Growth Factors in Leukemia

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Abstract

The role of myeloid growth factors, such as granulocyte colony-stimulating factor and granulocyte-macrophage colony-stimulating factor, in the management of acute myeloid and acute lymphoblastic leukemias has been evaluated extensively in multiple clinical trials. Growth factors have been given before, concurrently, or sequentially with chemotherapy with the goal of reducing the duration of neutropenia and consequently the incidence and severity of infections, and improving the rate of remissions and overall survival. They also have been studied as chemotherapy-sensitizing agents in an effort to recruit dormant myeloid stem cells into the sensitive phase of the cycle. Additionally, growth factors, shown to stimulate proliferation and differentiation of leukemia cells in vitro, were evaluated as monotherapy in patients with acute leukemia. Most studies show modest improvement in the duration of the neutropenia, which does not consistently correlate with the severity of infection, rate or duration of remissions, or disease-free and overall survival. Attempts to enhance the chemosensitivity of the leukemic cells and decrease drug resistance failed to improve the rate of remission and survival in several large series. However, more recent reports suggested an improved outcome in younger patients with acute myeloid leukemia with normal karyotype. Several anecdotal case reports have shown that growth factor monotherapy can induce a complete remission in patients with acute leukemia. Data from the published clinical trials do not seem to support emergence of drug-resistant leukemia, worsening toxicity, and bone marrow failure with growth factor administration. (*JNCCN* 2007;5:203–215)

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Granulocyte Colony-Stimulating Factor and Granulocyte Macrophage Colony-Stimulating Factor

Granulocyte colony-stimulating factor (G-CSF) promotes the survival, proliferation, and differentiation of neutrophil progenitor cells, whereas granulocyte macrophage colony-stimulating factor (GM-CSF) promotes the growth of myeloid colony–forming cells, increases the number of circulating neutrophils and monocytes, enhances the phagocytic functions of mature myeloid cells, and increases antigen presentation by macrophages and dendritic cells[1,2] Inflammatory mediators, such as tumor necrosis factor and interleukin-1, stimulate production of GM- and G-CSF through the monocytes, macrophages, endothelial cells, and fibroblasts. Knockout experiments in mice suggest that G-CSF is essential for neutrophil development, whereas elimination of GM-CSF negatively impacts the number and function of alveolar macrophages[3,4]

Two recombinant forms of GM-CSF are used in clinical practice, sargramostim (yeast-expressed GM-CSF) and molgramostim (*Escherichia coli*–expressed GM-CSF), with only molgramostim approved by the U.S. Food and Drug Administration (FDA) for clinical use in the United States. In addition to filgrastim, which is a recombinant non-glycosylated G-CSF expressed in *E. coli* that is approved by the FDA, and lenograstim, which is a glycosylated G-CSF expressed in mammalian cell lines, a pegylated filgrastim (pegfilgrastim) has been introduced for single-dose administration in the clinical setting. A recently published, retrospective, case-control analysis suggested that a single administration of pegfilgrastim with hyper-CVAD (cyclophosphamide, vincristine, doxorubicin, dexamethasone) chemotherapy in patients with acute lymphoblastic leukemias (ALLs) and non-Hodgkin lymphoma led to kinetics of neutrophil recovery ($P = .75$), risk for febrile neutropenia ($P = .16$), frequency

of documented infections (P = .85), and delay in the next cycle of chemotherapy (P = .75) that were similar to daily filgrastim.[5]

Clinical trials evaluating the role of growth factors in patients with acute leukemias were initiated in the early 1990s, after G-CSF and GM-CSF were purified and molecularly cloned in 1984 and 1985, respectively. Recombinant growth factors have been shown to shorten the duration of neutropenia in patients undergoing intensive chemotherapy for lung cancer.[6]

Growth Factors in Acute Myeloid Leukemia

Growth Factors Decrease the Duration of Neutropenia

Infections are the major source of morbidity and mortality, particularly in older patients with acute leukemia undergoing intensive chemotherapy. Therefore, many clinical trials investigated the addition of growth factors to induction and consolidation therapy to decrease the incidence and severity of neutropenia-associated infection (Table 1). Furthermore, growth factors were expected to prevent delay in administering subsequent cycles of consolidation chemotherapy and permit the delivery of more intensive regimens.

The most consistent outcome of clinical trials using growth factors is the reduction in duration of neutropenia by approximately 2 to 7 days without significant effect on the frequency and length of severe fungal and bacterial infections.[7–16] Aside from the results of the European acute myeloid leukemia (AML) cooperative group, the Eastern Cooperative Study Group (ECOG), and European Organisation for Research and Treatment of Cancer-Gruppo Italiano Malattie Ematologiche dell'Adulto trials, most studies failed to show improvement in rate of complete remission and overall survival.

Usuki et al.[16] evaluated the influence of G-CSF administered after induction therapy on the infection-related parameters and outcome of therapy in patients with de novo AML. Patients older than 15 years who experienced remission after induction chemotherapy were randomized to treatment with G-CSF (120 patients) and no G-CSF (125 patients) until the recovery of blood counts. The median duration of the febrile neutropenia was significantly shorter (3 vs. 4 days; P = .0001) and time to neutrophil recovery was significantly faster (12 vs. 18 days; P = .0001) in the

G-CSF group than the control group. However, the complete remission rates (80.8% vs. 76.8%), 5-year probability of disease-free survival rates (34.5% vs. 33.6%), and overall survival rates (42.7% vs. 35.6%) were similar among the groups.[16] Although 40% of patients in the control group were treated with the G-CSF after a documented infection, analysis performed on an as-treated basis did not show complete remission improvement in the G-CSF group. Similarly, in the Cancer and Leukemia Group B (CALGB) trial, patients older than 60 years with de novo AML were randomly assigned to receive GM-CSF (193 patients) or placebo (195 patients) the day after competing the standard "7 + 3" induction chemotherapy.[8] Although the median duration of neutropenia was shorter in the GM-CSF arm (15 vs. 17 days, P = .02) compared with the placebo arm, the rate of complete remission and treatment-related mortality were similar in both groups.

Correspondingly, administering the growth factor after consolidation therapy to patients with AML in remission failed to improve the overall outcome.[14,17] In a study by Harousseau et al.,[14] patients experiencing remission from AML were randomized to treatment with either a G-CSF (100 patients) or no G-CSF (94 patients) after each of the 2 cycles of intensive consolidation chemotherapy (ICC). The mean duration of neutropenia was dramatically reduced, both after ICC 1 (12 vs. 19 days; P < .001) and ICC 2 (20 vs. 28 days; P < .001) in the G-CSF group. The median duration of hospitalization (24 vs. 27 days; P < .001 after ICC 1; and 29 vs. 34 days, P < .001 after ICC 2) and intravenous antibiotics and antifungal therapy use was significantly reduced in the G-CSF arm. However, the incidence of documented infections, the toxic death rate, and 2-year overall survival were not affected by G-CSF administration. Furthermore, the median interval between ICC 1 and ICC 2 was reduced by only 2 days, and the proportion of patients undergoing ICC 2 was not increased in the G-CSF arm.

A randomized study by Dombret et al.[9] showed an improved complete remission rate but not overall survival, whereas the ECOG study by Rowe et al.[10] showed improved overall survival but not complete remission rate (although a trend was present) in patients receiving growth factors compared with those receiving placebo. In the ECOG double-blind randomized clinical trial, patients with AML aged between 55 and 70 years who achieved aplasia after standard "7 + 3" induction regimen received yeast-derived GM-CSF

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Table 1 Prospective Randomized Trials Evaluating the Effect of Growth Factors on the Neutropenia-Related Complications in Acute Myeloid Leukemia

Reference	N	Age, Type	Growth Factor Type	Time of Administration	Neutrophil Recovery	Frequency of the Documented Infection	Length of Hospitalization	CR	Survival (DFS, OS)
CALGB Stone et al.,[8] 1995	388	> 60 de novo, un-treated	GM-CSF (E. coli) vs. placebo	Day 8 induction	Improved (15 d vs. 17 d; P = .02)	Similar	Similar (28 d vs. 30 d; P = .11)	Similar (5% vs. 54%; P = .61)	Similar OS (9.4 mo)
ECOG Rowe et al.,[10] 1995	124	55–70	GM-CSF (yeast) vs. placebo	Day 11 induction consolidation	Improved (13 d vs. 17 d; P = .001)	Improved (P = .002)	Similar (36 d vs. 38 d; P = .29)	Similar (60% vs. 44%; P = .08)	Improved OS (10.6 mo vs. 4.8 mo; P = .048) SimilarDFS (8.5 mo vs. 9.6 mo; P = .95)
AML Cooperative Study Group Dombret et al.,[9] 1995	233	> 65 de novo, un-treated	G-CSF (mam-malian cell line) vs. placebo	48 h after induction (day 9)	Improved (21 d vs. 27 d; P < .001)	Similar (48%)		Improved (70% vs. 47%; P = .002)	Similar OS (P = .76)
EORTC-GIMEMA Zittoun et al.,[55] 1996	102	15–45	GM-CSF vs. control	GM-CSF (days 0–7, +/–) vs. GM-CSF (days 8–28, –/+) vs. GM-CSF (days 0–28, +/+) vs. control (–/–)[a]	Similar			Trend toward improvement in control arm	Similar (trend toward decreased OS in /+ compared with /–; OR 1.51; 95%, CI, 0.92–2.49)
HOVON and Swiss Group for Clinical Cancer Research Löwenberg et al.,[32] 1997	253	15–60 un-treated	GM-CSF vs. control	GM-CSF with chemotherapy (+/–) vs. during and after chemotherapy (+/+) vs. after chemotherapy (–/+) vs. control (–/–)[a]	Improved in (–/+) (26 d vs. 30 d; P < .001)	Similar		Similar	Similar
Inter-national AML Leukemia Study Group Heil et al.,[12] 1997	521	> 16 de novo, un-treated	G-CSF (E. coli) vs. placebo	Day + 1 induction consolidation	Improved (20 d vs. 25 d; P = .0001)	Similar (37% vs. 36%, P = .85)	Improved (20 d vs. 25 d; P = .0001)	Similar (69% vs. 68%; P = .47)	Similar (10.1 mo vs. 9.4 mo; P = –.99)
SWOG 9031 Godwin et al.,[13] 1998	234	> 55 de novo/ second-ary	G-CSF (E. coli) vs. placebo	Day 10 after induction	Improved (15% reduction; P = .014)	Similar	Similar (P = .27)	Similar (41% vs. 50%; P = .89)	Similar DFS (6 mo vs. 9 mo; P = .71) Similar OS (12.5 mo vs. 14 mo; P = .83)
GOELAM Witz et al.,[56] 1998	240	55–75 un-treated	GM-CSF (E. coli) vs. placebo	Days 1–28 Induction	Improved (24 d vs. 29 d; P = .0001)	Similar (67% vs. 72%; P = .42)	Similar (P = .1)	Similar (63% vs. 60.5%; P = .79)	Improved 2-y DFS (48% vs. 21%; P = .003)[b] Similar 2-y OS (P = .08)[c]

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Table 1 Continued										
GOELAM Harousseau et al.,[14] 2000	194	15–60 de novo in CR	G-CSF (E. coli) vs. control	Day 1 consolidation (2 cycles)	Improved (12 d vs. 19 d; P < .001 cycle 1; 20 d vs. 28 d; P < .001– cycle 2)	Similar (55% vs. 66%; P = .16 for cycle 1; 40.5% vs. 55.5%; P = .07 for cycle 2)	Improved (24 d vs. 27 d; P < .001)	n/a	Similar 2-y OS (64% vs. 63%; P = .24) Similar 2-y DFS (47% vs. 43%;
ALSG Bradstock et al.,[59] 2001	112	16–60 un-treated	G-SCF (mam-malian cell line) vs. control	Day 8 induction	Improved (18 d vs. 22 d; P = .0005)			Similar (81% vs. 75%; P = .5)	Similar
MRC AML11 Goldstone et al.,[15] 2001	226	> 56 de novo/second-ary, un-treated	G-CSF vs. placebo	Day 8 induction	Improved by 5 days			Similar	Similar
Gran AML Study Group Usuki et al.,[16] 2002	245	15–87 de novo, un-treated	G-CSF (E. coli) vs. control	48 h after induction	Improved (12 d vs. 18 d; P = .0001)	Similar (83% vs. 91%; P = .08)		Similar (80.8% vs. 76.8%; P = .532)	Similar OS (20.8 mo vs. 18.8 mo; P = .59); Similar 20-mo DFS (14 mo vs. 12.5 mo; P = .94)
EORTC-GIMEMA Amadori et al.,[58] 2005	722	61–80 de novo/second-ary, un-treated	G-CSF (mam-malian cell lines) vs. control	G-CSF (+/–) vs. G-CSF (+/+) vs. G-CSF (–/+) vs. control (–/–)[a]	Improved with G-CSF given after chemother-apy (20 d vs. 25 d; P < .001)	Similar	Improved with G-CSF given after chemotherapy (27.2 d vs. 29.7 d; P < .001)	Improved with G-CSF given with chemother-apy (P = .009)	Similar

[a] +/+, GF administered concurrently and subsequently to chemotherapy; +/–, GF administered concurrently with chemotherapy; –/+, GF administered subsequently to chemotherapy; –/–, no GF administration.
[b] Highly significant in patients aged 55–64 years (P = .002), marginally significant in patients older than 60 years (P = .22).
[c] Improvement of OS was statistically significant in younger patients (aged 55–64 years).
Abbreviations: ALSG, Australia Leukemia Study Group; AML, acute myeloid leukemia; CALGB, Cancer and Leukemia Group B; CI, confidence interval; CR, complete remission; DFS, disease free survival; ECOG, Eastern Cooperative Study Group; EORTC, European Organisation for Research and Treatment of Cancer; G-CSF, granulocyte colony-stimulating factor; GIMEMA, Gruppo Italiano Malattie Ematologiche Dell'Adulto; GM-CSF, granulocyte macrophage colony-stimulating factor; GOELAM, Groupe Ouest Est Leucemies Aigues Myeloblastiques; HOVON, Dutch Belgian Hemato-Oncology Cooperative Group; MRC, Medical Research Council; N/A, not applicable; OS, overall survival; SWOG, Southwest Oncology Group.

(52 patients) or placebo (47 patients) until neutrophil recovery.[10] In the GM-CSF arm, the median duration of neutropenia (P = .001), overall treatment-related toxicity (P = .049), and infectious toxicity (P = .015) were reduced compared with the placebo arm. The median survival of patients in the GM-CSF arm was 10.6 months versus 4.8 months for those in the placebo arm (P = .048). However, the length of hospital stay and rate of complete remission were not significantly different. In the European AML cooperative group study, lenograstim or placebo was randomly adminis-tered to patients with AML older than 65 years on day 9 after completion of induction chemotherapy.[9] Although the median duration of neutropenia (P < .001) was significantly shorter and the rate of complete re-mission was significantly higher (70% vs. 47%; P = .002) in the G-CSF arm compared with the placebo arm, the mortality rate at 8 weeks and overall survival did not differ between the groups.

Limitations of Growth Factor Studies

Direct comparison of the various studies is difficult because of the variability in type, schedule, and dose

of the chemotherapeutic agents and the type, timing, and duration of growth factor administration; differences in the patient population characteristics and the outcome of the placebo group; and the inconsistency in the schedule of antibiotic administration, hospitalization, and blood counts monitoring.[18] For example, in the study by Rowe et al.,[10] which was the only study that showed benefit in overall survival, the shorter-than-expected median survival in the placebo arm might have contributed to the outcome.

Economics of Growth Factors

Several studies suggest that administering growth factors is economically beneficial because it reduces the length of hospital stay, duration of the parenteral antibiotics use, and time of febrile neutropenia.[19–21] According to the economic analysis of the ECOG trial, administration of GM-CSF resulted in cost savings ($2310) comparable to those reported by Lu et al.[20] ($2230). Similarly, cost-effectiveness analysis of GM-CSF administration in the Groupe Ouest Est Leucemies Aigues Myeloblastiques study showed significant cost savings and "in younger patients group saving were synonymous with GM-CSF."[21] However, an analysis of the Southwest Oncology Group (SWOG) data showed no reduction in the overall costs of supportive care, despite improvement in infection severity and duration of neutropenia.[22] The median cost of supportive care was similar in the G-CSF ($8768) and placebo arms ($8616) in the report by Pui et al.[23] The cost of therapy in the placebo arms was significantly different among these trials, suggesting that cost analysis could be institution-specific.

Recommendations for Growth Factor Administration in AML

Administering growth factors after the induction of chemotherapy in patients with AML is not standard practice. Administering G-CSF or GM-CSF shortly after the completion of induction chemotherapy in older patients (> 55 years) may be reasonable, with the goal of modestly decreasing the duration of neutropenia and possibly decreasing the risk for severe infection and length of hospital stay. The growth factors are not expected to have a favorable impact on the rate of complete remission, disease-free survival, and overall survival.

Administering growth factors after consolidation chemotherapy can be recommended in patients with AML to shorten the duration of neutropenia (more profound improvement compared with after-induction administration) and decrease the rate of infections requiring antibiotic therapy. No effect on the duration of the complete remission and overall survival should be anticipated.

Growth Factors as Chemotherapy-Sensitizing Agents

Despite advances made in AML, relapse caused by the presence of minimal residual disease and primary resistant leukemia remains the most important cause of treatment failure.[24,25] Several clinical trials have evaluated the safety and efficacy of G-CSF and GM-CSF as chemotherapy-sensitizing agents (Table 2). This strategy is based on the premise that growth factors may recruit the quiescent clonogenic leukemia cell into a sensitive cell cycle phase, and hence potentiate the cytotoxic effect of chemotherapy.[26] Numerous in vitro and in vivo studies have shown that receptors for growth factors exist on leukemia cells and that simultaneous exposure to growth factors and chemotherapeutic drugs such as cytarabine may enhance the cytotoxic activity of ara-C, increase the intracellular level of active cytarabine triphosphate (ara-CTP), and increase DNA uptake of radiolabel cytarabine.[27–29] Recently, G-CSF was shown to be a sensitizing agent to the gemtuzumab ozogamicin in cell lines and samples from patients with AML.[30] These preclinical studies, although varied in their methodology and the criteria of the cytotoxicity assessment, provided a reason for evaluating growth factors for modulating the myelosuppressive effects of chemotherapy in patients with AML. Despite the strong theoretic rationale, most of these studies did not show significant clinical benefit for growth factor administration in patients with either newly diagnosed or relapse and refractory disease in terms of complete remission, disease-free survival, and overall survival.

Löwenberg et al.[31] conducted a prospective multicenter clinical trial in which 640 patients with untreated AML aged 18 to 60 years were randomized to receive G-CSF 1 day before and concurrently with the 2 cycles of chemotherapy. Among the patients in complete remission, after a median follow-up of 55 months, a higher rate of disease-free survival was noted in the G-CSF group compared with the controls (at 4 years, 42% vs. 33%; $P = .02$), attributable to a reduced probability of relapse (relative risk [RR], 0.77; 95% confidence interval [CI], 0.61–0.99; $P = .04$). However, overall survival and disease-free survival rates were similar among the

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Table 2 Prospective Randomized Trials Evaluating the "Priming" Effect of Growth Factors in Acute Myeloid Leukemia

Reference	N	Age, Type	Growth Factor Type	Time of Administration	Neutrophil Recovery	Infections	CR	Survival (OS, DFS)
Heil et al.,[54] 1995	80	15–75 de novo	GM-CSF (*Escherichia coli*) vs. placebo	Day 1, induction, consolidation	Similar	Similar	Similar (81% vs. 79%; P = .57)	OS: Similar (43 mo: 45% vs. 49%; P = .66) RFS: Similar (41 mo: 42% vs. 41%; P = .89)
EORTC-GIMEMA Zittoun et al.,[55] 1996	102	15–45 untreated	GM-CSF (*E. coli*) vs. control	GM-CSF (days 0–7, +/–) vs. GM-CSF (days 8–28, –/+) vs. GM-CSF (day 0–28, +/+) vs. control (–/–)[a]	Similar (P = .28)	Similar	Similar (trend toward improvement in control arm)	Similar (trend toward decreased OS in + compared with –; odds ratio, 1.51; 95% CI, 0.92–2.49)
EORTC-HOVON Lowenberg et al.,[32] 1997	318	> 60 de novo/ secondary	GM-CSF (*E. coli*) vs. control	induction, consolidation	Improved (23 d vs. 25 d; P = .0002)	Similar	Similar (56% vs. 55%; P = .98)	Similar (2-y: 15% vs. 19%; P = .69)
GOELAM Witz et al.,[56] 1998	240	55–75 de novo	GM-CSF (*E. coli*) vs. placebo	Days 1–28 induction	Improved (24 d vs. 29 d; P = .0001)	Similar	Similar (63% vs. 60.5%; P = .79)	Similar (P = .82) Improved (2-y: 49% vs. 21%; P = .003)
EMA91 Thomas et al.,[35] 1999	192	16–65 relapsed/ refractory	GM-CSF (*E. coli*) vs. placebo	Days 4–8, induction	Similar (38 d vs. 37 d)	Similar (45 vs. 51%; P > .1)	Similar (65% vs. 59%; P = .35)	Similar OS (303 vs. 254; P = .32) Similar DFS (251 d vs. 240 d; P = .45) Improved time to progression (median, 152 d vs. 115 d; P = .08)
Hast et al.,[57] 2003	93	35–90	GM-CSF vs. control	Start day 1, induction consolidation	Similar (18 d vs. 21 d; P = .21)	Similar (24 vs. 29)	Similar 43%	Similar
HOVON Löwenberg et al.,[31] 2003	640	18–60 de novo /secondary, untreated	G-CSF (mammalian cell line) vs. control	Start day 0, induction consolidation	Similar	Similar	Similar (79% vs. 83%; P = .24)	Improved DFS (4-y: 42% vs. 33%; P = .02); Reduced risk of relapse (RR, 0.77; 95% CI, 0.61–0.99) OS: Similar (P = .16)
Löfgren et al.,[33] 2004	110	> 64 *de novo*	GM-CSF vs. control	Start day 0, induction, consolidation	Improved (17 d vs. 25 d; P = .03)	Improved (39 vs. 46; P = .05)	Similar (65% vs. 64%)	Similar (9 mo vs. 14 mo)
ECOG Rowe et al.,[36] 2004	245	> 55 untreated	GM-CSF (*E. coli*) vs. placebo	Day 1, induction	—	—	Similar (38% vs. 40%; P = .73)	Similar (5.3 mo vs. 8.5 mo; P = .11) Similar (6.9 mo vs. 5.1 mo; P = .73)
EORTC-GIMEMA Amadori et al.,[58] 2005	722	61–80	G-CSF (mammalian cell lines) vs. control	G-CSF (+/–) vs. G-CSF (+/+) vs. G-CSF (–/+) vs. control (–/–)[a]	Improved with G-CSF given after chemotherapy (20 d vs. 25 d; P < .001)	Similar	Improved with G-CSF given with chemother-apy (P = .009)	Similar

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Table 2 Continued							
Thomas et al.,[34] 2005	259	15–50	GM-CSF vs. control	Days 1–10, induction, consolidation		Similar (91% vs. 87%)	EFS: Improved (42% vs. 34%) OS: Similar

[a] +/+, GF administered concurrently and subsequently to chemotherapy; +/–, GF administered concurrently with chemotherapy; –/+, GF administered subsequently to chemotherapy; –/–, no GF administration.

Abbreviations: CI, confidence interval; CR, complete remission; DFS, disease free survival; ECOG, Eastern Cooperative Study Group; EFS, event-free survival; EORTC, European Organisation for Research and Treatment of Cancer; G-CSF, granulocyte colony-stimulating factor; GIMEMA, Gruppo Italiano Malattie Ematogeniche Dell'Adulto; GM-CSF, granulocyte macrophage colony-stimulating factor; GOELAM, Groupe Ouest Est Leucemies Aigues Myeloblastiques; HOVON, Dutch Belgian Hemato-Oncology Cooperative Group; OS, overall survival; RFS, relapse-free survival; RR, relative risk.

groups ($P = .16$). Subgroup analysis indicated that the major, if not entire, benefit of G-CSF was in the subgroup of patients with standard risk disease (by cytogenetics): the 4-year overall survival was 45% versus 35% (RR of death was 0.75; 95% CI, 0.59–0.95; $P = .02$) and disease-free survival was 45% versus 33% (RR, 0.70; 95% CI, 0.55–0.90; $P = .006$). The outcome of patients with unfavorable prognosis was not improved and the small number of patients in the favorable subgroup (~6%) limited the meaningful analysis.

A similarly designed randomized trial of GM-CSF in patients older than 60 years, conducted by the same group, failed to show improvement in the rate of complete remission and disease-free survival, possibly owing to the increased number of patients with abnormal cytogenetics (55%).[32] A Swedish multicenter randomized trial tested addition of the GM-CSF to MEC (mitoxantrone, etoposide, cytarabine) chemotherapy in older patients with de novo AML. The complete remission rate was 65% in patients who received GM-CSF and 64% in those who did not, the median complete remission duration was 6 versus 13 months, median overall survival was 9 versus 14 months, median time to neutrophils recovery was 17 versus 25 days, and the number positive blood cultures was 39 versus 46. Hence, adding GM-CSF before, during, and after chemotherapy did not improve the outcome of older patients with AML.[33]

The recent multicenter, prospective, randomized trial conducted by the Acute Leukemia French Association Group evaluated the role of GM-CSF priming on the outcome of 256 younger (15–50 years) patients with AML.[34] GM-CSF was administered from day 1 to 10 of induction and consolidation chemotherapy. After the induction therapy, the complete remission rate was similar in both groups (91% with GM-CSF vs. 87% without GM-CSF). After a median follow-up of 3 years, a trend occurred toward improvement of dis-

ease-free survival in the GM-CSF group (42% vs. 34%; $P = .06$) without improvement in overall survival. Subset analysis indicated that most of the benefit occurred in the patients with intermediate risk cytogenetics (3-year event-free survival, 50% vs. 35%; $P = .05$) owing in part to the lower risk for relapse (29% vs. 47%; $P = .05$) and reduced treatment-related mortality (19% vs. 23%) at 3 years. Administering GM-CSF did not improve outcome of patients with favorable ($P = .8$) and unfavorable ($P = .3$) cytogenetics. Of interest, patients with abnormal intermediate karyotype appeared to benefit more from GM-CSF administration (3-year event-free survival, 55% vs. 19%; $P = .03$) compared with those with normal karyotype (3-year event-free survival, 47% vs. 42%; $P = .4$).

Although multiple trials studied the efficacy of growth factors as priming agents in a clinical setting, only a few correlative studies were conducted to establish if the recruitment of the leukemic blasts into the chemotherapy sensitive cell phase occurred and correlated with the clinical outcome.[35,36] Cell cycle studies accompanying the EMA91 (etoposide, mitoxantrone, cytarabine) trial by Thomas et al.[35] showed increased recruitment of cells in the S phase between days 4 and 8 (days of administration of GM-CSF) in the GM-CSF group compared with the placebo group ($P = .006$). However, this finding did not correlate with the overall outcome of the group treated with GM-CSF. Similarly, in the ECOG trial reported by Rowe et al.,[36] priming for 48 hours with GM-CSF resulted in a significant increase of leukemia cells in the S cycle compared with treatment with placebo (2.05% vs. 0.25%; $P = .003$), which did not correlate with clinical benefit.

Risks of Growth Factor Administration

Using growth factors as priming agents in combination with chemotherapy for patients with AML raised the

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concern that stimulating the residual normal precursors could increase their sensitivity to the chemotherapy, causing prolonged bone marrow suppression. This theory has not been substantiated by published data, and no evidence of in vivo stimulation of residual leukemia cells by growth factors has been reported.

Using growth factors as a sensitizing agent in patients with AML (including those with de novo or secondary AML, and those who are high-risk, younger, or elderly) is not recommended, because they have no effect on disease-free survival and overall survival.

Growth Factors as Monotherapy in AML

Several case reports described achievement of complete remission with growth factor monotherapy in patients with newly diagnosed and relapsed/refractory acute leukemia (14 AML, 3 acute promyelocytic leukemia, 2 ALL).[37–40] Most patients presented with pancytopenia and infection. The time to response (from 2 weeks to 3 months) and its duration (from 2–10 months) ranged widely. The mechanisms of remission induction are unclear. Using G-CSF to stimulate the normal hematopoietic precursors more extensively than leukemia cells causes relative, rather than absolute, reduction in blast count. However, the presence of durable responses and occasional cytogenetic remissions argue against this theory. It has been established that blasts from patients with AML express high procaspase protein levels, enhanced by the GM-CSF administration.[41,42] In vitro data have shown that GM-CSF induces a dual effect: it stimulates cell proliferation (upregulates Bcl-2, Bcl-XL) and simultaneously triggers proapoptotic signal in AML cells (upregulates BAX, SOCS-2 and -3, procaspases 2 and 3, PARP cleavage). Faderl et al.[42] showed in the clonogenic assays that a low dose of GM-CSF stimulates colony proliferation, whereas the number of colonies decreases at concentrations exceeding 0.05 mcg/mL. Differential expression of the high- and low-affinity GM-CSF receptors may account for the difference in response.

Outside of a clinical trial, growth factor monotherapy to treat acute leukemia cannot be recommended.

Growth Factors in ALL

Significant advances have been made in the management of adult ALL in the past 30 years. Although the institution of high-intensity, multiagent pediatric regimens results in a complete remission rate of 80% to 90% in adult patients, the overall long-term disease-free survival is only 35% to 50%. Multiple clinical trials evaluated adding growth factors to induction or consolidation chemotherapy with the goal of improving outcome in patients with ALL (Table 3). The goals of most studies were to determine if growth factors are able to shorten the time of bone marrow recovery; reduce the incidences of febrile neutropenia, documented infections, and mortality caused by the infection; minimize hospital stay; and improve the rate and duration of complete remission. Because the dose intensity seems to influence the outcome, shortening the duration of neutropenia and infection through administering growth factors may improve adherence to the treatment schedule.

Similar to findings in patients with AML, the most consistent outcomes of prophylactic administration of growth factors during induction and consolidation chemotherapy in ALL were a shortened duration of neutropenia and earlier myeloid recovery.[43,44] Some studies also showed improved infection-related parameters, reduced hematologic toxicity of dose intensification, better compliance with the treatment schedule, and reduced infection-related mortality.[43–45] Only a few studies showed an increased rate of complete remission without improvement in overall survival.[44]

The study conducted by the Japan Adult Leukemia Study Group established 5 mcg/kg administered intravenously as the optimal dose to accelerate neutrophil recovery after intensive remission induction and consolidation chemotherapy.[43] In this small prospective clinical trial, 41 adult patients with newly diagnosed ALL were randomized to receive 0, 2, 5, or 10 mcg/kg of G-CSF. Neutrophil recovery after induction chemotherapy was significantly faster in the groups who received 5 mcg/kg (P = .047) and 10 mcg/kg (P = .011) compared with those who received 2 mcg/kg, but was similar between the 2 former groups. After consolidation therapy, neutrophil recovery was significantly faster in the groups that received 2, 5, and 10 mcg/kg G-CSF than in the group that received no G-CSF (P < .001), but did not differ in 3 former groups. Frequency of febrile neutropenia and incidence of documented infections seemed to be less in groups that received 5 and 10 mcg/kg than in the groups that received 0 and 2 mcg/kg.

In a double-blind, randomized trial of 198 patients with de novo ALL conducted by the CALGB, administering G-SCF, 5 mcg/kg subcutaneously, on day 4 of induction chemotherapy seemed to shorten the duration of neutropenia (29 vs. 16 days; P < .001),

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Table 3 Prospective Randomized Trials Evaluating the Role of Growth Factors in Acute Lymphoblastic Leukemia

Reference	N	Age	Growth Factor Type	Time of Administration	Time to Completion of Chemotherapy	Neutrophil Recovery	Episodes of Febrile Neutropenia	Frequency of the Documented Infection	Death During Induction	CR	Survival (DFS, OS)
Ohno et al.,[43] 1993	41	15–65 y	G-CSF (0, 2, 5,10 mcg/kg)	Induction, at nadir. Consolidation	Not addressed	Improved with higher dose of GFs	Improved	Improved	Similar	Not addressed	Not addressed
Ottmann et al.,[46] 1995	67	16–65 y	G-CSF vs. control	Induction (2nd phase, week 4 of 8)	Improved ($P = .008$)	Improved (8 vs. 12.5; $P < .002$)	Similar (35% vs. 47%; $P = .28$)	Similar (43% vs. 56%; $P = .25$); non-viral infections reduced by 50%	1 in control group	Similar	Similar
Welte et al.,[52] 1996	34	0.25–18 y	G-CSF vs. control	Induction (from day 7)	Improved ($P = .007$)	Improved	Improved (17% vs. 40%; $P = .007$)	Improved (8% vs. 15%; $P = .04$)	Similar	Similar	Similar
Geissler et al.,[53] 1997	53	16–79 y	G-CSF vs. control	Induction (from day 2)	Not addressed	Improved (16 d vs. 26 d; $P < .001$)	Improved (12% vs. 42%; $P < .05$)	Improved (40% vs. 77%; $P < .05$)	2 in control group and 1 in G-CSF group None	Similar	Similar
Pui et al.,[23] 1997	148	2 mo–17 y	G-CSF vs. placebo	Induction (from day 30)	Improved ($P < .001$)	Improved (5.3 d vs. 12.7 d; $P = .007$)	Similar (58% vs. 68%; $P = .23$)	Overall-improved (12% vs. 27%; $P = .009$); severe infection-similar (5% vs. 6%)	None	Similar (99% vs. 99%)	Similar
Larson et al.,[44] 1998	198	>15 y	G-CSF vs. placebo	Induction (from day 4)	Similar	Improved (16 d vs. 22 d; $P < .001$)	Similar (46% vs. 45%; $P = 1$)	Similar	Similar (<60: 10% vs. 25%; $P = .24$; > 60: 4% vs. 8%; $P = .32$)	Improved (87% vs. 77%; $P = .04$)	Similar
Ifrah et al., 1999	67	15–55 y	GM-CSF vs. placebo	Induction (from day 7)	Improved time to allo-BMT	Similar (16 d vs. 18 d)	Similar (median, 9 d vs. 10 d; $P = .07$)	Not addressed	No toxic death	Not addressed	Not addressed
Thomas et al.,[45] 2004	148	15–55 y	GM-CSF vs. G-CSF vs. control	Induction (from day 9 or 17)	Not addressed	Similar (22 vs. 21 vs. 22)	Similar (20 d vs. 19 d vs. 22 d)	Similar (15% vs. 24% vs. 22%)	Similar	Overall: improved (81% vs. 72% vs. 66%; $P = .008$)	Overall: similar (3 year DFS, 28% vs. 40% vs. 23%; 5-year DFS, 18% vs. 32% vs. 23%)
Thomas et al.,[45] 2004	88	15–55 y	GM-CSF vs. G-CSF vs. control	Induction (from day 4)	Not addressed	Improved (18 d vs. 16 d vs. 23 d; $P < .05$)	Similar (20 d vs. 17 d vs. 20 d)	Improved (19% vs. 3% vs. 28%; $P = .01$)	Similar		

Abbreviations: BMT, bone marrow transplant; CR, complete remission; DFS, disease free survival; G-CSF, granulocyte colony-stimulating factor; GF, growth factor; GM-CSF, granulocyte macrophage colony-stimulating factor; OS, overall survival.

decrease the hospital stay (28 vs. 22 days; P = .02), and reduce induction mortality (11% vs. 4%; P = .04). However, no significant decrease in the incidence or severity of infections, mucositis, or bleeding was observed. This discrepancy may be explained by the fact that chemotherapy-induced complications tend to occur early in the course of chemotherapy, at the nadir of white blood count, before the bone marrow response to growth factor stimulation. Nevertheless, the more rapid resolution of neutropenia may lead to a prompt resolution of toxicity, because patients treated with growth factors spent fewer days in the hospital during the induction course than those treated with placebo. The complete remission rates were higher with G-CSF (90% vs. 81%; P = .04), whereas disease-free survival at 4.7 years was not affected (although the study was not designed to detect significant difference).[44]

Interestingly, the neutrophil recovery end points and the length of hospitalization were similar among younger (aged < 60 years) and older patients. Platelet recovery was significantly faster in older patients treated with G-CSFs (17 vs. 26 days; P = .04). Additionally, in this patient group the complete remission rate (81% vs. 55%; P = .1) and mortality rate (10% vs. 25%; P = .24) favored patients treated with G-CSFs; the lack of statistical significance was likely caused by the small number of patients. In addition, despite the improved response rate and fewer deaths during induction therapy, patients in the G-CSF arm were unable to complete the first 3 months of prescribed chemotherapy more rapidly than those in the placebo group. Therefore, the intensity of the leukemia therapy could not be increased by shortening the time required to deliver the treatment. This conclusion was different from the results of the German ALL study group, in which 76 adults with de novo ALL were randomized to receive G-CSF or no G-CFS during the last 4 weeks of an 8-week remission-induction regimen.[46] Although similar to the CALGB study, the duration of neutropenia (8 vs. 12.5 days; P < .002) was significantly reduced without an effect on the incidence of infections in the G-CSF arm and the prolonged interruptions of chemotherapy were less frequent; delays of more than 2 weeks occurred in 24% of patients receiving G-CSF versus 46% of patients in the control arm (P = .01). Therefore, planned chemotherapy was completed more rapidly with the use of G-CSF (median, 39 vs. 44 days; P = .008), although the clinical significance of this improvement is uncertain.

The French Groupe d'Etude et de Traitement de la Leucemie Aiguë Lymphoblastique de l'Adulte (GET-LALA) group conducted 2 consecutive prospective, randomized, open-label, multicenter phase III trials comparing G-CSF, GM-CSF, and no growth factors administered with a 4-week 4-drug LALA-94 induction regimen in adult patients with de novo ALL.[45] In the first trial, growth factors were administered from the last day of anthracycline infusion (day 9 in the idarubicin arm and day 17 in the daunorubicin arm), and in the second trial, growth factors were started on day 4 of induction chemotherapy and administered until neutrophil recovery occurred. The G-CSF arm included 95 patients, the GM-CSF arm included 67, and the control group contained 74. Overall, a trend that did not reach statistical significance seemed to occur toward reducing the duration of neutropenia (21 days in control group, 18 days in GM-CSF, and 17 days in G-CSF), severity of the infection (16% with growth factors vs. 24% without), and duration of antibiotic administration (medians, 18 days with G-CSF, 19 days with GM-CSF, and 23 days without growth factors) in the group treated with growth factors. However, if evaluated separately, the shortened duration of neutropenia (23 days in control group, 18 days in GM-CSF, and 16 days in G-CSF; P < .05) and decreased incidence of severe infection (3% vs. 28%; P = .01) were only evident in the second study, whereas no difference was seen among the groups in the first trial. Although the GM-CSF group seemed to have an improved complete remission rate (69% in G-CSF, 81% in GM-CSF, and 66% in the control group; P = .08), no difference was seen in therapy-related mortality, disease-free survival, and overall survival.

A randomized study by Alvarado Ibarra et al.[47] compared the efficacy and side effect profile of G- and GM-CSF in 71 patients with acute leukemia (ALL and acute nonlymphocytic leukemia) undergoing induction and consolidation therapy. Time to neutrophil recovery (19 days for G-CSF vs. 16 days; P = .08), episodes of febrile neutropenia (85% vs. 78%; P = .45), and frequency of side effects (gastrointestinal, cutaneous, and musculoskeletal manifestations) were similar among the groups.

The safety concerns about administering growth factors to the patients with ALL are similar to those for patients with AML. Investigators were concerned that adding growth factors may sensitize normal hematopoietic cells to the cytotoxic effect of cell cycle–active chemotherapy and cause prolonged bone

marrow suppression. Additionally, because certain subgroups of ALL patients may express receptors for G-CSF (blasts coexpressing myeloid markers, patients with t(9;22) ALL and T-cell ALL), the theoretic possibility of stimulating the proliferation of leukemia had to be excluded.[48–51] Based on clinical trials in adult and pediatric patients with ALL, no evidence shows that administering growth factors stimulates proliferation of lymphoblasts or accelerates regrowth of leukemia.[23,46] Subset analysis of patients randomized to treatment with G-CSF or placebo, such as patients with Ph+ ALL showed no difference in the rate of hematologic recovery or overall outcome.[44] The cumulative incidence of developing AML at 3 years did not differ significantly between the groups of pediatric patients with ALL (G-CSF and placebo, administered after the completion of the induction therapy); was 5.1% (95% CI, 0.1–10) in the G-CSF arm; and was 3.9% (95% CI, 0.0–8.4) in the placebo group (P = .36).[23] However, no long-term analysis evaluating the risk for developing AML has been published.

Recommendations for Growth Factor Administration in ALL

For patients with ALL undergoing intensive chemotherapy, the most significant impact of growth factors is likely to be in a subset of patients who are expected to experience a delay in hematologic recovery, such as elderly patients, those who have undergone multiple courses of myelosuppressive chemotherapy, and those with ongoing infection.

References

1. Welte K, Gabrilove J, Bronchud MH, et al. Filgrastim (r-metHuG-CSF): the first 10 years. Blood 1996;88:1907–1929.
2. Spiekermann K, Roesler J, Emmendoerffer A, et al. Functional features of neutrophils induced by G-CSF and GM-CSF treatment: differential effects and clinical implications. Leukemia 1997;11: 466–478.
3. Lieschke GJ, Grail D, Hodgson G, et al. Mice lacking granulocyte colony-stimulating factor have chronic neutropenia, granulocyte and macrophage progenitor cell deficiency, and impaired neutrophil mobilization. Blood 1994;84:1737–1746.
4. Lieschke GJ, Stanley E, Grail D, et al. Mice lacking both macrophage- and granulocyte-macrophage colony-stimulating factor have macrophages and coexistent osteopetrosis and severe lung disease. Blood 1994;84:27–35.
5. Lane SW, Crawford J, Kenealy M, et al. Pegfilgrastim compared to granulocyte colony stimulating Ffctor (G-CSf) with hyper-CVAD chemotherapy regimen for aggressive lymphoid malignancy [abstract]. Blood 2005;106. Abstract 4274.
6. Crawford J, Ozer H, Stoller R, et al. Reduction by granulocyte colony-stimulating factor of fever and neutropenia induced by chemotherapy in patients with small-cell lung cancer. N Engl J Med 1991; 325:164–170.
7. Ohno R, Tomonaga M, Kobayashi T, et al. Effect of granulocyte colony-stimulating factor after intensive induction therapy in relapsed or refractory acute leukemia. N Engl J Med 1990;323:871–877.
8. Stone RM, Berg DT, George SL, et al. Granulocyte-macrophage colony-stimulating factor after initial chemotherapy for elderly patients with primary acute myelogenous leukemia. Cancer and Leukemia Group B. N Engl J Med 1995;332:1671–1677.
9. Dombret H, Chastang C, Fenaux P, et al. A controlled study of recombinant human granulocyte colony-stimulating factor in elderly patients after treatment for acute myelogenous leukemia. AML Cooperative Study Group. N Engl J Med 1995;332: 1678–1683.
10. Rowe JM, Andersen JW, Mazza JJ, et al. A randomized placebo-controlled phase III study of granulocyte-macrophage colony-stimulating factor in adult patients (> 55 to 70 years of age) with acute myelogenous leukemia: a study of the Eastern Cooperative Oncology Group (E1490). Blood 1995;86:457–462.
11. Maslak PG, Weiss MA, Berman E, et al. Granulocyte colony-stimulating factor following chemotherapy in elderly patients with newly diagnosed acute myelogenous leukemia. Leukemia 1996;10: 32–39.
12. Heil G, Hoelzer D, Sanz MA, et al. A randomized, double-blind, placebo-controlled, phase III study of filgrastim in remission induction and consolidation therapy for adults with de novo acute myeloid leukemia. The International Acute Myeloid Leukemia Study Group. Blood 1997;90:4710–4718.
13. Godwin JE, Kopecky KJ, Head DR, et al. A double-blind placebo-controlled trial of granulocyte colony-stimulating factor in elderly patients with previously untreated acute myeloid leukemia: a Southwest Oncology Group study (9031). Blood 1998;91:3607–3615.
14. Harousseau JL, Witz B, Lioure B, et al. Granulocyte colony-stimulating factor after intensive consolidation chemotherapy in acute myeloid leukemia: results of a randomized trial of the Groupe Ouest-Est Leucemies Aigues Myeloblastiques. J Clin Oncol 2000;18: 780–787.
15. Goldstone AH, Burnett AK, Wheatley K, et al. Attempts to improve treatment outcomes in acute myeloid leukemia (AML) in older patients: the results of the United Kingdom Medical Research Council AML11 trial. Blood 2001;98:1302–1311.
16. Usuki K, Urabe A, Masaoka T, et al. Efficacy of granulocyte colony-stimulating factor in the treatment of acute myelogenous leukaemia: a multicentre randomized study. Br J Haematol 2002;116:103–112.
17. Moore JO, Dodge RK, Amrein PC, et al. Granulocyte-colony stimulating factor (filgrastim) accelerates granulocyte recovery after intensive postremission chemotherapy for acute myeloid leukemia with aziridinyl benzoquinone and mitoxantrone: Cancer and Leukemia Group B study 9022. Blood 1997;89:780–788.
18. Estey EH. Growth factors in acute myeloid leukaemia. Best Pract Res Clin Haematol 2001;14:175–187.
19. Bennett CL, Stinson TJ, Tallman MS, et al. Economic analysis of a randomized placebo-controlled phase III study of granulocyte macrophage colony stimulating factor in adult patients (> 55 to 70 years of age) with acute myelogenous leukemia. Eastern Cooperative Oncology Group (E1490). Ann Oncol 1999;10:177–182.
20. Lu Z, Luo R, Erder H, et al. Cost impact of filgrastim as an adjunct to chemotherapy for patients with acute myeloid leukemia [abstract]. Blood 1996;88(suppl 1):209a.

21. Woronoff-Lemsi M, Demoly P, Arveux P. Cost-effectiveness analysis of GOELEM SA3, a randomized placebo-controlled protocol of GM-CSF for elderly patients with acute myeloid leukemia [abstract]. Blood 1997;90(suppl 1):72a.

22. Bennett CL, Hynes D, Godwin J, et al. Economic analysis of granulocyte colony stimulating factor as adjunct therapy for older patients with acute myelogenous leukemia (AML): estimates from a Southwest Oncology Group clinical trial. Cancer Invest 2001;19:603–610.

23. Pui CH, Bovett JM, Hughes WT, et al. Human granulocyte colony-stimulating factor after induction chemotherapy in children with acute lymphoblastic leukemia. N Engl J Med 1997;336:1781–1787.

24. Lowenberg B, Downing JR, Burnett A. Acute myeloid leukemia. N Engl J Med 1999;341:1051–1062.

25. Schiffer CA. Hematopoietic growth factors and the future of therapeutic research on acute myeloid leukemia. N Engl J Med 2003; 349:727–729.

26. Hiddemann W, Kiehl M, Zuhlsdorf M, et al. Granulocyte-macrophage colony-stimulating factor and interleukin-3 enhance the incorporation of cytosine arabinoside into the DNA of leukemic blasts and the cytotoxic effect on clonogenic cells from patients with acute myeloid leukemia. Semin Oncol 1992:19(suppl 4):31–37.

27. Miyauchi J, Kelleher CA, Wang C, et al. Growth factors influence the sensitivity of leukemic stem cells to cytosine arabinoside in culture. Blood 1989;73:1272–1278.

28. Cannistra SA, DiCarlo J, Groshek P, et al. Simultaneous administration of granulocyte-macrophage colony-stimulating factor and cytosine arabinoside for the treatment of relapsed acute myeloid leukemia. Leukemia 1991;5:230–238.

29. Lowenberg B, Touw IP. Hematopoietic growth factors and their receptors in acute leukemia. Blood 1993;81:281–292.

30. Rutella S, Bonanno G, Procoli A, et al. Granulocyte colony-stimulating factor enhances the in vitro cytotoxicity of gemtuzumab ozogamicin against acute myeloid leukemia cell lines and primary blast cells. Exp Hematol 2006;34:54–65.

31. Lowenberg B, van Putten W, Theobald M, et al. Effect of priming with granulocyte colony-stimulating factor on the outcome of chemotherapy for acute myeloid leukemia. N Engl J Med 2003; 349:743–752.

32. Lowenberg B, Suciu S, Archimbaud E, et al. Use of recombinant GM-CSF during and after remission induction chemotherapy in patients aged 61 years and older with acute myeloid leukemia: final report of AML-11, a phase III randomized study of the Leukemia Cooperative Group of European Organisation for the Research and Treatment of Cancer and the Dutch Belgian Hemato-Oncology Cooperative Group. Blood 1997;90:2952–2961.

33. Lofgren C, Paul C, Astrom M, et al. Granulocyte-macrophage colony-stimulating factor to increase efficacy of mitoxantrone, etoposide and cytarabine in previously untreated elderly patients with acute myeloid leukaemia: a Swedish multicentre randomized trial. Br J Haematol 2004;124:474–480.

34. Thomas X, Raffoux E, De Botton S, et al. Effect of priming with granulocyte-macrophage colony-stimulating factor (GM-CSF) in younger adults with newly diagnosed acute myeloid leukemia (AML): a trial by the Acute Leukemia French Association (ALFA) group [abstract]. Blood 2005;106:530a. Abstract 1862.

35. Thomas X, Fenaux P, Dombret H, et al. Granulocyte-macrophage colony-stimulating factor (GM-CSF) to increase efficacy of intensive sequential chemotherapy with etoposide, mitoxantrone and cytarabine (EMA) in previously treated acute myeloid leukemia: a multicenter randomized placebo-controlled trial (EMA91 Trial). Leukemia 1999;13:1214–1220.

36. Rowe JM, Neuberg D, Friedenberg W, et al. A phase 3 study of three induction regimens and of priming with GM-CSF in older adults with acute myeloid leukemia: a trial by the Eastern Cooperative Oncology Group. Blood 2004;103:479–485.

37. Takamatsu Y, Miyamoto T, Iwasaki H, et al. Remission induction by granulocyte colony-stimulating factor in hypoplastic acute myelogenous leukemia complicated by infection. A case report and review of the literature. Acta Haematol 1998;99:224–230.

38. Ferrara F, Di Noto R, Viola A, et al. Complete remission in acute myeloid leukaemia with t(8;21) following treatment with G-CSF: flow cytometric analysis of in vivo and in vitro effects on cell maturation. Br J Haematol 1999;106:520–523.

39. Nimubona S, Grulois I, Bernard M, et al. Complete remission in hypoplastic acute myeloid leukemia induced by G-CSF without chemotherapy: report on three cases. Leukemia 2002;16:1871–1873.

40. Piccaluga PP, Martinelli G, Malagola M, et al. Complete remission in acute myeloid leukemia with granulocyte-colony stimulating factor without chemotherapy. Report of cytogenetic remission of a t(9;11)(p22q23) positive AML patient and review of literature [e-case]. Haematologica 2003;88:ECR28.

41. Faderl S, Thall PF, Kantarjian HM, et al. Caspase 2 and caspase 3 as predictors of complete remission and survival in adults with acute lymphoblastic leukemia. Clin Cancer Res 1999;5:4041–4047.

42. Faderl S, Harris D, Van Q, et al. Granulocyte-macrophage colony-stimulating factor (GM-CSF) induces antiapoptotic and proapoptotic signals in acute myeloid leukemia. Blood 2003;102:630–637.

43. Ohno R, Tomonaga M, Ohshima T, et al. A randomized controlled study of granulocyte colony stimulating factor after intensive induction and consolidation therapy in patients with acute lymphoblastic leukemia. Japan Adult Leukemia Study Group. Int J Hematol 1993;58:73–81.

44. Larson RA, Dodge RK, Linker CA, et al. A randomized controlled trial of filgrastim during remission induction and consolidation chemotherapy for adults with acute lymphoblastic leukemia: CALGB study 9111. Blood 1998;92:1556–1564.

45. Thomas X, Boiron JM, Huguet F, et al. Efficacy of granulocyte and granulocyte-macrophage colony-stimulating factors in the induction treatment of adult acute lymphoblastic leukemia: a multicenter randomized study. Hematol J 2004;5:384–394.

46. Ottmann OG, Hoelzer D, Gracien E, et al. Concomitant granulocyte colony-stimulating factor and induction chemoradiotherapy in adult acute lymphoblastic leukemia: a randomized phase III trial. Blood 1995;86:444–450.

47. Alvarado Ibarra ML, Borbolla Escoboza JR, Lopez-Hernandez MA, et al. Neutrophil recovery time and adverse effects in acute leukemia patients treated with intensive chemotherapy and concomitant G or GM-CSF. Rev Invest Clin 1999;51:77–80.

48. Tsuchiya H, Adachi N, Asou N, et al. Responses to granulocyte colony-stimulating factor (G-CSF) and granulocyte-macrophage CSF in Ph1-positive acute lymphoblastic leukemia with myeloid surface markers. Blood 1991;77:411–413.

49. Jenkins CS, Ozer H, Parker JC. Mobilization of calla-positive lymphoblasts during treatment with granulocyte colony stimulating factor [abstract]. Blood 1992;80:2944.

50. Shimoda K, Okamura S, Harada N, et al. Granulocyte colony-stimulating factor receptors on human acute leukemia: biphenotypic leukemic cells possess granulocyte colony-stimulating factor receptors. Cancer Res 1992;52:3052–3055.

51. Shinjo K, Takeshita A, Ohnishi K, Ohno R. Granulocyte colony-stimulating factor receptor at various differentiation stages of normal and leukemic hematopoietic cells. Leuk Lymphoma 1997;25:37–46.

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52. Welte K, Reiter A, Mempel K, et al. A randomized phase-III study of the efficacy of granulocyte colony-stimulating factor in children with high-risk acute lymphoblastic leukemia. Berlin-Frankfurt-Munster Study Group. Blood 1996;87:3143–3150.

53. Geissler K, Koller E, Hubmann E, et al. Granulocyte colony-stimulating factor as an adjunct to induction chemotherapy for adult acute lymphoblastic leukemia—a randomized phase-III study. Blood 1997;90:590–596.

54. Heil G, Chadid L, Hoelzer D, et al. GM-CSF in a double-blind randomized, placebo controlled trial in therapy of adult patients with de novo acute myeloid leukemia (AML). Leukemia 1995;9:3–9.

55. Zittoun R, Suciu S, Mandelli F, et al. Granulocyte-macrophage colony-stimulating factor associated with induction treatment of acute myelogenous leukemia: a randomized trial by the European Organization for Research and Treatment of Cancer Leukemia Cooperative Group. J Clin Oncol 1996;14:2150–2159.

56. Witz F, Sadoun A, Perrin MC, et al. A placebo-controlled study of recombinant human granulocyte-macrophage colony-stimulating factor administered during and after induction treatment for de novo acute myelogenous leukemia in elderly patients. Groupe Ouest Est Leucemies Aigues Myeloblastiques (GOELAM). Blood 1998;91:2722–2730.

57. Hast R, Hellstrom-Lindberg E, Ohm L, et al. No benefit from adding GM-CSF to induction chemotherapy in transforming myelodysplastic syndromes: better outcome in patients with less proliferative disease. Leukemia 2003;17:1827–1833.

58. Amadori S, Suciu S, Jehn U, et al. Use of glycosylated recombinant human G-CSF (lenograstim) during and/or after induction chemotherapy in patients 61 years of age and older with acute myeloid leukemia: final results of AML-13, a randomized phase-III study. Blood 2005;106:27–34.

59. Bradstock K, Matthews J, Young G, et al. Effects of glycosylated recombinant human granulocyte colony-stimulating factor after high-dose cytarabine-based induction chemotherapy for adult acute myeloid leukaemia. Leukemia 2001;15:1331–1338.

60. Ifrah N, Witz F, Jouet JP, et al. Intensive short term therapy with granulocyte-macrophage-colony stimulating factor support, similar to therapy for acute myeloblastic leukemia, does not improve overall results for adults with acute lymphoblastic leukemia. GOELAMS Group. Cancer 1999;86:1496–1505.