1. INTRODUCTION

Older adults with acute myeloid leukemia (AML) present a complex array of therapeutic dilemmas. As a result of host factors making chemotherapy less well tolerated, and disease factors making response to antineoplastic strategies less likely, difficult decisions abound. Therapeutic options, including aggressive chemotherapy, supportive care, or less intense therapy (e.g., clinical trials), have vastly different implications. The choice among these requires prolonged discussions with the patient and family members. Because of the poor results obtained in this age group, there is a need for the development of novel targeted, less toxic, and more effective therapies.

2. DIAGNOSIS AND CLASSIFICATION

The disease-related workup of an older adult with AML is similar to that in younger patients. Unexplained cytopenias, the presence of immature cells in the peripheral blood, or extramedullary deposits of myeloblasts should trigger a more precise delineation of the situation. A bone marrow examination should be performed with cells aspirated for morphological and cytochemical analysis, immunophenotype, and cytogenetics. Two classification systems are used. The older FAB system (1) is largely morphologically based and subcategorizes AML into eight subtypes: M0 through M7. The therapeutic approach to each is virtually identical except for M3 AML (acute promyelocytic leukemia [APML]). This entity, relatively unusual in older adults, is characterized by leukopenia, the presence of granule-laden malignant promyelocytes, and presentation with bleeding because of a disseminated intravascular coagulopathy (2). Acute promyelocytic leukemia, confirmed by the finding of the characteristic t(15;17) chromosomal translocation and/or the associated APML-RARα fusion transcript, presenting at any age is treated with a combination of anthracycline-based chemotherapy and all-trans-retinoic acid (3). The newer classification system, the so-called WHO scheme (4),
emphasizes the importance of increasing cytogenetic and genetic understanding of acute leukemia. Moreover, this classification scheme denotes the presence of greater than 20% myeloblasts in the bone marrow as indicating AML, compared with the 30% requirement in the FAB classification system. Such a change is based in part on the finding that age and cytogenetics are much more important with regard to predicting response to chemotherapy than is the percentage of marrow blasts (5).

3. PROGNOSIS

Although the white count and lactate dehydrogenase at presentation have some impact, the two most important prognostic characteristics for AML are the age of the patient and the chromosome findings at diagnosis (6,7). Within the older age cohort, there is general agreement that patients 70–80 years of age fare more poorly than do those patients aged 55–70. Moreover, patients who present with AML in the ninth decade of life do extremely poorly. For younger adults there is a clear demarcation of prognosis based on chromosome findings at diagnosis (7,8). About 15% of patients have chromosomal translocations that alter transcription factor biology, including inv16, t(8;21), and t(15;17), which are associated with a good prognosis if intensive chemotherapy is employed. Another 15% of patients have the type of chromosomal abnormalities typically seen in treatment-related AML or AML occurring after myelodysplastic syndrome (MDS), including loss of the long arm or all of chromosomes 5 or 7 or complex cytogenetic abnormalities. These patients have a dismal prognosis with chemotherapy. The other 70% of patients have so-called intermediate cytogenetics: normal, abnormalities at 11q23, trisomy 8, or other abnormalities. Recently, within the normal cytogenetic category, those with activating mutations in the FLT3 tyrosine kinase gene (occurring in about 30–40% of this cohort) have also been found to have an inferior prognosis (9). These chromosomal patterns probably also have prognostic relevance for older adults (6), but because of the generally overwhelmingly negative influence of patient age, the distinctions are less pronounced. Moreover, the increased incidence of adverse prognosis chromosomal abnormalities in older adults accounts in part for their inferior prognosis (10). The percentage of older adults presenting with a so-called favorable chromosomal abnormality is much lower than the 15% value seen in the younger patients with this disease (6).

The overall results with chemotherapy in older adults with AML are very discouraging. The likelihood of achieving remission is between 40 and 50% compared to 60–80% in younger adults with the same disease (11). Those patients who achieve remission are much less likely to remain free of disease for long periods of time (disease-free survival is about 40–50% in younger adults who achieve remission compared with 10–20% in the older adults) (11). The inability to achieve remission and/or to stay in remission yields a very disappointing cure rate of about 5–10% in this population.

The reasons for the inferior prognosis are a combination of host and disease factors. Clearly, older adults have a higher likelihood of comorbid diseases, decreased stem cell reserve, and an inability to excrete chemotherapy, which makes them much more susceptible to morbidity and mortality from sepsis (12). Some of these issues can be subsumed into the performance status, which is an important prognostic factor at presentation; however, a more precise measure of fitness for treatment needs to be delineated. As already mentioned, the higher incidence of adverse chromosomal abnormalities suggests that AML in the older adult emanates from a more proximal stem cell in the hematopoietic hierarchy than that seen in the younger adults. Other data that support this notion include the increased likelihood of