TABLE 46-10 PROGNOSTIC FACTORS IN ACUTE LYMPHOBLASTIC LEUKEMIA

FACTOR	FAVORABLE	UNFAVORABLE
Age	2-10 yr	<2 yr or >10 yr
White blood cell count at diagnosis	<30,000/μL	>50,000/μL
Phenotype	Precursor B	Precursor T
Chromosome number	Hyperdiploidy	Pseudo/hypodiploidy, near tetraploidy
Chromosome abnormality	t(12;21)	*MYC* alterations: t(8;14), t(2;8), t(8;22) mixed-lineage leukemia alterations (11q23) Philadelphia chromosome: t(9;22), creating *BCR-ABL*
Central nervous system disease at diagnosis	No	Yes
Sex	Women	Men
Ethnicity	White	African American, Hispanic
Time to remission	Short (7-14 days)	Prolonged time to remission or failure to achieve remission

Leukostasis (i.e., hyperleukocytosis syndrome) caused by high levels of circulating blasts (>80,000 to 100,000) leads to diffuse pulmonary infiltrates and acute respiratory distress. Blast cells may also injure surrounding vasculature, causing life-threatening CNS bleeding and thromboses. High blast cell numbers result in the release of cellular breakdown products (i.e., tumor lysis syndrome), leading to hypokalemia, acidosis, and hyperuricemia with resultant renal failure.

Treatment of leukostasis should be instituted as soon as possible for all patients with white blood cell counts in excess of 100 to 200 $\times 10^9$/L. Treatment consists of leukapheresis, hydroxyurea, and initiation of induction chemotherapy to inhibit further production of circulating tumor cells. Hydration, urine alkalinization to reduce urine crystallization, allopurinol, or rasburicase, or a combination, should be initiated as indicated. Red blood cell transfusions are often contraindicated in patients with high numbers of circulating blast cells because of the risk of further increases in blood viscosity. CNS complications such as intracranial bleeding, cranial nerve invasion, and leukemic meningitis are treated with emergency whole brain irradiation or radiation directed to affected sites.

Laboratory evaluation of patients with AML typically shows white blood cell counts ranging from neutropenic levels ($<1 \times 10^9$/L) to extreme leukocytosis ($>100{,}000 \times 10^9$/L). Severe thrombocytopenia, normocytic anemia, and circulating peripheral blasts are common. Bone marrow aspirate and biopsy typically show a profusion of myeloblasts (20% to 100%) and depressed production of normal mature cells.

Diagnosis

Diagnostic marrow aspirates are typically evaluated using morphology, flow cytometry, cytogenetic, and molecular analyses to distinguish between AML and ALL and to determine AML disease subsets for therapeutic purposes. In the past, AML subsets were classified based largely on morphologic criteria and immunohistochemical staining as FAB subtypes M0 through M7, which are defined by the stage of cellular differentiation of the abnormal cells (see Table 46-8 and E-Fig. 46-3).

Some FAB subsets correlate with specific clinical syndromes, which helps to determine treatment approaches and prognosis. The most common FAB subtype of adult AML is M2. Patients with AML M3 (i.e., acute promyelocytic leukemia) often exhibit spontaneous bleeding from disseminated intravascular coagulation (discussed later). Patients with AML M4 or M5 disease (i.e., acute monocytic-myelomonocytic leukemias) have high levels of circulating white blood cells and may have swollen gums resulting from tissue infiltration with leukemic blasts. Patients with megakaryoblastic leukemia (AML M7) have significant marrow fibrosis and usually exhibit organomegaly and pancytopenia similar to those seen in patients with myelofibrosis and myeloid metaplasia.

In 2008, AML was reclassified as new subtypes defined primarily by unique karyotypic abnormalities—specifically t(8;21), inv(16), and t(15;17)—and gene mutations in a dysplastic bone marrow, independent of the number of marrow blasts. Because finding these specific cytogenetic abnormalities is crucial for the diagnosis, therapy, and prognosis for AML patients, karyotypic analysis is considered essential for any suspected AML diagnosis. Evidence of marrow dysplasia after prior chemotherapy, irradiation, or other myeloablative therapy is considered therapy-related AML rather than myelodysplastic syndrome (MDS), independent of the blast count (see Table 46-8).

Treatment and Prognosis

Chemotherapy for AML involves induction chemotherapy (administered in the inpatient setting) followed by two to four cycles of consolidation chemotherapy administered over 4 to 6 months. Standard induction regimens employing cytosine arabinoside (i.e., cytarabine) with high-dose anthracycline (i.e., daunorubicin or idarubicin) lead to complete remission in 60% to 80% of younger adults with de novo AML. Lower remission rates are achieved for older adults (>60 years) and in patients with antecedent hematologic diseases evolving into AML.

After achieving complete remission after induction, patients may be offered additional consolidation chemotherapy or treatment with allogeneic or autologous SCT (see Chapter 45). Patients whose AML fails to respond to initial induction therapy have a grim overall prognosis and may be retreated with experimental agents or with non–cross-reactive chemotherapy drugs such as epipodophyllotoxins, or both, to obtain remission.

Given the biologic heterogeneity of this disease, the AML risk category constitutes the most crucial determinant of an appropriate therapeutic strategy for individual patients. In the past, AML outcome could be predicted to some degree by clinical factors such as patient age, disease manifestation (i.e., white blood cell count), and history of antecedent hematologic or therapy-related disease (see Table 46-9). In the current era, AML risk is defined by diagnostic AML cytogenetics and molecular abnormalities and is typically divided into three categories: favorable, intermediate, and poor risk.