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New Treatments and Strategies in Acute Myeloid Leukemia

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Abstract

Despite considerable progress in the treatment of acute myeloid leukemia in the past several decades, the prognosis of the majority of patients with this disease remains guarded. Advances in supportive care and better characterization of disease subsets through cytogenetics and molecular analysis have led to significant success in treating specific subsets of patients, such as those with acute promyelocytic leukemia and core binding factor leukemias, particularly among the younger patients who are able to better tolerate the effects of cytotoxic chemotherapy. However, overall, only about 40% of younger patients and <10% of older patients with this disease are alive at 5 years. Current research is focusing on the identification of new cellular targets amenable to specific inhibitors, designing the best strategies for combining these novel agents with traditional chemotherapy regimens, and determining prognostic indicators that may allow us to better stratify therapy.

Keywords

AML; Therapy; New strategies

Recent Developments in the Treatment of Acute Myeloid Leukemia

Frontline Treatment of Younger and/or Fitter Patients

Treatment of patients with acute myeloid leukemia (AML) continues to be a challenge for a significant majority. Although, mainly through improvements in the supportive care and advances in the management of specific favorable subgroups, the overall 5-year survival for patients younger than 60 years old has significantly improved over the past several decades, the outcome for those 60 years and older has generally remained dismal with <10% surviving long term. Clearly, traditional regimens need to be refined in both younger and

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older patients, and new agents and novel regimens are needed, particularly for the older patients with AML who constitute the majority.

Intensification of the dose of cytosine arabinoside (ara-C) and/or anthracyclines has been advocated by a number of groups. Kern and Estey¹ demonstrated a significant benefit for use of high-dose ara-C in induction, in patients with AML and younger than 60 years, in a meta-analysis of several published randomized trials. More recently, investigators from the ECOG (Eastern Cooperative Oncology Group) demonstrated a higher complete remission (CR) rate, equivalent induction mortality, and a better survival for the higher dose of daunorubicin, when they randomized 657 patients with AML, younger than 60 years old, to receive either 45 mg/m² or 90 mg/m² daunorubicin, in addition to 7 days of continuous infusion ara-C at 100 mg/m² daily.² However, when they examined various subsets of the patients, no difference in outcome was observed for those older than 55 years old, those with unfavorable risk cytogenetics, or those with FLT3 mutations. Similarly, Lowenberg et al³ showed a higher CR when 813 patients older than 60 years old with AML were randomized to receive daunorubicin 90 mg/m² vs. 45 mg/m² in addition to ara-C 200 mg/m² daily for 7 days (64% vs. 54%). The early death rate was similar between the 2 groups. Although, overall, there was no difference in survival between patients treated with the standard- vs. escalated-dose daunorubicin, there was a statistically significant advantage for patients aged 60–65 years treated with the higher dose of the anthracycline.³ Therefore, it appears that there is a population of patients with AML (younger, more favorable cytogenetics, and without the adverse mutations) who may benefit from the escalation of the dose of the traditional cytotoxic agents. However, such dose escalation is generally detrimental in those patients with more adverse features (older, with adverse cytogenetics and molecular features, particularly those with organ dysfunction and poor performance status).

The question of the best anthracycline to use in induction is still under debate and evaluation. Results of the ALFA (Acute Leukemia French Association) 9801 study were recently published.⁴ A total of 468 patients aged 50 to 70 years and with AML were randomized to receive ara-C 200 mg/m² daily for 7 days, in addition to daunorubicin 80 mg/m² daily for 3 days, idarubicin 12 mg/m² daily for 3 days, or idarubicin 12 mg/m² daily for 4 days. Although there was a significant advantage for achievement of CR for the idarubicin arms (and, in particular, idarubicin for 3 days; $P = .04$), there was no benefit for any of the 3 arms in terms of disease-free or overall survival.⁴

Other strategies that use hematopoietic growth factors, such as GCSF and GM-CSF, for “priming” leukemic cells into the S-phase of the cell cycle (where they are more susceptible to the effects of drugs such as ara-C)⁵ as well as intensification of treatment by using strategies such as double induction or timed sequential therapy^{6,7} have been extensively evaluated and have shown promise in patient subsets in some but not all trials.^{6,8} As a result, these strategies have not been adapted by most US groups in their standard practice.

These studies suggest that we may be close to a ceiling in obtaining benefit from traditional cytotoxic agents and novel agents and strategies that incorporate targeted agents into a personalized approach are needed. One such agent, gemtuzumab ozogamicin (GO), was evaluated in combination with chemotherapy in 2 recently reported large randomized trials.

In the Medical Research Council AML 15 trial, more than 1100 mostly younger patients with AML were randomized to receive 1 of 3 ara-C and anthracycline induction regimens with or without GO (3 mg/m²).⁹ After achieving CR, there were different consolidation strategies and a further randomization to receive or not receive GO.

Overall, there was no difference in survival between patients receiving or not receiving GO. However, a predefined analysis by cytogenetic risk groups showed a significant survival benefit for patients with favorable risk disease and a trend for those with intermediate risk. An internally validated prognostic index identified approximately 70% of patients with intermediate risk, with a predicted benefit of 10% in 5-year survival.⁹

However, a study by the SWOG (Southwest Oncology Group) randomized 627 patients aged 18 to 60 years to receive ara-C, daunorubicin 45 mg/m² daily for 3 days, and GO (6 mg/m²) or the same dose of ara-C with daunorubicin 60 mg/m² daily for 3 days.¹⁰ They reported no benefit with the addition of GO in the response rate, overall survival, and relapse-free survival for the entire group. However, again patients with favorable risk cytogenetics appeared to derive a significant benefit from the addition of GO.¹⁰ There also was higher induction mortality for the patients who received GO (5.8% vs. 0.8%), which led to the recommendation by the US Food and Drug Administration to withdraw the drug from the market.

The fms-like tyrosine kinase-3 (FLT3) is a receptor tyrosine kinase important in the cellular differentiation and proliferation of hematopoietic progenitor cells.¹¹ The mutations of the *FLT3* gene occur in about a third of patients with AML (particularly diploid), and their presence is associated with shorter relapse-free and overall survival.¹² A number of inhibitors of FLT3 kinase are under evaluation in AML. Midostaurin has been evaluated in phase I and II studies with demonstrated activity particularly against FLT3 mutated AML.¹³ A large randomized trial of ara-C and anthracycline chemotherapy, with or without midostaurin, in patients with FLT3-mutated AML is currently in progress. Sorafenib, a multikinase inhibitor, approved for the treatment of patients with renal cell and hepatocellular cancer also has potent activity against the FLT3 kinase, both as a single agent and in combination with cytotoxic agents.¹⁴ More recently, AC220, a highly specific and very potent second-generation inhibitor of the FLT3 tyrosine kinase, has been evaluated in a phase I study in patients with multiply relapsed leukemia with promising initial results; among the 13 patients with FLT3 internal tandem duplication mutation and multiply relapsed AML, approximately 50% of the patients achieved a response (CR, complete remission with incomplete recovery of counts [CRi], and partial remission [PR]).¹⁵ A phase II study of AC220 in relapsed FLT3-mutated AML is ongoing.

Allogeneic stem cell transplantation continues to have a pivotal role in the postremission treatment of younger patients with AML. Although there is continuing debate about the role of this modality in the management of patients with intermediate risk disease, a number of new predictors of outcome are being used to determine the suitability of individuals.^{16,17} A recent meta-analysis has suggested that a relapse risk in excess of 35% can provide a useful threshold to identify patients in whom allogeneic transplantation may confer a survival advantage.¹⁸ However, it is important to recognize that these data are related to the

availability of human leucocyte antigen (HLA)-matched sibling donors and should not be extrapolated to transplantation from alternative donor sources. The limited availability of sibling donors has led to a number of ongoing studies investigating the potential for such alternate strategies. Analysis of recent data suggests that the outcome after allogeneic stem cell transplantation from fully matched unrelated donors (by molecular high-resolution HLA typing) can be equivalent to that when using sibling donors, which leads to the recommendation that such a strategy may be acceptable in patients with unfavorable risk disease in first remission.¹⁷

Treatment of AML in the Elderly

Until recently, many of the trials conducted in AML were confined to the younger population, despite the high incidence of this disease in the older adults. This reflected a reluctance by both patients and physicians to expose the older patients to the toxic effects of antileukemic therapy. By using the linked SEER (Surveillance, Epidemiology, and End Results)-Medicare database, Menzin et al¹⁹ retrospectively evaluated the outcomes of approximately 3500 elderly patients with AML and reported that only about a third of the patients received induction chemotherapy, which ranged from 7% of patients 85 years of age to 49% of patients 65–74 years of age. Clearly, the decision-making process is highly influenced by the attitudes of patients and their physicians and their expectations of success. Juliusson et al,²⁰ by using the Swedish Leukemia Registry data, retrospectively evaluated the outcomes of 506 patients with AML aged 70–79 years from 6 Swedish health regions with known differing attitudes toward remission induction. Although the 5-year survival of the overall 70–79-year-old population in these regions was similar, the survival of 70–79-year-old patients with AML was significantly better in regions where more elderly patients were judged eligible for remission induction.²⁰

Although the outcome of treatment for the older patients with AML is generally inferior to that in the younger patients, it is possible to identify subgroups of patients based on their disease biology and clinical condition who are likely to fare better with the more-intensive standard regimens. Previous studies of traditional chemotherapy in selected older patients have reported relatively high CR rates.²¹ However, in the majority of these studies, there is a selection against patients with poor performance status and poor organ function, and, in some studies, patients with a history of antecedent hematologic disorder such as myelodysplastic syndromes (MDS) or myeloproliferative disorders (MPD) are excluded. A number of risk scores have been developed that can be used to identify patients less likely to benefit from the traditional induction regimens that contain cytarabine.^{22–24} Furthermore, cytogenetic and molecular characteristics of the disease as well as clinical characteristics of the patient can be used to determine their potential from benefiting from such regimens.²⁵

The question then arises as to whether we have time in our practices to evaluate patients for these predictors before assigning them specific therapy. Sekeres et al²⁶ were able to identify 3 subgroups in their elderly AML population based on age older than or younger than 70 years and the presenting white blood cell count. They reported no difference in survival for any of these risk groups based on the time from diagnosis to initiation of therapy for more than or fewer than 5 days, thereby suggesting that a delay to initiate therapy in the older

population is feasible and not detrimental.²⁶ However, it should be noted that they did find a worse CR rate and a worse survival for patients younger than 60 years old, with a longer time from diagnosis to initiation of treatment.

Currently, a decision regarding the best strategy in an elderly patient should be based on the expected outcome when using these risk score and biologic characteristics. Perhaps those with the expectation of a low 8-week mortality, high CR rate, and a reasonable 3-year survival should be treated by using conventional regimens and those with a high expectation of initial mortality, and low long-term survival be offered low-intensity investigational agents.²⁷ Arguments may be offered both for and against intensive chemotherapy for patients with risk-benefit expectations between these 2 groups.²⁷

A number of agents are being evaluated in those older patients who are deemed unlikely to benefit from traditional regimens based on their disease and clinical characteristics. Clofarabine was used in a multi-institutional phase II study to treat patients with adverse features (very advanced age of >70 years old, the presence of antecedent hematologic disease, performance status of 2, or nonfavorable cytogenetics).²⁸ A total of 112 patients were enrolled, with a median age of 71 years. The overall response rate was 46%, with a CR rate of 38%. Similar CRs were noted in patients with age >70 years, with antecedent hematologic disease and with unfavorable cytogenetics. Thirty-day mortality was less than 10%. By landmark analysis, the patients who achieved CR had a survival benefit compared with those without a response.²⁸ Clofarabine also has been combined with other agents. In a randomized phase II study, the patients received clofarabine alone or in combination with low-dose subcutaneous ara-C.²⁹ A higher CR rate was reported for the combination that was associated with an improvement in survival and disease-free survival.

Hypermethylation of promoter regions of tumor suppressor genes has been associated with an adverse outcome in both high-risk MDS and AML. This, as well as a relative lack of toxicity has led to the investigation of the hypomethylating agents in older patients with AML. In a phase II study, 55 patients with a median age of 74 years were treated with decitabine, at a dose of 20 mg/m² daily for 5 days, repeated monthly.³⁰ An overall response rate of 25% was reported, with a median survival duration of 7.7 months. The regimen was well tolerated, with toxicity mainly attributable to myelosuppression.³⁰ Of note, responses were more likely to occur in patients with a low presenting peripheral blood absolute blast count, which suggests less activity in more proliferative disease. In another study, decitabine was administered at a daily dose of 20 mg/m² for 10 days to 53 patients older than 60 years and who were unsuitable for standard chemotherapy or who refused it.³¹ The overall response rate among 53 patients was 64%, including 47% CR and 17% CRi. Death within 30 days of initiation of treatment occurred in 2% of patients (1), and death within 8 weeks in 15% of patients.³¹

On the AZA-001 trial in patients with myelodysplastic syndrome diagnosed based on the French American British criteria, 113 patients had presenting bone marrow blast percentages of 20%–29%, which classified them as having AML by the World Health Organization criteria.³² As a part of the study, 55 patients were randomized to azacytidine and 58 to conventional care regimens. Although the CR rate was similar between the 2 groups,

azacytidine was better tolerated, with fewer infections and fewer incidences of hospitalization. The median and 2-year survival was significantly better for patients treated with azacytidine.³² In a follow-up report, a retrospective analysis of elderly patients treated in France with azacytidine on a compassionate-use basis, an overall response rate of 19%, with a median response duration of 6.9 months, and a median survival of 9.4 months was reported.

Combining decitabine and azacytidine with other epigenetic modulators has been evaluated. In a study of decitabine and valproic acid in patients with AML and MDS, an overall response rate of 22% that included 40% CR in previously untreated patients was reported.³³ A randomized study that examined the benefit of adding valproic acid to decitabine has completed accrual at our institution, and the results will be reported soon. In another strategy, we are evaluating the combination of clofarabine and low-dose ara-C alternating with decitabine. In a preliminary analysis, an overall response rate of 66%, including a CR rate of 58% with few early relapses was reported.³⁴

Relapsed AML

Treatment of patients with relapsed and/or refractory disease remains problematic, with few long-term survivors reported in various studies. A number of predictors of response to salvage therapy in first relapse have been identified, including age, cytogenetics at diagnosis, duration of the first CR, and whether the patient underwent an allogeneic stem cell transplantation in first CR.³⁵ Of these, the duration of first CR appears most important, with very poor outcome for those with CR duration <6 months and particularly those with primary refractory disease.³⁶ Outcome for patients in second relapse and beyond is similarly dismal.³⁷

A number of regimens have been evaluated in this setting, and, by default, high-dose ara-C-based regimens are considered standard, with a number of combinations that show an improvement in response rate but not disease-free or overall survival over ara-C alone.^{38–41} Recently, cloretazine was evaluated in combination with ara-C in a randomized study.⁴² Although the response rate was higher for the combination arm, 30-day mortality was higher, and the overall survival and median response duration was similar for the 2 groups.⁴² Based on the data from a phase I/II study that combined clofarabine and high-dose ara-C, a multicenter randomized trial of this combination vs. ara-C alone has been conducted, the results of which are awaited.⁴³

Lestaurtinib, a FLT3 kinase inhibitor, also has been evaluated in the setting of first relapse in patients with FLT3-mutated AML.⁴⁴ The patients received either high-dose ara-C or a combination of mitoxantrone, etoposide and ara-C, depending on their duration of the first CR, and were randomized to receive Lestaurtinib 80 mg orally twice daily or not after the completion of chemotherapy.⁴⁴ Overall, the final analysis did not demonstrate a benefit in CR rate or overall survival in patients who received lestaurtinib. A target of >85% inhibition of FLT3 kinase maintained at trough (predose) was defined from previous studies. Of the 79 patients tested, 46 (58%) achieved this degree of FLT3 inhibition on day 15. FLT3 ligand concentrations rose from baseline (15.6 pg/mL) to day 15 (1148 pg/mL), and α -1 acid glycoprotein concentrations rose by an average of 52% over the same period, both of which

may have reduced the degree of FLT3 inhibition. Of the 46 patients with target FLT3 inhibition on day 15, 18 (39%) achieved CR/CR without recovery of platelets (CRp), whereas only 3 (9%) of the 32 patients with below-target FLT3 inhibition achieved CR/CRp. Furthermore, there was a statistically significant benefit in survival in patients who achieved >85% target inhibition compared with those with <85%. Analysis of these data suggests that pharmacokinetic and pharmacodynamic factors other than the drug potency may influence the activity of FLT3 inhibitors, both in the relapse and frontline settings.⁴⁴

A number of other agents also are under investigation, including voserixin (an anticancer quinolone derivative with the ability to intercalate DNA as well as topoisomerase II inhibition),⁴⁵ tosedostat (an aminopeptidase inhibitor),⁴⁶ amonafide (a DNA intercalator),⁴⁷ sapacitabine (a nucleoside analog),⁴⁸ CPX-351 (a liposome encapsulated 5:1 molar combination of ara-C and daunorubicin),⁴⁹ and a number of other agents that target various aspects of leukemic cell machinery. Because the outcome of patients with relapsed disease and unfavorable risk disease in the frontline setting remains unsatisfactory, participation in clinical trials is highly recommended.

Although the role of allogeneic stem cell transplantation in the elderly remains to be fully defined, the introduction of reduced intensity regimens has allowed further evaluation of this strategy in this population.⁵⁰ In a recent study from a single institution, only a select number of older patients actually underwent the procedure due to a number of reasons related to the availability of donors, perceived lack of ability of the patients to withstand the procedure, and refusal of the patients and treating physicians to participate.⁵¹

Conclusion

Treatment of AML continues to be challenging in the majority of patients. However, progress in understanding the biology of the disease has significantly increased our potential therapeutic targets, and a number of promising agents are in development. Better characterization of the prognosis and identification of pre- and posttreatment factors that predict outcome is likely to further improve the survival of patients when using a risk-adapted approach that would limit the more-intensive postremission strategies for the patients more likely to relapse. Although advanced age has been an important predictor of adverse outcome, it is likely that identification of more target-specific agents will lead to improved outcomes in this population as well.

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