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.

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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 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 Estey[1] 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/m^2 or 90 mg/m^2 daunorubicin, in addition to 7 days of continuous infusion ara-C at 100 mg/m^2 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 al[3] showed a higher CR when 813 patients older than 60 years old with AML were randomized to receive daunorubicin 90 mg/m^2 vs. 45 mg/m^2 in addition to ara-C 200 mg/m^2 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

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468 patients aged 50 to 70 years and with AML were randomized to receive ara-C 200 mg/m^2 daily for 7 days, in addition to daunorubicin 80 mg/m^2 daily for 3 days, idarubicin 12 mg/m^2 daily for 3 days, or idarubicin 12 mg/m^2 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 GMCSF, 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/m^2).[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/m^2 daily for 3 days, and GO (6 mg/m^2) or the same dose of ara-C with daunorubicin 60 mg/m^2 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 al[19] 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