Therapeutic strategies are evolving for the treatment of patients with newly diagnosed acute myelogenous leukemia (AML), as well as for those with relapsed or refractory disease. Clinical and laboratory studies have demonstrated that AML is not a single disease, but a heterogeneous group of diseases with different clinical features and natural histories. There are variable responses to therapy depending on both the biologic characteristics of the disease and the clinical characteristics of the patient. Nevertheless, studies evaluating the outcomes of relatively large numbers of patients with newly diagnosed AML show that the majority still die of their disease.[1-3]

Older adults with AML fare particularly poorly.[1-3] However, patients with several subtypes identified by specific cytogenetic abnormalities, including inv(16) or t(16;16); t(8;21); or t(15;17), have a much more favorable outcome with contemporary strategies.[4-11] Although much progress has been made in the treatment of AML patients with favorable karyotypes, the lack of progress in both older adults and those with unfavorable karyotypes has been disappointing. These cohorts of patients represent the major challenge for the future.

Dr. Estey, in his concise and comprehensive article, has provided us with the armamentarium to meet these challenges. His most important message focuses on the identification of patients with less than favorable prognoses and the importance of their enrollment into clinical trials that rationally test novel antileukemic agents and therapeutic strategies. Many of these new agents are based on the discovery of new molecular and immunophenotypic targets. The number of new agents available to explore is impressive.

**New Agents and New Targets for AML**

The anti-CD33 calicheamicin immunocinjugate, gemtuzumab ozogamicin (Mylotarg), is the first of these new targeted agents approved by the US Food and Drug Administration for clinical use in AML.[12] The overall remission rate is 30%, which includes complete remissions by standard definitions plus complete remissions by all criteria with the exception of incomplete platelet recovery. Although similar remission rates can be achieved in patients in first relapse using a variety of other chemotherapy regimens (including high-dose cytarabine [ara-C]),[13] gemtuzumab ozogamicin represents novel technology: an antibody linked to a potent cytotoxic agent that can be administered on an outpatient basis. Furthermore, it appears that this agent is effective not only in patients with favorable prognostic karyotypes, but also in those with intermediate- or poor-prognosis cytogenetics.[12]

A second new class of agents is the farnesyl transferase inhibitors,[14] which have shown encouraging results in a preliminary trial.[15] Dr. Estey raises the exciting possibility that the bcr-abl tyrosine kinase inhibitor imatinib mesylate (STI571, Gleevec), which is so effective in patients with chronic myeloid leukemia,[16] may also play a role in patients with AML because of its ability to inhibit the tyrosine kinase associated with c-kit.[17,18]

**Overview of Prognostic Factors**

Not only has Dr. Estey supplied us with ammunition for the challenges ahead, but he also has provided suggestions for the setting in which to study these new agents. He spends considerable time focusing on the prognostic factors that will predict for a satisfactory response to standard therapy or will identify patients for whom the results of standard therapy are sufficiently poor that one is justified in considering investigational treatment.
Physicians are not accustomed to departing from the standard anthracycline/ara-C-based induction regimen in previously untreated patients. However, those with poor-prognosis cytogenetics, a normal karyotype but secondary AML, an antecedent myelodysplastic syndrome or myeloproliferative syndrome, leukemic cells that express significant MDR1, or adults over the age of 70 to 80 years are all candidates for investigational approaches. It is likely that this kind of forward thinking will facilitate meaningful clinical progress.

Clinical Experience With Stem Cell Transplantation
Dr. Estey gives his perspective on the role of hematopoietic stem cell transplantation in the treatment of patients with AML. He points out that prospective trials have not consistently shown an advantage for allogeneic transplantation or autologous transplantation for patients with AML in first complete remission. Patients with core-binding-factor leukemias [inv(16), t(16;16), and t(8;21)] appear to have an excellent outcome with multiple cycles of intensive ara-C-based chemotherapy and, in general, are not recommended for transplantation.

In contrast, the US intergroup trial did show an advantage among patients with unfavorable karyotypes for allogeneic transplantation over consolidation or autologous transplant.[19] This trial also showed an advantage for autologous transplantation over consolidation in favorable-risk patients. Although this trial did not demonstrate the excellent outcomes with ara-C-based consolidation in favorable-risk patients reported by others, the consolidation in the intergroup trial was less intensive (one cycle of high-dose ara-C) than others.[8] These findings may also reflect the small numbers of patients with certain cytogenetic abnormalities when subset analyses are carried out.

For the majority of patients, there have been conflicting data regarding the best postremission therapy. Most large, prospective, randomized trials take many years to complete, and Dr. Estey emphasizes that progress continues both in chemotherapy strategies and in transplantation techniques.

Factors Predicting Relapsed or Refractory Disease
Finally, Dr. Estey addresses the most difficult area in the treatment of AML—namely, the treatment of patients with relapsed or refractory disease. It is important to identify those patients with advanced disease who are unlikely to benefit from conventional salvage programs.

The duration of first complete remission appears to be the most significant prognostic factor in determining which patients will have a better outcome with conventional salvage approaches, including high-dose ara-C. However, very few patients with advanced disease are cured, and it may be useful to eliminate the concept of "conventional salvage" chemotherapy. If this battle is to be won, all patients with relapsed or refractory AML should be treated in clinical trials evaluating the many new agents or strategies now available. Furthermore, correlative ancillary laboratory studies should be conducted.

Conclusions
Dr. Estey closes his review on an optimistic note when he discusses progress in the treatment of acute promyelocytic leukemia (APL). It can be anticipated that 70% to 80% of patients currently may well be cured of their disease with the combination of all-trans-retinoic acid (ATRA, Vesanoid) and anthracycline-based chemotherapy. Progress in this particular subtype of AML has been so rapid and gratifying similar to the successful treatment of patients with Hodgkin’s disease that investigators have begun to develop strategies for minimizing the toxicity of apparently curative therapy. Patients now can receive induction with ATRA and anthracyclines, consolidation with anthracyclines alone, followed by maintenance therapy with ATRA and low-dose chemotherapy.[11]

Indeed, remarkable progress has been made in certain subtypes of AML. However, for the majority of patients with this disease, better treatments will be required. There is no lack of potentially effective antileukemic agents or strategies to test. The biggest challenge ahead is to recruit patients into well-designed clinical trials in a timely way.

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