There has been much interest in the clinical development of TKIs blocking mutant FLT3 signaling pathways for the treatment of FLT3 mutant AML, similar to BCR/ABL inhibitors in CML. The most effective FLT3 inhibitor, AC220 (quizartinib), resulted in a composite complete remission rate of approximately 50% in relapsed or refractory FLT3 ITD mutant AML in the phase II setting. However, multiple signaling pathways in AML cells and rapid proliferation of AML clones likely contribute to the rapid development of drug resistance. The results of additional studies examining the efficacy of FLT3 inhibitors combined with chemotherapy for relapsed and newly diagnosed FLT3-positive AML patients are eagerly awaited.

ACUTE PROMYELOCYTIC LEUKEMIA

Definition, Epidemiology, and Pathology

Acute promyelocytic leukemia (APL), formerly known as the FAB M3 subtype of AML (see Table 46-8), is a rare malignancy that represents 10% to 15% of adult AML. The incidence is increased among younger patients (median age, 40 years). The annual incidence in the United States ranges from 600 to 800 cases.

APL is different from other acute leukemias because of its unique disease biology. Morphologically, APL blasts are distinctive immature promyelocytic cells containing large granules and typically high numbers of Auer rods diagnostic of AML. APL is characterized by a chromosomal translocation—t(15;17)(q22;q12)—involving the promyelocytic leukemia gene *(PML)* on chromosome 15 and the retinoic acid receptor-α gene *(RARA)* on chromosome 17. Sequestration of the resulting PML/RARA fusion protein with other proteins produces a complex that represses the gene transcription essential for granulocytic differentiation, effectively arresting differentiation of leukemia cells at the promyelocytic stage.

Clinical Presentation

Clinically, patients with APL often exhibit life-threatening bleeding caused by disseminated intravascular coagulation related to high levels of procoagulant factors released from APL granules. Bleeding complications in the CNS and other sites can be rapidly fatal if the disease is not recognized and treated as a medical emergency. All patients suspected of having APL should be started empirically with all-*trans*-retinoic acid (ATRA) therapy (discussed later) and treated aggressively with transfusions of fresh-frozen plasma, fibrinogen, and platelets until resolution of coagulopathy and disease confirmation.

Unlike patients with other AML subsets, APL patients typically have cytopenias rather than leukocytosis. High-risk APL patients are defined as those with white blood cell counts greater than 10×10^9/L.

Treatment and Prognosis

Treated appropriately, APL is the most curable acute leukemia in adults. The centerpiece of APL treatment is the use of agents that induce the terminal differentiation of leukemic promyelocytes followed by senescence and spontaneous apoptosis. ATRA is an oral derivative of vitamin A shown to overcome growth arrest and permit differentiation of immature APL blast cells into neutrophils by altering the configuration of *PML/RARA* to allow normal gene transcription.

Patients initiated on ATRA must be closely observed for development of retinoic acid or APL differentiation syndrome, which is life-threatening acute cardiopulmonary distress characterized by bilateral pulmonary effusions and infiltrates. This serositis-like disorder is attributed to adhesion of differentiating neoplastic cells to the pulmonary vasculature and carries a 5% to 10% mortality rate. Treatment consists of early initiation of corticosteroids and aggressive diuresis. In severe cases, ATRA should be temporarily withheld.

Although ATRA alone induces clinical remissions in up to 90% of patients with APL, high relapse rates observed after monotherapy led to the practice of combining ATRA with anthracycline with or without cytarabine chemotherapy in initial induction regimens. Using this approach, complete remission rates for APL rose to between 90% and 95%, and more than two thirds of patients with APL treated with standard ATRA-containing induction, consolidation, and maintenance chemotherapy regimens achieved long-term remission.

Relapsed APL patients were treated with arsenic trioxide, a naturally occurring compound used both as a poison and a drug in many countries. Low-dose arsenic therapy promotes APL cell differentiation and apoptosis and induces remission rates in up to 90% of relapsed APL cases. APL differentiation syndrome and prolongation of the QT interval are common side effects of arsenic therapy. Based on its tolerability and non-overlapping cytotoxicities with conventional cytotoxic drugs, arsenic was successfully used for consolidation therapy in APL patients and improved clinical outcomes.

Although highly effective, combination ATRA and chemotherapy regimens for newly diagnosed APL patients were associated with an overall mortality rate of 10% to 20% during the first month of treatment. Most deaths resulted from uncontrolled hemorrhage, differentiation syndrome, and complications of prolonged myelosuppression after cytotoxic therapy, particularly in older individuals. To address these concerns, a phase III trial randomized lower-risk APL patients to dual-differentiation therapy with ATRA and arsenic only (without cytotoxic chemotherapy) or to standard ATRA and chemotherapy during induction and consolidation. The trial results demonstrated that ATRA plus arsenic treatment was not inferior to ATRA plus chemotherapy and was not associated with increased toxicity.

The trial results led to establishment of differentiation therapy alone as the standard of care for lower-risk APL patients. Patients with residual PML/RARA-positive cells after standard induction and consolidation therapy containing ATRA and arsenic should be considered for autologous or allogeneic SCT.

ACUTE LYMPHOBLASTIC LEUKEMIA

Definition, Epidemiology, and Pathology

ALL is a neoplasm of immature lymphoblasts expressing markers of B-cell or T-cell lineage. ALL is predominantly a pediatric malignancy, with most cases occurring in children younger than 6 years. The prior FAB classification system divided ALL into three subtypes (i.e., L1, L2, and L3) based on the morphology of malignant cells (E-Fig. 46-3). The WHO system reclassified the