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Managing Patients With Acute Myeloid Leukemia—Importance of Supportive Care Measures

Selected Presentations From
AML Treatment in the 21st Century:
A Consensus Meeting
Held May 18, 2007, in Dallas, Texas

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Managing Patients With Acute Myeloid Leukemia—Importance of Supportive Care Measures

Selected Presentations From AML Treatment in the 21st Century: A Consensus Meeting, Held May 18, 2007, in Dallas, Texas

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Significant advances have been made in the treatment of acute myeloid leukemia (AML). With the advent of molecular markers, prognostic factors have better defined patient populations that stand to benefit from induction and consolidation therapy. Progress has also been made to improve outcomes in allogeneic transplants using reduced-intensity regimens in related and unrelated donors. Moreover, the era of targeted therapy has concretely benefited patients with myeloid malignancies. Indeed, when it was once believed that the elderly should be spared the ravages of induction and consolidation therapy, there is now a greater emphasis on treating this population with appropriate induction and consolidation regimens or enrolling them in clinical trials that are evaluating "gentler" treatment options.

Efforts to improve clinical outcomes with more tolerable therapeutic choices are to be applauded; however, sorely lacking are supportive care measures that may help patients better tolerate treatment or even have an improved quality of life as they battle or succumb to their disease. The two presentations included here—"Difficulties and Healthcare Utilization/Costs Associated With the Management of Fungal Infections in Patients With Acute Myeloid Leukemia" and "Quality-of-Life Issues in Patients Treated for Acute Myeloid Leukemia"—concentrate on the management of patients treated for AML with respect to supportive care treatment.

Clinical vigilance is necessary to appropriately manage toxicities and side effects of treatment. Treatment with an anthracycline and cytarabine is associated with significant complications. Extravasation is a common situation associated with anthracycline therapy that may not be apparent to healthcare providers. Cytarabine is associated in some patients with neurotoxicity and corneal toxicity, which can be avoided. Use of all-*trans*-retinoic acid (ATRA) to treat a subset of patients with AML is associated with retinoic acid syndrome (RAS). Strategies for managing these situations are discussed.

Mucositis is another complication seen in up to 75% of patients who receive intensive chemotherapy for AML or undergo bone marrow transplantation (BMT). Until

recently, treatment of mucositis was limited to pain medication and topical cleansing; however, new drugs such as palifermin and velafermin are being evaluated specifically to resolve mucositis. Data from published studies are summarized. These new supportive care measures may soon provide a significant improvement in the management of mucositis.

Clinicians who treat patients with AML are aware that morbidity and mortality are increasingly associated with invasive fungal infections that arise from patients undergoing an extensive period of neutropenia. Amphotericin B is empirically administered to patients as a supportive care measure; however, increased morbidity and mortality arise from organisms resistant to amphotericin B. Challenges surrounding infectious complications can be numerous and include changing epidemiology, early and correct diagnosis, inability to reduce/eliminate predisposing factors, and resistance to standard antifungal therapies. Approaches to addressing these challenges are presented herein.

Although neutropenia poses the greatest risk of life-threatening complications, also related to treatment outcomes is the extended period of thrombocytopenia that may lead to bleeding complications. Anemia and thrombocytopenia are routinely treated with blood and platelet transfusions, respectively, and are associated with extended hospital stays that utilize a significant amount of healthcare resources.

In clinical studies, hematopoietic growth factors, which have been approved as supportive care treatment following induction therapy in the allogeneic and autologous BMT settings, have been shown to shorten the periods of neutropenia and thrombocytopenia in patients undergoing treatment for AML. Clinicians appear to have been reluctant to use hematopoietic growth factors for reasons of cost and perceived toxicity. However, use of hematopoietic growth factors has demonstrated significant benefits in both clinical outcomes and improved quality of life of patients treated for AML. Most importantly, hematopoietic growth factors have been demonstrated in multiple clinical studies to be safe. In its practice guidelines, the National Comprehensive Cancer Network has also acknowledged the benefits of hematopoietic growth factors as supportive care measures, but has left their use to the discretion of the institution administering treatment. To date, numerous studies, for which data are presented, have provided evidence confirming the benefits of hematopoietic growth factors as supportive care treatment for patients with AML. Also, studies point to the savings associated with treating patients with AML with hematopoietic growth factors.

The concern regarding leukemic stimulation in the use of hematopoietic growth factors has been resolved. Irrespective of the hematopoietic growth factor used, all but one very small study disprove the notion of leukemic stimulation.

In conclusion, it is important that when clinicians treat solid-tumor and hematologic malignancies, they also manage the side effects associated with treating the malignancies. The management of these effects in turn improves clinical outcomes and provides patients with an improved quality of life.

Difficulties and Healthcare Utilization/Costs Associated With the Management of Fungal Infections in Patients With Acute Myeloid Leukemia

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An anthracycline plus cytarabine forms the backbone of most intensive induction regimens used for the treatment of AML.[1] Postremission consolidation therapy includes strategies used in induction therapy followed by autologous stem cell transplantation (SCT) or allogeneic SCT obtained from sibling or unrelated donors.[1]

Although induction therapy is associated with better complete remission (CR) rates for patients under 60 years of age, several multicenter trials have shown that early treatment-induced death is a significant concern of AML treatment (Table 1).[2-12] Risk of treatment-induced death is associated with performance status, infection, and albumin, β2-microglobulin, bilirubin, and creatinine levels.[13] In addition to neutropenia and infectious complications associated with induction therapy, BMT for hematologic malignancies is associated with invasive fungal infections (IFIs) and infectious complications that increase the rates of morbidity and mortality.[14-16] This review discusses the need to treat or prophylactically ameliorate IFI and the difficulties involved in its clinical management.

Change in Spectrum of IFIs in Patients With AML

Invasive fungal infections may be treatment-related or arise from impaired host defenses. In records from the National Institutes of Health of 454 patients with AML, 189 fungal infections were documented in 161 patients.[14] In this study, the majority of infections were from *Candida* species and, compared to a control group, a significantly higher proportion of patients had granulocyte counts below 1,500/μL prior to the onset of fungal infections ($P<.05$).[14]

With the advent of new antifungal agents, the incidence of IFI has decreased in patients receiving BMT; however, breakthrough infections and changes in the spectrum of *Candida* spp have been reported in patients receiving triazole-based antifungal prophylaxis.[15,16] The emergence of *Candida krusei* and *Candida glabrata* is probably associated with selection pressure associated with the use of fluconazole and itraconazole.[17] In patients undergoing high-risk allogeneic BMT, non-albicans *Candida* spp have emerged as breakthrough infections in patients receiving low-dose fluconazole prophylaxis.[17]

Although incidence rates are lower compared with *Candida* infections, in one retrospective study invasive *Aspergillus* infections were reported in up to 11% of patients after hematopoietic BMT. IFIs tend to occur late after transplantation: the median time from transplantation to diagnosis was 136 days.[18] Indeed, only 14% of IFIs in this study were diagnosed during the neutropenic period after BMT and were due to *Candida* and *Absidia* spp.[18] Most *Aspergillus* infections are associated with *Aspergillus fumigatus*. Although patients diagnosed in this study were treated with antifungal agents, 90% of them died. Mean survival time from diagnosis was 28 days, and in 68% of patients death was attributed to IFIs.[18]

Several studies have established risk factors for developing IFIs in BMT recipients. Host variables include age[19] and underlying disease.[18,20] Unrelated donors were associated with a higher risk of IFI. Acute and chronic graft-versus-host disease (GVHD), secondary neutropenia, cytomegalovirus disease, and respiratory virus infection were additional risk factors for IFI.[18,19] Several prognostic factors contributed to mortality from IFI, including dissemination of disease, presence of pleural effusion, use of high-dose steroids (≥2 mg/kg) at the time of diagnosis,

Table 1. Complete Remission Rates and Early Deaths in Patients on Induction Therapy

	Patients ≥60 Years		Patients <60 Years	
Study (Year)	**CR (%)**	**ED (%)**	**CR (%)**	**ED (%)**
AMLCG (1985)[3]	39	34	68	25
BMRC (1986)[4]	48	52	73	22
CALGB (1987)[5]	41	31/45	65	21
CALGB (1991)[6]	41	54	69	15
SECSG (1992)[7]	53/63	20	63/79	N/A
CALGB (1994)[8]	47	31	71	13
AMLCG (1995)[9,10]	42/54	27/17	68	14
BMRC (1996)[11]	46	30	73	12
IAMLSG (1997)[12]	64*	N/A	74*	N/A

AMLCG=German AML Cooperative Group; BMRC=British Medical Research Council; CALGB=Cancer and Leukemia Group B; CR=complete remission; ED=early death; IAMLSG=International Acute Myeloid Leukemia Study Group; N/A=not applicable; SECSG=Southeastern Cancer Study Group.

* Age groups ≥50 and <50 years.

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prolonged (>2 months) administration of steroids, and uncontrolled GVHD.[20]

Infections due to filamentous molds are also on the increase. The emergence of black molds such as *Scedosporium prolificans* and disseminated infections due to *Fusarium* spp, *Pseudallescheria* spp, *Scedosporium apiospermum*, and other dematiaceous molds have been responsible for failure of standard amphotericin B–based therapy; these infectious fungal agents are either resistant to standard therapy or have variable drug susceptibility profiles.[21] However, because of the increased incidence of zygomycosis with voriconazole prophylaxis, amphotericin B is still used in clinical practice. Therefore, a key issue in treating specific fungal infections is the difficulty in making an accurate diagnosis.

Issues With Diagnosing IFIs

Even with current technologic advances, the diagnosis of IFIs continues to pose a challenge. Fever, radiograph abnormalities, and other symptoms are often confused with those associated with bacterial infections. Indeed, it is common for patients with severe fungal infections to remain afebrile and show normal radiographs. *Aspergillus* and *Candida* spp are ubiquitous in nature, and their presence in the throat, sputum, urine, or stool may not indicate infection.[14] Definitive culture diagnosis of an IFI, which is difficult, requires histologic demonstration in tissue samples; often, these tests are not readily available in common clinical practice.[14,21] In severely immunocompromised patients, isolation of saprophytic molds from blood specimens and other fungi from bronchoalveolar lavages may not have a significant association with IFI.[22,23]

In high-risk patients, emphasis is on minimally invasive tests with better diagnostic power than conventional culture-based methods.[21] In a study of chest computed tomography (CT) findings for 235 patients with invasive pulmonary aspergillosis, most patients (94%) showed one or more macronodules and 61% also had halo signs.[24] Interestingly, patients in whom halo signs were noted had better responses to antifungal therapy and greater survival to 84 days.[24]

A new enzyme immunoassay (EIA) that detects fungal-specific antigens (ie, galactomannans and d-glucans) has raised several issues.[21] Although the EIA has 71% sensitivity and 89% specificity for patients with hematologic malignancies, its sensitivity is significantly compromised in patients treated for fungal infections and in patients receiving mold-active antifungal prophylaxis. In addition, false-positive tests have been seen due to cross-reactivity with piperacillin-tazobactam. Anecdotal evidence suggests that the value of the assay lies in its sequential use, especially in the absence of mold-active agents.

Diagnostic tests such as polymerase chain reaction (PCR) may not be routinely available in clinical practice. With 67–92% sensitivity, 88–95% specificity, a high negative predictive value of 90–99%, and a positive predictive

value of 60–67%, PCR is promising in its 77% diagnostic concordance with EIA and CT findings.[21] Although accurate diagnosis is possible in the academic and research setting, lack of access to appropriate testing facilities makes diagnosis a challenge in the clinical setting, resulting in a significant utilization of healthcare resources.

Healthcare Resource Utilization in Patients With AML

Invasive fungal infections in patients with hematologic malignancies, especially the elderly, is associated with significant utilization of healthcare resources, as reported in several randomized cooperative group studies. In the UK Medical Research Council AML11 trial (N=1,314), the three induction regimens tested (daunorubicin/cytarabine/etoposide; daunorubicin/cytarabine/thioguanine; and mitoxantrone/cytarabine) provided similar profiles for neutropenic and platelet recovery.[25] In addition, patients receiving any of the three regimens had similar healthcare resource utilization with respect to units of blood and platelets received, days on intravenous antibiotics, and hospital stay (Table 2). In a second study, conducted by the Southwest Oncology Group (N=328), fatal toxicity was 23% and 18% for patients receiving mitoxantrone/etoposide versus cytarabine/daunorubicin, respectively, and was predominantly due to infections (89% vs 82%). However, length of recovery and hospital stays were similar for patients in the mitoxantrone/etoposide and cytarabine/daunorubicin arms (neutrophil recovery, 33 vs 30 days; platelet recovery, 33 vs 34 days; and hospital stay, 30 vs 28 days, respectively).[26]

A retrospective analysis of 3,439 patients (≥65 years old) with AML using the linked Surveillance, Epidemiology, and End Results (SEER)–Medicare database indicated that costs and overall healthcare resource utilization—with the exception of those related to hospice use and chemotherapy—did not significantly change over the decade of the analysis (1991–1999).[27] This finding was primarily due to high early mortality: the median survival across all study patients was 2.4 months and 2-year survival was less than 7%. Average total costs, determined from Medicare payments, were $51,888.

In an Eastern Cooperative Oncology Group (ECOG) phase III study, an economic analysis was undertaken for 117 patients with AML randomized to receive either granulocyte-macrophage colony-stimulating factor (GM-CSF) for supportive care (n=60) or placebo (n=57).[28] Cost estimates for patients who received one cycle of induction therapy were similar between the two groups ($38,617 vs $37,037, respectively); however, markedly lower costs were estimated for patients receiving GM-CSF who proceeded to receive a second round of induction therapy ($37,467 vs $59,902). The estimated lower costs were attributed to shorter hospital stays and a lower incidence of grade 3–5 infections.[28]

Although relatively few cost-analysis studies are available to determine the burden of AML and its accompanying complications, the data suggest that improvement in patients' well-being merits attention. In addition, when antifungal agents have been used in the management of IFIs, increased clinical benefit has been seen in patients with AML and other hematologic malignancies.

Table 2. Toxicity and Supportive Care Requirements of Induction Courses 1 and 2

	Course 1	Course 2
	DAT/ADE/MAC	*DAT/ADE/MAC*
Hematologic toxicity, median days from end of course to:		
Neutrophils >1.0 3 10^9/L	20/19/24	19/18/22
Platelets >100 3 10^9/L	21/22/22	20/19/20
Supportive care		
Mean units of blood	12/12/11	5/6/6
Mean units of platelets	51/48/39	18/21/22
Mean days on IV antibiotics	20/20/18	8/12/11
Median days in hospital	28/27/25	20/21/22

ADE=daunorubicin, cytarabine, etoposide; DAT=daunorubicin, cytarabine, thioguanine; IV=intravenous; MAC=mitoxantrone, cytarabine.

Adapted with permission. This research was originally published in *Blood.* Goldstone AH, Burnett AK, Wheatley K, et al; for the Medical Research Council Adult Leukaemia Working Party. Attempts to improve treatment outcomes in acute myeloid leukemia (AML) in older patients: the results of the United Kingdom Medical Research Council AML11 trial. 2001;98:1302-1311.[25] © The American Society of Hematology.

Suboptimal Outcomes With Antifungal Therapy

In allogeneic transplant settings, most preemptive treatment is undertaken empirically. Amphotericin B and its lipid formulations were considered the gold standard of antifungal therapy; however, its clinical use has been associated with suboptimal benefits. In an analysis of 1,223 cases of invasive aspergillosis, although all patients with leukemia and BMT were treated with amphotericin B, mortality was 66%.[29] A retrospective analysis corroborated these findings: the case-fatality rate was highest (87%) for

BMT patients with invasive aspergillosis.[30] Compared with amphotericin B, voriconazole is associated with better clinical outcomes for patients with invasive aspergillosis but is also associated with visual disturbance in some patients.[31] In addition, voriconazole use may be associated with an increase in the incidence of invasive, life-threatening zygomycosis.[32]

Several studies have evaluated caspofungin, an echinocandin, alone or in combination with other antifungal agents, for the treatment of invasive aspergillosis. In one study (N=83), 45% of patients refractory or resistant to other antifungal therapy (eg, amphotericin B, itraconazole, voriconazole) responded to caspofungin administered for a median of 28 days; the mortality rate was 48% and 28% of deaths were related to IFI or infection-related complications.[33] Caspofungin has also been used in combination with other antifungal agents as salvage therapy for patients with hematologic malignancies.[34,35] The combination of caspofungin and amphotericin B, administered for a median of 24 days, was associated with favorable antifungal outcomes in 18 of 30 patients. In patients with acute leukemia, antifungal response was not dependent on response of the underlying leukemia.[34] In another study, the same combination administered over a median of 20 days was associated with an overall response rate of 42%.[35] In addition, in BMT recipients with late posttransplant invasive aspergillosis, salvage therapy of caspofungin in combination with voriconazole was associated with an improved 3-month survival rate compared with voriconazole alone (hazard ratio, 0.42; 95% confidence interval, 0.17–1.1; *P*=.048).[36]

In an attempt to improve clinical outcomes with caspofungin, high-dose caspofungin (HD; 100 mg daily) was compared with standard-dose caspofungin (SD; initial 70 mg dose followed by 50 mg daily) in patients with hematologic malignancies and undergoing hematopoietic SCT.[37] Although significantly more patients in the HD versus SD group had extrapulmonary infections (29% vs 8%; *P*=.0053), had non–*Aspergillus* spp infections (21% vs 6%; *P*=.05), and had received prior antifungal therapy (71% vs 33%; *P*=.0004), 44% of patients on the HD arm responded to therapy compared with 29% of patients on the SD arm. It is worth noting that markedly more patients on the HD arm (41% vs 14% in the SD group) had also received GM-CSF for immune enhancement.[37]

These data support the contention that even with several antifungal agents at our disposal, their efficacy, alone or in combination, is suboptimal. Indeed, there is reason to believe that addition of immune modulators to antifungal prophylaxis or treatment might provide additional benefits not seen with the use of antifungal agents alone.

Immune Enhancement Strategies in the Treatment of IFIs

The evaluation of immune enhancement strategies in the treatment of IFIs appears warranted in the face of the changing epidemiology of IFIs, the issues associated with early and correct diagnosis of IFIs, the inability to reduce/eliminate predisposing factors, and the suboptimal clinical outcomes seen with antifungal therapies used in supportive care practices. Given that an intact immune system is essential to successfully combat fungal infections, several factors adversely affect host immune defenses in patients with hematologic diseases and IFI, including hematologic malignancy, neutropenia associated with chemotherapeutic agents used in induction, consolidation, and conditioning regimens; BMT; GVHD; and immunosuppressive agents used to combat GVHD. In preclinical studies, immune enhancement strategies have been shown to activate Th1 responses that promote antifungal activity via the activation of several cytokines, including interleukin (IL)-12/IL-23, IL-18, IL-2, and interferon-gamma.[21]

In clinical studies, the value of GM-CSF was first documented in adults with AML.[38] In a phase I/II study, adult patients with early or multiple relapse AML or over 65 years of age with newly diagnosed AML received GM-CSF if their bone marrow was aplastic with less than 5% blasts 3 days after the end of induction chemotherapy (n=30). Patients received a continuous intravenous infusion of GM-CSF 250 mcg/m^2/day until a neutrophil count of 2,000/µL was achieved and maintained for 4 days, at which time the GM-CSF dose was reduced to 125 mcg/m^2/day and continued for an additional 4 days. Compared with historic controls (n=56), median time to achieve 500/µL blood neutrophils was significantly shorter for patients receiving GM-CSF (*P*=.043) and associated with a clearance of infections. In addition, GM-CSF administration was associated with higher CR rates (50% vs 32% for controls; *P*=.09) and decreased early death rates (14% vs 39%; *P*=.009). In two other pilot trials, GM-CSF was also associated with markedly higher CR rates for patients who received antibiotics and GM-CSF as supportive care compared with patients who received only antibiotics. In both studies, GM-CSF was associated with a faster neutropenic recovery.[39]

In a prospective, randomized, double-blind, placebo-controlled, phase III ECOG study, patients (55–70 years) newly diagnosed with AML were randomized to receive yeast-derived GM-CSF (sargramostim) or placebo as supportive care after one or two courses of induction therapy.[40] Patients proceeding to consolidation therapy continued to receive the study drug (GM-CSF or placebo) in addition to the consolidation regimen. Three

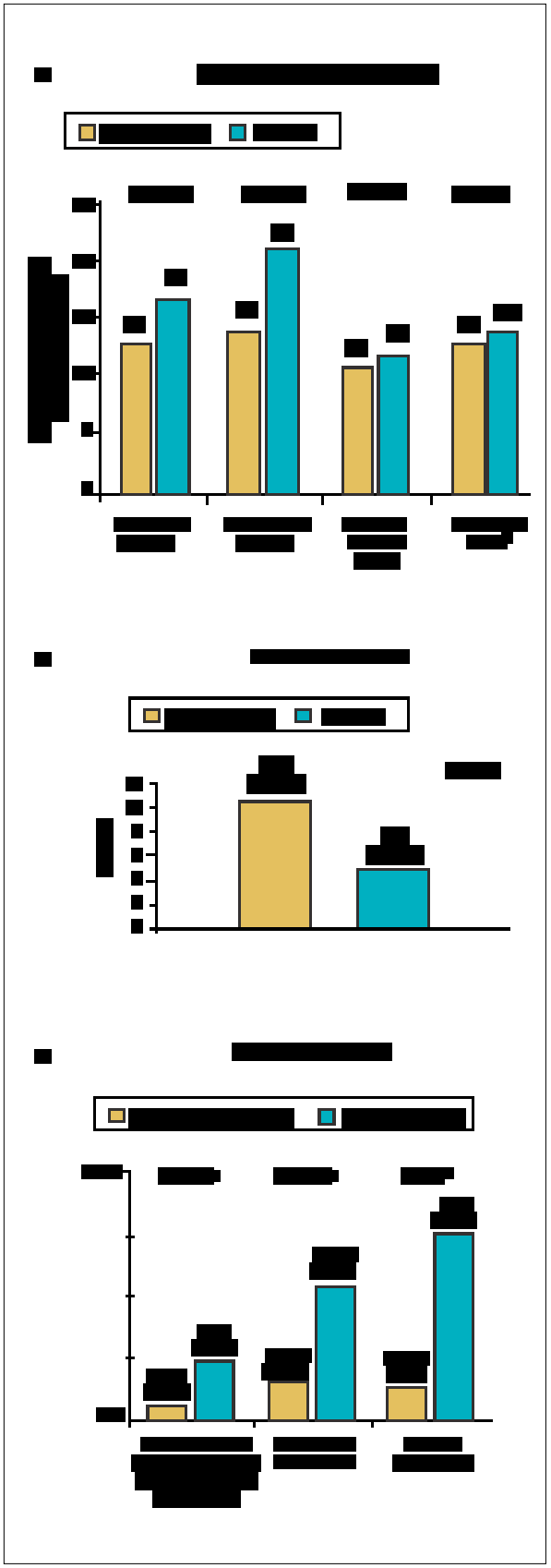

Figure 1. Effect of granulocyte-macrophage colony-stimulating factor (sargramostim) on (A) median days to achieve hematologic responses; (B) median overall survival in months; and (C) percent patients with fatal infections, death from pneumonias, and fatal fungal infections.

*Competing risk test was stratified by number of cycles. *P* values included from the Leukine package insert. Statistical method used was generalized Wilcoxon (not the log-rank test in which patients who die without recovery are censored); patients missing data were censored.

†Recovery of platelets (>20,000/μL) and red blood cells to transfusion independence.

‡Fisher exact test.

ANC=absolute neutrophil count; IFI=invasive fungal infection.

Data from 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(2):457-462; Leukine® (sargramostim) [package insert]. Seattle, WA: Berlex Laboratories; 2006; and Rowe JM, Rubin A, Mazza JJ, et al. Incidence of infections in adult patients (>55 years) with acute myeloid leukemia treated with yeast-derived GM-CSK (sargramostim): results of a double-blind prospective study by the Eastern Cooperative Oncology Group. In: Hiddemann W, Büchner T, Wörmann B, et al, eds. *Acute Leukemias V: Experimental Approaches and Management of Refractory Diseases.* Berlin: Springer; 1996:178-184.

aspects of hematologic response were studied in this trial: 1) time to neutrophil recovery (to an absolute neutrophil count [ANC] >500/μL and to an ANC >1,000/μL); 2) time to platelet recovery (>20,000 platelets/μL); and 3) time to independence from red blood cell transfusions. Recovery times were measured from day 11 after induction chemotherapy. The primary endpoint was to detect a 7- to 9-day reduction in the median duration of neutropenia.[40] Administration of GM-CSF met the primary endpoint of the study. In addition, secondary endpoints were also significantly in favor of patients receiving GM-CSF. Hematologic responses, overall survival, and fatal infections are summarized in Figure 1.[40-42] Median time to neutropenic recovery was significantly shorter for patients receiving GM-CSF; median times to platelet recovery and red blood cell transfusions were not significantly different between the two groups.[40] Overall survival was also significantly in favor of patients receiving GM-CSF (10.6 vs 4.8 mo for placebo; *P*=.048).[40] In a separate analysis, the incidence of fatal infections during and within 30 days of completing study, death from pneumonia, and fatal fungal infections in patients showing grade 3/4 fungal infection were significantly lower in patients receiving GM-CSF (Figure 1C).[42] In addition, both the combined incidence of grade 3/4/5 infections (severe, life-threatening, and fatal) and the combined

incidence of grade 4/5 infections were significantly lower for patients receiving GM-CSF compared with placebo (51.9% vs 74.5% and 9.6% vs 36.2%, respectively; *P*=.024 for both).[42]

Other immune enhancement strategies have also been evaluated in addressing IFI in patients with hematologic malignancies, including recombinant interferon-gamma,[43] donor granulocyte transfusions,[44] adaptive T-cell therapy,[45] and dendritic cell vaccines.[46] The pathogen-specific cellular immune transfer and antifungal vaccine strategies are in early stages of preclinical development. However, all of these strategies acknowledge the importance of reducing time to neutropenic recovery, restitution of innate and adaptive T cell–mediated immune response, and targeted therapy for invasive fungal infections in patients with hematologic malignancy and recipients of hematopoietic SCT.

Conclusion

Invasive fungal infections are serious complications in patients with AML and other hematologic malignancies and are associated with lower CR rates and early mortality in patients. Neutropenia associated with induction, consolidation, and salvage regimens used to treat AML contribute to the early onset of IFIs. Identifying the culprit pathogen is fraught with difficulties in routine clinical practice, resulting in empirical or preemptive treatment with antifungal agents that alone or in combination offer suboptimal clinical benefits. Clinical and preclinical data indicate that immune enhancement strategies may offer a marked improvement in supportive care practices for addressing optimal resolution of IFIs in patients with AML and other hematologic malignancies.

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Quality-of-Life Issues in Patients Treated for Acute Myeloid Leukemia

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Induction and consolidation therapies involved in the treatment of AML with the intent to achieve CR are associated with side effects that must be appropriately managed. Anthracycline-based regimens used in induction therapy are associated with drug extravasation. Treatment of acute promyelocytic leukemia (APL), a subset of AML, with ATRA is associated with RAS. High-dose cytarabine used in consolidation therapy is associated with mucositis. Neutropenia and thrombocytopenia are toxicities associated with infections and bleeding complications. Successfully managing toxicities associated with induction and consolidation therapies will have a significant bearing on improving patients' quality of life. This review summarizes some of the salient toxicities seen in patients with AML and offers guidance on management strategies.

Management of Anthracycline Extravasation

Described as a leakage of drugs from the portal of entry into the surrounding tissue, extravasation can occur

early and cause severe, sometimes irreversible, local injuries. Classified as Group 1 vesicants (ulcerogens), anthracyclines used in remission induction, such as daunorubicin and idarubicin, bind nucleic acids; their local absorption directly leads to cell death. Following endocytosis, the drug released from neighboring dead cells causes additional death of surrounding cells. The repetitive nature of the process impairs wound healing, leading to progressive and chronic tissue injury. Pain associated with erythema and edema within a few hours of anthracycline administration may be an immediate manifestation of anthracycline extravasation. Skin ulceration and necrosis in underlying structures such as fascia, tendons, and periosteum typically occur within 1–3 weeks.[1] The extent of damage depends on several factors, including concentration and volume of anthracyclines used, infusion site, and condition of the tissue.[1]

As in every good clinical practice, prevention is better than cure. It is recommended that published guidelines and institutional policies for the management of extravasation of intravenous drugs be reviewed and strictly followed.[2] Risk factors associated with extravasation should be evaluated before administering chemotherapy; the potential for toxicity and complications associated with extravasation should not be underestimated. Central venous access devices (eg, subcutaneously implanted ports and peripherally inserted central catheter lines) reduce extravasation. Peripheral lines should be used only for short infusions and must first be tested with intravenous fluids delivered at a high rate to determine the patency of the vessel to be used; patients should be continuously monitored until a good blood return is established.

Anthracyclines, like all vesicants, should be administered through a central line. Hyperthermia aggravates anthracycline toxicity; hence, ice packs around the injection site are recommended as a nonpharmacologic management procedure. Intermittent topical cooling for 24–48 hours is also recommended.[1]

Anthracycline extravasation is pharmacologically managed with the use of antidotes such as dimethyl sulfoxide (DMSO). DMSO enhances skin permeability, penetrates tissues, and facilitates the absorption of anthracyclines. It is administered via the original intravenous line. Up to 2 mL of a 50–99% weight/volume solution can be used for intravenous administration; topical administration is recommended every 6–8 hours. Although corticosteroids such as hydrocortisone are used in the management of anthracycline-related extravasation, their efficacy to act as antidotes has not been prospectively demonstrated in clinical studies.[1] The usefulness of hydrocortisone may lie in its ability to mitigate venous flare reactions that have been observed with anthracyclines.

Management of Retinoic Acid Syndrome

In studies of patients with newly diagnosed APL treated with ATRA and chemotherapy, up to 94% of patients achieved CR; RAS was observed in 15–25% of patients overall.[3,4]

RAS, a cardiopulmonary distress syndrome, has a median onset of 7–11 days and clinically manifests as dyspnea, weight gain, pleural and pericardial effusions, episodic hypotension, pulmonary infiltrates, and acute renal failure.[3,4] At the earliest indication of RAS, treatment with intravenous dexamethasone (10 mg bid for 3 days) is important and should not be delayed until a diagnosis is established.

ATRA, a derivative of vitamin A administered in combination with chemotherapy, is associated with high CR rates and is recommended for all patients suspected to have APL.[2] Used while RAS is mild, ATRA should be discontinued when RAS is moderate or extreme and re-administered when RAS resolves.[5] In patients who present with high white cell counts (>10,000/mL), the prophylactic administration of dexamethasone is recommended.

Management of Mucocutaneous, Corneal, and Cerebellar Toxicities

Cytarabine administered at a dose of at least 1 g/m^2 is associated with mucocutaneous, corneal, and cerebellar toxicities. Not related to dose or treatment schedule, mucocutaneous toxicity manifests as a blistering, erythematous rash that affects predominantly the trunk, hands, and feet.[5] The eruption is self-limiting and fades within days of discontinuation of the drug. There is no treatment for this minor complication, nor is one necessary. Rarely, toxic epidermal necrolysis, which is a potentially fatal disorder, can occur.[6] Corticosteroids are usually successful in resolving this problem.

Corneal toxicity can occur with high-dose cytarabine.[7,8] Clinical manifestations include conjunctival hyperemia, ocular pain, photophobia, blurred vision, and a sensation of a foreign body in the eye. Associated with an inhibition of corneal DNA synthesis,[7] corneal toxicity resolves within 1–2 weeks of discontinuation of cytarabine.[9] However, cataracts, although uncommon, do not resolve with drug discontinuation. Corneal toxicity can be preempted by the prophylactic administration of corticosteroid eye drops 12 hours prior to the initiation of high-dose cytarabine.[9] Though an equally efficacious and more specific treatment, 2-deoxycytidine eye drops are not generally available.[10]

Neurotoxicity, an uncommon complication of high-dose cytarabine, is the most serious side effect. High-dose cytarabine usually implies regimens that use individual doses of 1 g/m^2 or higher; although rare, this complication

can occur at lower levels.[11] Cerebellar toxicity has been demonstrated particularly in the elderly and patients with hepatic and renal impairment; incidence rates are below 1% in patients younger than 40 years of age. In 95% of patients, the toxicity resolves if cytarabine is discontinued at the first sign. Hence, daily examination of cerebellar signs is important. With an onset of 4–8 days after treatment initiation, cerebellar dysfunction is characterized by ataxia, nystagmus, and dysarthria.[11-13] Toxicity is related to cumulative dose exposure. In patients with no hepatic or renal impairment, recommended cytarabine doses are dependent on patient age. There are several acceptable ways of administering high-dose cytarabine. The following is one such established protocol:

- For patients <55 years: 36 g/m^2 (3 g/m^2 IV over 1 hour every 12 hours for 6 days)
- For patients ≥55 years and <70 years: 18 g/m^2 (1.5 g/m^2 every 12 hours x 12 doses)
- For patients ≥70 years: 9 g/m^2 (1.5 g/m^2 every 12 hours x 6 doses)

Management of Mucositis

Oral mucositis is observed in up to 75% of patients receiving BMT.[14] Its higher prevalence in younger patients is perhaps related to the more rapid turnover of oral epithelial mucosa, which is sensitive to injury by chemotherapy.[15] Until recently, mucositis was primarily treated with analgesics, topical agents, oral cleansing, and rinsing.[15]

The recombinant keratinocyte growth factor palifermin received approval from the US Food and Drug Administration for decreasing the incidence and duration of severe mucositis in patients with hematologic malignancies receiving myelotoxic therapy requiring hematopoietic stem cell support. Support for the approval was based on data from a double-blind study that compared the incidence of mucositis in 212 patients with hematologic malignancies receiving either palifermin 60 mcg/kg/day (n=106) or placebo (n=106) in addition to conditioning therapy.[16] Palifermin or placebo was administered for 3 consecutive days before initiating conditioning therapy and after BMT. Oral mucositis was evaluated daily for 4 weeks after BMT. A second study (N=64) also evaluated the efficacy of palifermin to reduce the incidence of oral mucositis in patients with colorectal cancer following treatment with 40 mcg/kg palifermin (n=28) or placebo (n=36) for 3 consecutive days.[17] As summarized in Figure 2, palifermin significantly reduced the incidence of grade 3/4 mucositis in both patients with hematologic malignancies (P<.001) or colorectal cancer (P=.003).[16,17] In patients with hematologic malignancies, the incidence of grade 3/4 oral mucositis was 63% for patients receiving palifermin and 98% for patients receiving placebo (P<.001).[16] The median duration of grade 3/4 oral mucositis among all patients was 3 days for patients on the palifermin arm compared with 9 days for patients on the placebo arm (P<.001).[16]

Velafermin, a fibroblast growth factor, is another agent that was evaluated in a phase II, multicenter, randomized, double-blind, placebo-controlled trial for the prevention of oral mucositis in 212 patients receiving autologous hematopoietic SCT.[18] Incidence of grade 3/4 mucositis was 18% and 37% for patients receiving velafermin and placebo, respectively. With the availability of palifermin and the evaluation of other agents for decreasing the incidence and duration of oral mucositis, these data indicate that the management of oral mucositis in patients with AML will change significantly.

Shortening the Periods of Neutropenia and Thrombocytopenia

The therapeutic options available for treating AML in the induction and consolidation phases are associated with hematologic toxicities of thrombocytopenia, anemia, and neutropenia leading to bleeding and infections. Typically treated with platelet and blood transfusions, these toxicities are associated with increased length of hospital stays and utilization of significant healthcare resources, especially in the elderly.[19] In addition, the length of thrombocytopenia and neutropenia predisposes patients to bleeding and infectious complications. Shortening the periods of thrombocytopenia and neutropenia is, therefore, desirable in all patients treated for AML, with particular attention given to patients with anticipated high risk for treatment-related morbidity and mortality.

The addition of hematopoietic growth factors to other supportive care measures has significant value. With the introduction of hematopoietic growth factors over the past decade, multiple studies have been conducted in an attempt to define the use of cytokines in AML. Apart from reducing the period of neutropenia, growth factors enhance antimicrobial function, prime immature cells and ready them for recruitment in the S phase of the cell cycle, induce the differentiation of leukemic cells, interrupt autocrine-paracrine loops, and have direct antileukemic effects.[20]

In 18 controlled trials, nearly 5,000 patients have been treated with hematopoietic growth factors such as granulocyte colony-stimulating factor (G-CSF) and GM-CSF. These cytokines have been shown to significantly reduce the periods of absolute neutropenia by approximately 1 week. Data from these studies are summarized in Table 3.[19,21-37] In all of these studies a significant reduction in the neutropenic period was noted with patients receiv-

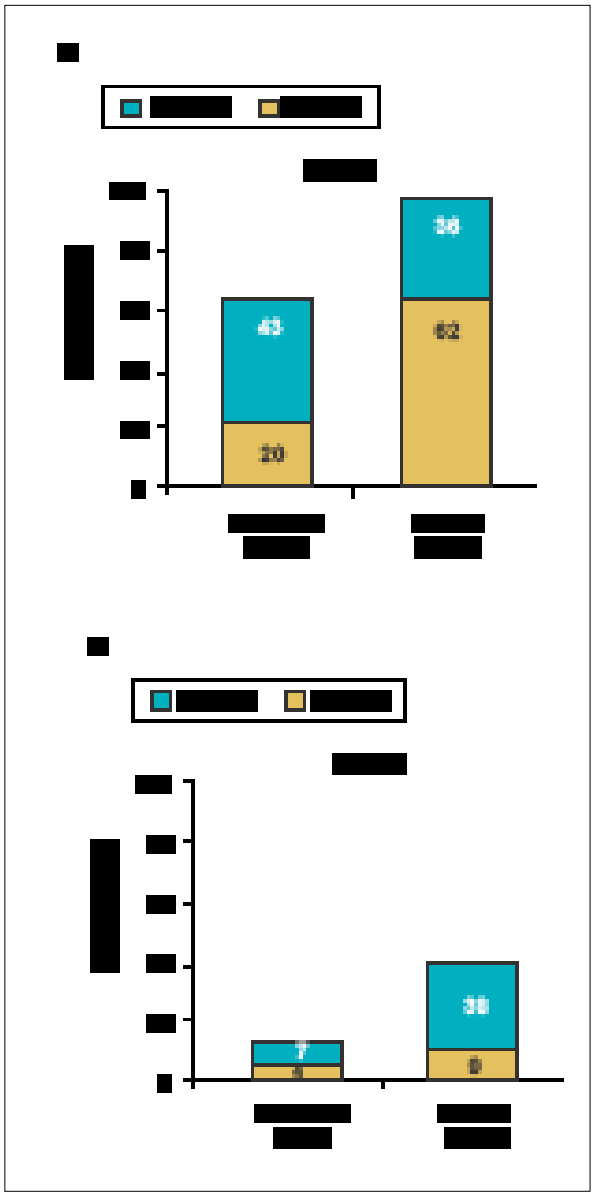

Figure 2. Compared with placebo, palifermin significantly decreases the incidence of grade 3/4 mucositis (A) in patients with hematologic malignancies and (B) in patients with colorectal cancer. Data in panel B are shown for patients after the second cycle of chemotherapy.

Adapted with permission from: Spielberger R, Stiff P, Bensinger W, et al. Palifermin for oral mucositis after intensive therapy for hematologic cancers. *N Engl J Med*. 2004;351:2590-2598, copyright © 2007 Massachusetts Medical Society. All rights reserved; Rosen LS, Abdi E, Davis ID, et al. Palifermin reduces the incidence of oral mucositis in patients with metastatic colorectal cancer treated with fluorouracil-based therapy. *J Clin Oncol*. 2006;24:5194-5200, reprinted with permission from the American Society of Clinical Oncology.

ing GM-CSF or G-CSF. The studies further showed that cytokines are safe and well tolerated.

In addition to significantly decreasing the neutropenic period, considerable data in the preclinical as well as in the clinical setting suggest significant enhancement of antimicrobial function, especially by GM-CSF. Although most of these studies are not prospective in nature, in one prospective, randomized, double-blind, placebo-controlled, phase III ECOG study, the incidence of fatal infections during and within 30 days of completing the study, death from pneumonia, and fatal fungal infections in patients showing grade 3/4 fungal infection were significantly lower in newly diagnosed AML patients receiving GM-CSF (Table 4).[38] Of patients receiving GM-CSF (n=52) or placebo (n=47), 8 and 12, respectively, had documented fungal infections. Mortality was 13% (1/8 patients) versus 75% (9/12 patients) for patients receiving GM-CSF or placebo, respectively.[20,38] Although caution is appropriate in interpreting these data due to the relatively small patient numbers involved, the percentage of patients who died from pneumonia was significantly reduced among those receiving GM-CSF (14% vs 54%; *P*=.046).[38] In addition, unlike patients receiving placebo who died from fungal infections, most patients receiving GM-CSF survived similar infections. It remains uncertain whether this improvement reflects direct antimicrobial action, enhancement of neutrophil recovery, or both.[38]

Of several studies that used GM-CSF or G-CSF as "priming" during and after induction of patients with newly diagnosed leukemia, two studies showed significant improvement in disease-free survival (DFS).[25,26] In the first prospective study, patients received idarubicin and cytarabine in cycle 1 of induction therapy; in cycle 2, patients received either chemotherapy (amsacrine/cytarabine; n=319) alone or chemotherapy and G-CSF (n=321).[26] Although G-CSF was not associated with significantly better survival and the authors concluded that priming with G-CSF offered no clinical benefits, patients on the G-CSF arm showed a higher overall rate of DFS (42% vs 33% for no G-CSF support at 4 years; *P*=.02) and lower relapse rate. In the second prospective study, patients received GM-CSF and chemotherapy (idarubicin and cytarabine; n=114) or chemotherapy alone as induction therapy (n=126).[26] Although the rate of CR was similar for both arms of the study (63% vs 61%, respectively), 2-year DFS significantly favored patients on the GM-CSF arm of the study (48% vs 21%; *P*=.003). In addition, a trend toward longer survival was observed in patients on the GM-CSF arm of the study.

The controversy abounding in the use of cytokines for the management of AML is still unclear. Concern

Table 3. Controlled Trials of Growth Factors After Induction Therapy in Acute Myeloid Leukemia.[19,21-37]

Study	N	Reduction in Days to ANC 1,000/µL	Documented Reduced Morbidity	Leukemic Stimulation
GM-CSF (sargramostim)				
Büchner (1991)[21]	86	6-9*	+	No
Rowe (1995)[22]	117	6*	+	No
GM-CSF (molgrastim)				
Stone (1995)[23]	379	2*		No
Zittoun (1996)[24]	53	—		Yes
Löwenberg (2003)[25]	316	5*		No
Witz (1998)[26]	209	6*		No
Löfgren (2004)[27]	110	8*	+	No
G-CSF (lenograstim)				
Dombret (1995)[28]	173	6*		No
Link (1996)[29]	187	6*		No
Goldstone (2001)[19]	803	5*		No
Amadori (2005)[30]	722	5*	+	No
G-CSF (filgrastim)				
Ohno (1990)[31]	67	12*	+	No
Ohno (1994)[32]	58	6*		No
Heil (1997)[33]	521	5*	+	No
Godwin (1998)[34]	234	3–4*	+	No
Usuki (2002)[35]	270	6*	+	No
Lehrnbecher (2007)[36]	317	5*		No
Estey (1992)[37]	197	13*		No

ANC=absolute neutrophil count; G-CSF=granulocyte colony-stimulating factor; GM-CSF=granulocyte-macrophage colony-stimulating factor.

*$P \leq .05$

that the use of growth factors may stimulate the growth of leukemic cells is unwarranted. Data from several studies summarized in Table 3 indicate that this concern is not substantiated. A meta-analysis of the many studies that use growth factors is unfortunately not possible due to the significant variability between studies in both design and conduct. Patient selection and study endpoints, for example, make it difficult to draw consensus on the use of cytokines for managing AML. However, good clinical practice suggests that cytokines should be considered an important supportive care measure similar to how central venous catheters are considered. Central venous catheters are not cost effective, they increase rather than decrease infections, and they do not shorten hospitalizations, but they are important for the well being and comfort of patients. Similarly, cytokines, besides showing other clinical benefits, are an important aspect of supportive care and can effectively and significantly reduce the period of neutropenia and should be administered to at least all patients at risk for morbidity and mortality.

Recently, a thrombopoiesis-stimulating protein, AMG 531, has been shown to increase platelet counts in patients with immune thrombocytopenic purpura.[39] Although it is too early to evaluate its significance in treating thrombocytopenia in patients with AML, its value as

Table 4. Therapy-Related Mortality and Infectious Toxicity From the Eastern Cooperative Oncology Group 1490 Study[38]

	GM-CSF (n=52)	Placebo (n=47)	*P* Value
Therapy-related mortality	3/52 (6%)	8/47 (15%)	.110
Infection			
Grades 3–5	27/52 (52%)	35/47 (75%)	.024
Grade 4/5	5/52 (10%)	17/47 (36%)	.002
Fatal infections while on study drug	3/52 (5.8%)	8/47 (17%)	.110
Fatal infections during and within 30 days of completing study	3/52 (5.8%)	11/47 (23.4%)	.019
Death from pneumonia (grade 3/4)	2/14 (14%)	7/13 (54%)	046
Fatal fungal infections			
All subjects given study drug	1/52 (1.9%)	9/47 (19.1%)	.006
Grade 3/4	1/8 (13%)	9/12 (75%)	.02

GM-CSF=granulocyte-macrophage colony-stimulating factor.

Adapted with permission from: Rowe JM, Rubin A, Mazza JJ, et al. Incidence of infections in adult patients (> 55 years) with acute myeloid leukemia treated with yeast-derived GM-CSF (sargramostim): results of a double-blind prospective study by the Eastern Cooperative Oncology Group. In: Hiddemann W, Büchner T, Wörmann B, et al, eds. *Acute Leukemias V: Experimental Approaches and Management of Refractory Diseases*. Berlin: Springer; 1996:178-184.

a supportive care measure will be monitored closely for clinical benefits.

Conclusion

Intensive induction and consolidation therapies designed to achieve remission in patients with AML are associated with significant morbidity and quality-of-life issues. Successful management of AML mandates effective treatment of the side effects resulting from the intensive regimens used. As clinicians, it is incumbent upon us to recognize patient quality of life as an important aspect of patient care. Patients must be monitored for side effects of corneal, skin, and neurotoxicity directly related to high-dose cytarabine; management of these side effects is also of significant importance in managing patients with AML. The argument that some of these supportive care measures may not be cost-effective is mitigated by reduced hospital stay, reduced morbidity and mortality, and improved quality of life. Hence, their use has significant value to patients and must be considered for all high-risk patients.

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