor is one agent clearly superior to the other, because no large randomized trials have compared them directly. Both agents are approved for use in adults with AML (GM-CSF in patients > 55 years) in the United States. Despite a decrease in the duration of neutropenia, however, evidence suggests that growth factors in AML provide no clinical benefit. Therefore, routine use in supportive care for all patients undergoing therapy for AML is unwarranted.

**Growth Factor Priming for Treatment**

Growth factors have also been extensively studied to assess their efficacy in priming strategies. Only a small subset of leukemia blasts is clonogenic, meaning they have the ability to proliferate and form colonies. These clonogenic leukemia cells are relatively quiescent and are therefore immune to the S-phase–dependent mechanism of cell killing inherent to chemotherapeutic agents such as cytarabine. This population of quiescent leukemia cells thus represents a potential mechanism of resistance and relapse. In vitro studies show that co-culturing leukemia cells with GM-CSF, G-CSF, or interleukin 3 (IL-3) results in a higher proportion of cells entering S-phase. When used in combination with cytarabine, growth factors enhance the incorporation of cytarabine into the DNA of leukemia cells, which then confers a greater cytotoxic effect of cytarabine on clonogenic leukemia cells.
### Table 1  G-CSF or GM-CSF in Newly Diagnosed Acute Myeloid Leukemia

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Median Age (y)</th>
<th>Growth Factor Timing</th>
<th>Median Reduction in Days to ANC Recovery</th>
<th>Decreased Infection</th>
<th>Other Benefit(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stone et al. a</td>
<td>388</td>
<td>69</td>
<td>A</td>
<td>2 (500)</td>
<td>No difference</td>
<td>No difference in CR, OS, or DFS</td>
</tr>
<tr>
<td>Rowe et al. b</td>
<td>124</td>
<td>≥ 55</td>
<td>A</td>
<td>7 (1000)</td>
<td>GM-CSF group had less therapy-related mortality, grade 4/5 documented infection (P = .002), and death from grade 3/4 pneumonia</td>
<td>Median survival 10.6 vs. 4.8 months for GM-CSF over placebo (P = .021)</td>
</tr>
<tr>
<td>Goldstone et al. a</td>
<td>226</td>
<td>66</td>
<td>A</td>
<td>5 (1000)</td>
<td>No difference</td>
<td>No difference in CR or OS</td>
</tr>
<tr>
<td>Heil et al. b</td>
<td>521</td>
<td>54</td>
<td>A</td>
<td>5 (1000)</td>
<td>No difference</td>
<td>No difference in CR or OS; decrease in number of days hospitalized (5); reduced amount of antifungal treatment</td>
</tr>
<tr>
<td>Godwin et al. c</td>
<td>234</td>
<td>68</td>
<td>A</td>
<td>3 (1000)</td>
<td>No difference</td>
<td>No difference in CR, RFS, OS; decreased duration of infection</td>
</tr>
<tr>
<td>Dombret et al. d</td>
<td>173</td>
<td>71</td>
<td>A</td>
<td>6 (1000)</td>
<td>No difference</td>
<td>70% vs. 41% CR with G-CSF (P = .002); no difference in OS; no difference in induction death rates (23% vs. 27%; P = .60)</td>
</tr>
<tr>
<td>Bradstock et al. d</td>
<td>114</td>
<td>43</td>
<td>A</td>
<td>4 (500)</td>
<td>No difference</td>
<td>Fewer days on antibiotics in the G-CSF arm; fewer days with fever in G-CSF arm; no difference in CR or OS</td>
</tr>
<tr>
<td>Lowenberg et al. e</td>
<td>253</td>
<td>43</td>
<td>D, A</td>
<td>4 (1000)</td>
<td>No difference</td>
<td>Higher sepsis and lung infections in GM-CSF group; no difference in CR, OS, or DFS</td>
</tr>
<tr>
<td>Lowenberg et al. f</td>
<td>318</td>
<td>68</td>
<td>D, A</td>
<td>2 (500)</td>
<td>No difference</td>
<td>No difference in CR, OS, or DFS</td>
</tr>
<tr>
<td>Amadori et al. g</td>
<td>922</td>
<td>68</td>
<td>D, A</td>
<td>5 (500)</td>
<td>No difference in documented infections; no difference in fatal infection</td>
<td>58.3% vs. 48.6% CR with G-CSF during chemotherapy (P = .009); no difference in OS, DFS, or EFS; shorter hospital stay by 2 days for G-CSF after chemotherapy; decreased antibiotic use; decreased antifungal use</td>
</tr>
<tr>
<td>Witz et al. h</td>
<td>240</td>
<td>66</td>
<td>D, A</td>
<td>5 (500)</td>
<td>No difference</td>
<td>No difference in CR; trend toward better OS in GM-CSF group and 2-year DFS improved in the GM-CSF arm (48% vs. 21%; P = .003)</td>
</tr>
<tr>
<td>Estey et al. i</td>
<td>215</td>
<td>71</td>
<td>D, A</td>
<td>5 (1000)</td>
<td>No difference</td>
<td>No difference in CR, OS, and DFS</td>
</tr>
<tr>
<td>Zittoun et al. j</td>
<td>103</td>
<td>42–45</td>
<td>B, D, A</td>
<td>—</td>
<td>No difference</td>
<td>Trend toward lower CR in GM-CSF group</td>
</tr>
</tbody>
</table>

Abbreviations: A, after chemotherapy; ANC, absolute neutrophil count; B, before chemotherapy; CR, complete remission; D, during chemotherapy; DFS, disease-free survival; EFS, event-free survival; G-CSF, granulocyte colony-stimulating factor; GM-CSF, granulocyte macrophage colony-stimulating factor; OS, overall survival; RFS, relapse-free survival.
Myeloid Growth Factors in Acute Leukemia

Early trials using GM-CSF or G-CSF in a priming strategy have confirmed that growth factor administration increases the recruitment of leukemia cells into S-phase.\(^{23-25}\) Furthermore, some studies showed that the addition of a growth factor to chemotherapy correlated with response\(^{24}\) and hinted at an improved CR rate compared with historical controls.\(^{26-27}\) Larger randomized studies have been completed and a clear benefit of priming has not been identified in terms of OS,\(^{25,28-30}\) although some studies show an improvement in DFS or event-free survival (EFS).\(^{16,31-34}\)

In one of the largest studies, Lowenberg et al.\(^{31}\) randomized 640 patients between 18 and 60 years with newly diagnosed AML to receive 2 planned induction cycles with or without G-CSF priming. Notably, G-CSF was only administered the day before and during cytarabine administration in each cycle. No statistically significant difference was seen in CR rates between the G-CSF and control arms (79% vs. 83%; \(P = .24\)). At a median follow-up of 55 months, DFS was higher in the group that received G-CSF than in the control (42% vs. 33%; relative risk for relapse or death, 0.77; 95% CI, 0.62–0.96; \(P = .02\)). This was primarily because of a lower relapse rate in the G-CSF arm (46% vs. 54%; \(P = .04\)). However, at 4 years no statistically significant differences were seen between the groups in OS and EFS. A subgroup analysis showed that priming with G-CSF reduced the probability of relapse and improved overall survival among patients with standard-risk AML compared with the control (45% vs. 35%; \(P = .02\)), but had no effect for those in the AML groups with unfavorable risk; the number of patients in the favorable risk group was too low for any meaningful conclusions to be drawn.

Similarly, in another trial from France, 259 patients between 15 and 49 years with newly diagnosed AML were randomized to undergo a time-sequential induction regimen given alone or with GM-CSF priming.\(^{32}\) GM-CSF was administered concomitantly with chemotherapy during induction and all cycles of consolidation. CR rates were significantly improved in the GM-CSF arm (88% vs. 78%; \(P < .04\)). At 3 years, similar to the Lowenberg et al.\(^{4}\) trial, a trend was seen toward improvement in EFS for the GM-CSF-primed arm compared with the control (42% vs. 34%; \(P = .06\)), but no statistically significant difference occurred in OS. Again, in subgroup analysis, priming with GM-CSF improved EFS for those in the intermediate-risk category (\(P = .05\)). Preliminary data from the German AML Cooperative Group corroborate these results.\(^{34}\) In this trial, patients underwent induction, consolidation, and maintenance therapy with or without priming with G-CSF. Again, no difference was seen in CR rate or relapse-free survival between the groups, but subgroup analysis showed a trend toward longer relapse-free survival for those with intermediate-risk cytogenetics and primed with G-CSF.

Overall, priming with growth factors seems to be well tolerated and does not have a negative impact on CR or OS, but this strategy is not without its flaws. In a few studies, treatment had to be interrupted secondarily to leukocytosis.\(^{11,32}\) In the Lowenberg et al.\(^{31}\) trial, more deaths occurred within 50 days after cycles 1 and 2 of chemotherapy in the G-CSF group compared with the control arm, but this did not result in a statistically significant difference in CR or OS between the groups. Another trial, comparing 3 different anthracyclines in combination with cytarabine during induction with or without GM-CSF in patients older than 55 years, showed that the priming strategy delayed the initiation of chemotherapy.\(^{21}\) Patients who did not have a delay in chemotherapy had a higher CR rate than those who participated in the priming strategy (50% vs. 38%; \(P = .03\)).

Correlative studies have supported the rationale behind priming. Rowe et al.\(^{25}\) collected samples at days 0 and 2 in 106 patients (53 placebo and 53 GM-CSF) to measure the mean change in S-phase percentage blasts. The mean change in S-phase percentage for the GM-CSF group was statistically significantly higher than placebo (2.05% vs. 0.25%; \(P = .003\)), suggesting that GM-CSF priming resulted in a larger change in the S-phase percentage, as intended. However, the increase was minimal and did not differ between patients who experienced a CR and those who did not. Thus, the small change in S-phase percentage did not have a meaningful impact on important clinical end points. Data are lacking as to what effect priming has on the clonogenic leukemia cells.

**ALL**

**G-CSF and GM-CSF**

Similar to AML, significant heterogeneity occurred in trials examining the role of growth factor support in ALL. Table 2 outlines the characteristics and main results of the major trials. For the most part, the benefits are similar to those seen in AML, and concern
exists that growth factors would stimulate the leukemic clone. Many studies show a marked reduction in the duration of neutropenia during an initial induction and later consolidation phases.

The dose used is somewhat important. In one trial, 2, 5, or 10 mcg/kg/d doses of filgrastim were tested during induction and consolidation. The 2 higher doses resulted in a shorter duration of neutropenia during induction compared with the lowest dose, whereas no difference occurred in neutrophil recovery in subsequent consolidation cycles among all 3. During consolidation, each dose was associated with faster neutrophil count recovery than in the control.

In one of the largest randomized, controlled trials in ALL, 198 patients were randomized to receive G-CSF 5 µg/kg/d starting on day 5 or placebo. Patients who received G-CSF had a faster neutrophil count recovery during induction, higher CR (87% vs. 77%; P = .18), and fewer induction deaths (5% vs. 11%). Growth factors were used through 2 subsequent consolidation treatments and resulted in substantial decreases in time to neutrophil count recovery; however, G-CSF did not allow patients to complete the first 3 months of therapy any more quickly than on placebo. Furthermore, the higher CR rate did not translate into improved OS or DFS for the G-CSF

### Table 2 GM-CSF or G-CSF in Acute Lymphoblastic Leukemia

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Median Age (y)</th>
<th>Median Reduction in Days to ANC Recovery</th>
<th>Decreased Infection</th>
<th>Other Benefit(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Larson et al.</td>
<td>198</td>
<td>35</td>
<td>6 (course I) 9 (course IIa) 6 (course IIb)</td>
<td>No difference</td>
<td>Shorter hospitalization (P = .02); higher CR rate and fewer induction deaths with G-CSF; G-CSF did not complete first 3 cycles of therapy faster than the placebo group</td>
</tr>
<tr>
<td>Weiser et al.</td>
<td>199</td>
<td>36–38</td>
<td>1</td>
<td>No difference</td>
<td>G-CSF on day 5 vs. day 10</td>
</tr>
<tr>
<td>Hofmann et al.</td>
<td>50</td>
<td>37–31</td>
<td>—</td>
<td>No difference</td>
<td>Early vs. delayed starting of G-CSF; no difference; 40% less G-CSF administered; longer duration of hospitalization</td>
</tr>
<tr>
<td>Ottmann et al.</td>
<td>76</td>
<td>16–65</td>
<td>4.5 (1000)</td>
<td>No difference</td>
<td>Fewer fevers and infections (NSS); less-frequent delays in chemotherapy; no difference in DFS</td>
</tr>
<tr>
<td>Holowiecki et al.</td>
<td>64</td>
<td>26.5</td>
<td>3 (500) 7.5 (1000) 9 (1500)</td>
<td>No difference in documented infections</td>
<td>60% vs. 90% infections and symptoms during induction and consolidation treatment; less-severe grade 3/4 infections (NSS); 59% vs. 37% OS (P = .048); probability of relapse, 32% vs. 60% (P = .19)</td>
</tr>
<tr>
<td>Geissler et al.</td>
<td>53</td>
<td>40</td>
<td>10</td>
<td>Decreased documented infections 40% vs. 77% (P &lt; .05); decreased rate of fever 12% vs. 42% (P &lt; .05)</td>
<td>No difference in CR, OS, or DFS</td>
</tr>
<tr>
<td>Kantarjian et al. G-CSF</td>
<td>34</td>
<td>8</td>
<td>No difference</td>
<td>Decreased induction mortality in G-CSF group (6% vs. 21%; P = .08); no improvement in CR</td>
<td></td>
</tr>
<tr>
<td>Papamichael et al.</td>
<td>26</td>
<td>32</td>
<td>No difference</td>
<td>No difference in CR rate; did not shorten time between cycles</td>
<td></td>
</tr>
<tr>
<td>Ifrah et al.</td>
<td>64</td>
<td>31</td>
<td>2 (NSS)</td>
<td>No reduction in days on antibiotics</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: ANC, absolute neutrophil count; CR, complete remission; DFS, disease-free survival; G-CSF, granulocyte colony-stimulating factor; GM-CSF, granulocyte macrophage colony-stimulating factor; NSS, not statistically significant; OS, overall survival.
arm compared with placebo after almost 5 years of follow-up.

Much research has evaluated the optimal timing of growth factors in relationship to chemotherapy in ALL. In ALL, chemotherapy is given in multiple divided doses over extended periods. A few studies have examined whether initiating a growth factor later after chemotherapy resulted in improved outcomes or cost savings. Growth factor support after chemotherapy reduces the duration of neutrophil recovery compared with historical controls, whether it is started within 5 to 7 (early) or 10 to 12 days (delayed) from the start of chemotherapy.\(^{37,38}\) Incidence and severity of infection did not differ between the early and delayed administration groups, and the delayed administration did not negatively impact CR rates.\(^{37,38}\) Additionally, in one study, patients in the delayed administration arm had 40% less G-CSF administered but remained in the hospital a median of 2 days more than the early group, so how much impact a delayed schedule has on the cost of growth factor support is unclear.\(^{37}\) In another study, early (day 4) administration led to faster neutrophil recovery, less infectious complications, and less antibiotic and antifungal therapy than late (day 15) administration of G-CSF, but was associated with a higher cost.\(^{39}\)

Whether a benefit exists to a time-sequenced administration of growth factor and chemotherapy is unclear. Time-sequenced administration of growth factors and chemotherapy was hypothesized to protect normal hematopoietic precursors during chemotherapy administration. In one study, G-CSF treatment given 36 hours after and ending 48 hours before 4 weekly chemotherapy administrations resulted in an overall shorter treatment duration compared with controls (134 vs. 153 days from induction through consolidation; \(P = .005\)).\(^{40}\) This strategy showed a nonsignificant difference in severe infections (9% vs. 21%), fewer symptoms associated with infections, and a reduction in the median number of days of febrile neutropenia. However, another study that administered G-CSF concurrently with chemotherapy had similar results with fewer delays in chemotherapy.\(^{41}\)

A few studies have shown a benefit in clinical outcomes, including a decrease in documented infections,\(^{41,42}\) rates of fevers,\(^{41,42}\) and infectious symptoms with growth factor support, regardless of the growth factor schedule in relation to chemotherapy.\(^{43}\) GM-CSF support was associated with decreased induction deaths in one study of relapsed ALL, but this was not statistically significant (6% vs. 21%; \(P = .08\)).\(^{44}\) Unfortunately, all studies except one have shown that growth factor support has no impact on OS or DFS. This small study of 64 patients with a relatively short follow-up of 2 years reported a higher overall survival (59% vs. 27%; \(P = .04\)) and a lower relapse rate which was not statistically significant (32% vs. 60%; \(P = .19\)).\(^{45}\)

**Conclusions**

Evidence suggests that growth factors are helpful in reducing the duration and severity of neutropenia for individuals during induction and consolidation for AML and ALL. No evidence suggests that they are detrimental or contribute to inferior clinical outcomes, either in a priming strategy for AML or administered as part of supportive care after chemotherapy in AML or ALL. However, they are costly and little evidence suggests that a shorter duration of neutropenia results in a clinically significant benefit in acute leukemias. In solid tumors, neutropenia is usually due to chemotherapy, not to the disease, and has a shorter duration than in leukemia. As a result, growth factor support may obviate the risks of neutropenia in solid tumor patients. In contrast, patients with acute leukemia oftentimes present with neutropenia, which becomes more profound following chemotherapy and persists for many weeks. As such, multiple, large randomized studies have demonstrated that a shorter duration of neutropenia does not translate into end points of OS in AML. As a consequence, there is no clear consensus as to their use in AML. Given the lack of adverse data associated with their use, growth factor support in AML is reasonable in patients older than 60 or those who may not tolerate chemotherapy well. Furthermore, because of the lack of evidence demonstrating that they stimulate leukemic growth, they may be of use as part of supportive care for those undergoing consolidation chemotherapy. Numerous studies have shown no clear advantage to priming with growth factors before and during chemotherapy for AML. In ALL, randomized controlled trials have shown that growth factor support results in a faster neutrophil recovery, which has translated into modest improvements in clinical end points, such as induction death rates, incidence of severe infections, and dose intensity of chemotherapy.
References


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