AML characterized by t(8;21), inv(16) or del(16q), or t(15;17) aberrations is unusually responsive to induction chemotherapy followed by two to four cycles of high-dose cytosine arabinoside consolidation. Long-term 5-year survival rates of 55% to 60% can be obtained.

AML subtypes associated with a poor prognosis include those with known deletions in chromosome 5 or 7, 11q23 aberrations other than t(9;11), inv(3q), t(3;3), t(6;9), t(9;22) (i.e., Philadelphia chromosome), monosomal karyotype, or three or more karyotypic abnormalities (i.e., complex karyotype). Remission rates for these AML subtypes are low; if remission is achieved, patients remain at high risk for AML relapse with chemotherapy-refractory disease. Overall survival rates for poor-prognosis AML are 5% to 15%.

The remaining AML patients have intermediate-risk cytogenetics, which is defined as a normal karyotype, trisomy 8, t(9;11), or other cytogenetic abnormalities not included in the other groups. These patients have a 30% to 45% long-term survival rate with standard chemotherapy (see Table 46-10).

Large-scale genomic analyses of AML samples have revealed the vast molecular complexity of this disease and identified myriad gene mutations capable of further refining AML prognosis in conjunction with karyotype. For instance, up to one third of patients with normal-karyotype AML have constitutive activation of the FMS-like tyrosine kinase 3 (FLT3) receptor as a result of point mutations or internal tandem duplications (ITDs) not seen on routine karyotypic testing) in FLT3 kinase. FLT3 ITDs in AML patients predict low remission rates, high relapse rates, and shorter overall survival compared with FLT3-negative AML patients. Mutations that predict improved overall survival after chemotherapy include biallelic mutations in the transcription factor CCAAT/enhancer binding protein-α (CEBPA) and nucleophosmin 1 (NPM1) in the absence of FLT3 ITDs (Table 46-11).

After remission is achieved after induction, AML patients are offered additional therapy in the form of consolidation chemotherapy and autologous or allogeneic SCT. Decisions about the best time to perform SCT in patients are most often guided by clinical risk factors and prognostic risk category (see Tables 46-9 and 46-10). Although clinical outcomes are improved when patients undergo SCT after initial induction chemotherapy (i.e., during the first complete remission) rather than after disease relapse, chemotherapeutic regimens are also more effective in the first remission than they are after transplantation, and they may be better tolerated than SCT, which carries an overall mortality rate of 25% to 30%.

TABLE 46-11 PROGNOSIS OF ACUTE MYELOID LEUKEMIA BASED ON CYTOGENETIC AND MOLECULAR ABNORMALITIES

RISK STATUS	CYTOGENETICS	MOLECULAR ABNORMALITIES
Favorable	inv(16) or t(16;16) t(8;21), t(15;17)	Normal cytogenetics: *NPM1* mutation in the absence of *FLT3* ITDs or isolated biallelic *CEBPA* mutation
Intermediate	Normal cytogenetics +8 alone, t(9;11) Other undefined	t(8;21), inv(16), or t(16;16) in the presence of *KIT* mutation
Poor	Complex (≥3 aberrations) Monosomal karyotype −5, 5q−, −7, 7q− 11q23: non-t(9;11) inv(3), t(3;3), t(6;9), t(9;22)	Normal karyotype with *FLT3* ITDs

ITDs, Internal tandem duplications.

Allogeneic SCT is recommended for and represents the best chance for long-term cure of patients with poor-risk AML such as disease associated with unfavorable cytogenetic and molecular features, antecedent hematologic disease, or therapy-related or primary refractory disease. Poor-risk AML patients younger than 60 years undergoing allogeneic bone marrow transplantation from a matched donor have long-term overall survival rates of 40% to 60%, compared with cure rates after conventional chemotherapy of only 5% to 20%. AML patients with favorable disease features potentially responsive to high-dose cytarabine chemotherapy are encouraged to delay SCT until the time of relapse.

Intermediate- to high-risk AML patients (based on clinical or cytogenetic data) who are ineligible for allogeneic transplantation because of advanced age, other medical issues, or lack of HLA-compatible donors may be offered chemotherapy or autologous SCT instead. Whether autologous transplantation improves AML outcomes compared with chemotherapy alone is a matter of debate. However, the long-term survival rates after autologous transplantation range from 20% to 40% and are at least equivalent to consolidation chemotherapy regimens for these patients.

Because the median age at diagnosis of AML is 65 years, a sizable proportion of AML patients are elderly individuals with major comorbidities or antecedent hematologic or malignant diseases, rendering them poor candidates for standard induction chemotherapeutic regimens or myeloablative SCT. Infectious complications remain the major cause of morbidity and mortality during intensive inpatient chemotherapy despite advances in prophylactic growth factor support, antibiotics, and antifungal agents. The low expected remission rates (30% to 50%) and high mortality and morbidity rates associated with induction are additional reasons for many patients to decline aggressive therapy. For these patients, therapeutic options include supportive therapy with hydroxyurea, transfusion support alone, and hospice.

Patients unfit for and those who choose not to receive intensive therapy are increasingly being treated with low-dose chemotherapy regimens. Low-dose subcutaneous cytarabine is associated with remission rates of about 18%. Alternatively, hypomethylating agents (e.g., 5-azacytidine, decitabine) have been well tolerated in older AML patients and result in complete remission rates ranging from 20% to 47% in some studies. Individuals treated with these drugs also experience hematologic improvement and disease stabilization associated with prolonged overall survival, even in absence of complete remissions.

AML patients with relapsed or refractory disease after standard therapy should be considered for allogeneic SCT and clinical trials. Experimental therapies for AML, particularly nonmyeloablative SCT (see Chapter 45), have resulted in durable long-term remissions in a proportion of older AML patients and should be pursued based on patient preference, overall health status, and availability of an appropriate HLA-matched donor.