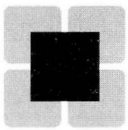

GARY S. HOFFMAN, MD, EDITOR

CLINICAL DECISION-MAKING: Acute myelogenous leukemia in first complete remission

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SUMMARY Most patients with acute myelogenous leukemia achieve complete remission but are not cured with chemotherapy alone. Bone marrow transplantation is an alternative to chemotherapy, but there is controversy as to which patients benefit from transplantation.

KEY POINTS Outcome can be predicted by, and therapy tailored to, specific prognostic factors such as age and karyotype. Younger patients with good-risk karyotypes such as t(8;21) and inv16 have a long-term disease-free survival rate of 75% or more with chemotherapy alone. Patients with poor-risk karyotypes have a survival rate less than 10% with chemotherapy alone and may benefit from bone marrow transplantation, which is associated with cures in up to 50% of patients. Most patients do not have a compatible donor for allogeneic transplantation. High-dose chemotherapy and autologous bone marrow transplantation is an option for patients with no marrow donor, and has cure rates of as high as 50%. Patients with intermediate-risk karyotypes generally have a survival rate between 20% and 50% with chemotherapy alone. It is uncertain if allogeneic or autologous bone marrow transplantation offers any additional advantage in this group.

INDEX TERMS: LEUKEMIA, MYELOCYTIC, ACUTE; BONE MARROW TRANSPLANTATION; CYTARABINE CLEVE CLIN J MED 1996; 63:91–93

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ALTHOUGH MOST patients with acute myelogenous leukemia (AML) can achieve a complete response with standard induction chemotherapy, only a minority are cured.[1] Efforts to increase the proportion of patients remaining in remission have focused on improving postremission chemotherapy. A recent study has established the importance of maximizing the dose of cytarabine (ara-C), the most active chemotherapeutic agent against AML in this situation.[2] Whether repeated cycles of high-dose ara-C represent the optimal postremission therapy, however, is uncertain, as bone marrow transplantation produces similar outcomes.[3] A working knowledge of the advantages and disadvantages of available options is important, since the selection of postremission therapy is crucial to the patient's ultimate outcome.

CASE HISTORY

A 30-year-old man with AML has undergone standard induction chemotherapy consisting of

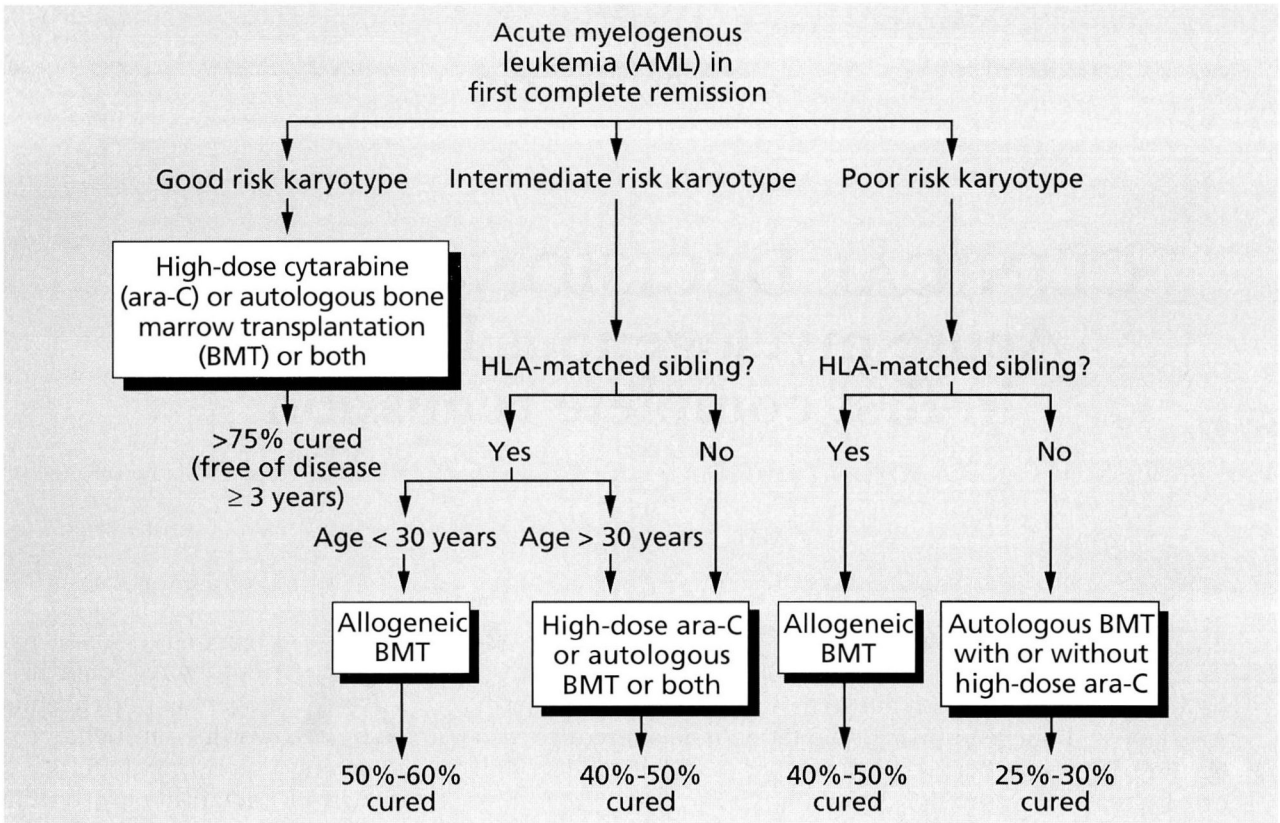

FIGURE. Suggested approach to patients with acute myelogenous leukemia who are in a first complete remission.

standard-dose ara-C and idarubicin. He is in complete remission. He had presented with pancytopenia, and a bone marrow aspirate had revealed hypercellular bone marrow with 90% myeloid blasts, consistent with AML. Cytogenetic analysis of the marrow aspirate had demonstrated no abnormalities. Chemotherapy had been complicated by the usual toxic effects, all of which have resolved. He has no current complaints, and his physical examination is normal. All laboratory data are normal except for mild anemia. What postremission therapy should be recommended?

STRATIFYING RISK, PLANNING TREATMENT

An approach to the patient in first complete remission of AML is given in the *Figure*. If cases of AML caused by antecedent hematologic disorders or cytotoxic chemotherapy are excluded, perhaps the most important prognostic factor other than age is the patient's karyotype.[4] Patients can be divided into those with good, intermediate, and poor prognoses on the basis of karyotypic abnormalities, and this information can help guide treatment decisions. Patients with either the chromosomal translocation t(8;21) or inv16 have a good prognosis when treated in remission with ara-C alone,[5] having an approximately 75% chance of remaining in remission longer than 5 years.[4]

Patients with normal karyotypes have an intermediate prognosis, as do patients with acute promyelogenous leukemia (APL) characterized by the translocation t(15;17).[4] Fewer than 40% of these patients are likely to be cured by high-dose ara-C, but it is unclear whether bone marrow transplantation offers an advantage. For patients younger than age 30 who have an HLA-compatible sibling, allogeneic bone marrow transplantation produces the best results reported to date.[6] Whether treatment with all-*trans* retinoic acid will improve the long-term outcome in APL is uncertain.[7]

All other cytogenetic abnormalities are associated with a poor prognosis; no patients who have them are cured with chemotherapy alone. Thus, all

such patients younger than age 50 should be offered allogeneic bone marrow transplantation if a suitable sibling donor is identified.[8]

PROBLEMS, CONCERNS

Unfortunately, most patients either do not have an HLA-compatible sibling or are older than age 50. For patients age 65 or younger with an intermediate or poor prognosis, high-dose chemotherapy with autologous stem-cell rescue is an appealing alternative to several cycles of high-dose ara-C. Several series have clearly documented a 40% to 50% long-term remission rate in patients treated once with high-dose chemotherapy and autologous stem-cell rescue.[9] These results are at least equal to results obtained with one or more courses of high-dose ara-C. One source of concern is the potential for reintroducing leukemia cells with the autologous stem-cell rescue. However, patients who receive marrow from an identical twin have a relapse rate of 50%, which indicates that the real problem is the inability of the chemotherapy to eradicate the leukemia in the first place.[10]

Another concern is the perceived toxicity of high-dose chemotherapy. Modern supportive management, including the use of peripheral stem cells and growth factors, has reduced the morbidity and mortality associated with high-dose chemotherapy and autologous stem-cell rescue to probably no more than that associated with repeated courses of high-dose ara-C.[11,12]

Finally, the one-time cost of high-dose chemotherapy and autologous stem-cell rescue is very high, but probably not much different from that of repeated cycles of high-dose ara-C, each of which entails hospitalization, transfusion support, and broad-spectrum antibiotics. No prospective study that included an analysis of cost and quality-of-life issues has compared the relative benefits of chemotherapy with those of bone marrow transplantation. Nevertheless, I favor one course of high-dose ara-C followed by prompt high-dose chemotherapy and autologous stem-cell rescue to take advantage of the potential superior outcome offered by both treatment modalities.

SUMMARY

The optimal management of AML requires the exploration of all potential options with the patient. Cure is possible in more than 30% of all patients who enter a first complete remission.[2] Early in remission, all patients should be evaluated at a transplantation center and their HLA type established. If an HLA-matched sibling can be found, the patient can undergo allogeneic bone marrow transplantation either immediately or in the event of a relapse; if not, the time-consuming search for an HLA-matched unrelated donor for use at the time of relapse can begin. In addition, autologous stem cells should be harvested and stored as backup for those undergoing allogeneic transplantation and as a source of rescue after high-dose chemotherapy in patients ineligible for allogeneic transplantation.

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