two or more prognostic gene mutations), the likelihood that distinct marker combinations may be more informative than single markers is being recognized.

Epigenetic changes (e.g., DNA methylation) and microRNAs are often involved in deregulation of genes involved in hematopoiesis, contribute to leukemogenesis, and are often associated with the previously discussed prognostic gene mutations. These changes not only have been shown to provide biologic insights into leukemogenic mechanisms, but also independent prognostic information. Indeed, it is anticipated that with the enormous progress made in DNA and RNA sequencing technology, additional genetic and epigenetic aberrations will soon be discovered and will contribute to classification and reporting systems and outcome risk determination in AML patients.

In addition to cytogenetics and/or molecular aberrations, several other factors are associated with outcome in AML. Age at diagnosis is one of the most important risk factors. Advancing age is associated with a poorer prognosis not only because of its influence on the ability to survive induction therapy due to coexisting comorbidities, but also because with each successive decade of age, a greater proportion of patients have an intrinsically more resistant disease. A prolonged symptomatic interval with cytopenias preceding diagnosis or a history of antecedent hematologic disorders including myeloproliferative neoplasms is often found in older patients and is a clinical feature associated with a lower complete remission (CR) rate and shorter survival time. The CR rate is lower in patients who have had anemia, leukopenia, and/or thrombocytopenia for >3 months before the diagnosis of AML when compared to those without such a history. Responsiveness to chemotherapy declines as the duration of the antecedent disorder(s) increases. AML developing after treatment with cytotoxic agents for other malignancies is usually difficult to treat successfully. Finally, it is likely that AML in older patients is also associated with poor outcome because of the presence of distinct biologic features that may increase the aggressiveness of the disease and reduce the likelihood of treatment response. The leukemic cells in older patients more commonly express the multidrug resistance 1 (MDR1) efflux pump that conveys resistance to natural product–derived agents such as the anthracyclines that are frequently incorporated into the initial treatment. In addition, older patients less frequently harbor favorable cytogenetic abnormalities [i.e., t(8;21), inv(16), and t(16;16)] and more frequently harbor adverse cytogenetic (e.g., complex and monosomal karyotypes) and/or molecular (e.g., *ASXL1*, *IDH2*, *RUNX1*, *TET2*) abnormalities.

Other factors independently associated with worse outcome are a low performance status that influences ability to survive induction therapy and thus respond to treatment and a high presenting leukocyte count that in some series is an adverse prognostic factor for attaining a CR. Among patients with hyperleukocytosis (>100,000/μL), early central nervous system bleeding and pulmonary leukostasis contribute to poor outcome with initial therapy.

Achievement of CR is associated with better outcome and longer survival. CR is defined after examination of both blood and bone marrow. The blood neutrophil count must be ≥1000/μL and the platelet count ≥100,000/μL. Hemoglobin concentration is not considered in determining CR. Circulating blasts should be absent. Although rare blasts may be detected in the blood during marrow regeneration, they should disappear on successive studies. The bone marrow should contain <5% blasts, and Auer rods should be absent. Extramedullary leukemia should not be present. Patients who achieve CR after one induction cycle have longer CR durations than those requiring multiple cycles.

CLINICAL PRESENTATION

Symptoms Patients with AML most often present with nonspecific symptoms that begin gradually or abruptly and are the consequence of anemia, leukocytosis, leukopenia or leukocyte dysfunction, or thrombocytopenia. Nearly half have had symptoms for ≤3 months before the leukemia was diagnosed.

Half of patients mention fatigue as the first symptom, but most complain of fatigue or weakness at the time of diagnosis. Anorexia and weight loss are common. Fever with or without an identifiable infection is the initial symptom in approximately 10% of patients. Signs of abnormal hemostasis (bleeding, easy bruising) are noted first in 5% of patients. On occasion, bone pain, lymphadenopathy, nonspecific cough, headache, or diaphoresis is the presenting symptom.

Rarely patients may present with symptoms from a myeloid sarcoma that is a tumor mass consisting of myeloid blasts occurring at anatomic sites other than bone marrow. Sites involved are most commonly the skin, lymph node, gastrointestinal tract, soft tissue, and testis. This rare presentation, often characterized by chromosome aberrations [e.g., monosomy 7, trisomy 8, *MLL* rearrangement, inv(16), trisomy 4, t(8;21)], may precede or coincide with AML.

Physical Findings Fever, splenomegaly, hepatomegaly, lymphadenopathy, sternal tenderness, and evidence of infection and hemorrhage are often found at diagnosis. Significant gastrointestinal bleeding, intrapulmonary hemorrhage, or intracranial hemorrhage occurs most often in APL. Bleeding associated with coagulopathy may also occur in monocytic AML and with extreme degrees of leukocytosis or thrombocytopenia in other morphologic subtypes. Retinal hemorrhages are detected in 15% of patients. Infiltration of the gingivae, skin, soft tissues, or meninges with leukemic blasts at diagnosis is characteristic of the monocytic subtypes and those with 11q23 chromosomal abnormalities.

Hematologic Findings Anemia is usually present at diagnosis and can be severe. The degree varies considerably, irrespective of other hematologic findings, splenomegaly, or duration of symptoms. The anemia is usually normocytic normochromic. Decreased erythropoiesis often results in a reduced reticulocyte count, and red blood cell (RBC) survival is decreased by accelerated destruction. Active blood loss also contributes to the anemia.

The median presenting leukocyte count is about 15,000/μL. Between 25 and 40% of patients have counts <5000/μL, and 20% have counts >100,000/μL. Fewer than 5% have no detectable leukemic cells in the blood. The morphology of the malignant cell varies in different subsets. In AML, the cytoplasm often contains primary (nonspecific) granules, and the nucleus shows fine, lacy chromatin with one or more nucleoli characteristic of immature cells. Abnormal rod-shaped granules called Auer rods are not uniformly present, but when they are, myeloid lineage is virtually certain (Fig. 132-1). Poor neutrophil function may be noted functionally by impaired phagocytosis and migration and morphologically by abnormal lobulation and deficient granulation.

Platelet counts <100,000/μL are found at diagnosis in ~75% of patients, and about 25% have counts <25,000/μL. Both morphologic and functional platelet abnormalities can be observed, including large and bizarre shapes with abnormal granulation and inability of platelets to aggregate or adhere normally to one another.

Pretreatment Evaluation Once the diagnosis of AML is suspected, a rapid evaluation and initiation of appropriate therapy should follow. In addition to clarifying the subtype of leukemia, initial studies should evaluate the overall functional integrity of the major organ systems, including the cardiovascular, pulmonary, hepatic, and renal systems (Table 132-4). Factors that have prognostic significance, either for achieving CR or for predicting the duration of CR, should also be assessed before initiating treatment, including cytogenetics and molecular markers (see above). Leukemic cells should be obtained from all patients and cryopreserved for future use as new tests and therapeutics become available. All patients should be evaluated for infection.

Most patients are anemic and thrombocytopenic at presentation. Replacement of the appropriate blood components, if necessary, should begin promptly. Because qualitative platelet dysfunction or the presence of an infection may increase the likelihood of bleeding, evidence of hemorrhage justifies the immediate use of platelet transfusion, even if the platelet count is only moderately decreased.

About 50% of patients have a mild to moderate elevation of serum uric acid at presentation. Only 10% have marked elevations, but renal precipitation of uric acid and the nephropathy that may result is a serious but uncommon complication. The initiation of chemotherapy may aggravate hyperuricemia, and patients are usually started immediately on allopurinol and hydration at diagnosis. Rasburicase (recombinant