kinase, altering drug binding and inhibitory effects. For this reason, it is recommended that patients requiring second-line therapy or beyond undergo testing for identification of mutations as a potential guide to therapy. CML patients with disease associated with a mutation at T315I are known to be resistant to imatinib, nilotinib, dasatinib, and bosutinib, but not to ponatinib, a third-generation BCR/ABL inhibitor.

Omacetaxine mepesuccinate is a natural alkaloid product with proven antitumor activity and efficacy in CML patients failing multiple TKIs or carrying the T315I mutation, or both. Its mechanisms of action are distinct from the TKIs and involve inhibition of protein synthesis and induction of apoptosis in tumor cells. Several clinical trials have confirmed the activity of this agent in this patient population. A major drawback is the need for subcutaneous injections administered twice daily for 7 to 14 days of every 28 days per month.

Unfortunately, although treatment with the newer BCR/ABL inhibitors can induce transient hematologic and cytogenetic responses in patients with accelerated or blast phase CML, these responses are short lived. The treatment modality known to result in eradication of all detectable BCR/ABL-expressing cells remains allogeneic SCT. Before the advent of targeted BCR/ABL kinase inhibitor therapy, young patients with an HLA-matched donor were routinely offered potentially curative allogeneic bone marrow transplantation at the time of diagnosis of chronic phase CML. Evidence indicated that the excellent response (50% to 75%) of CML patients to SCT was partly related to the active suppression of the disease by the newly transplanted graft, called the *graft-versus-leukemia effect*.

In the face of the excellent control and low overall toxicity of long-term BCR/ABL inhibitors for chronic phase CML, together with the known 20% to 30% mortality and morbidity rates after SCT, transplantation is viewed as an option only for patients with accelerated or blast phase disease or chronic phase CML failing multiple lines of prior therapy. Transplantation remains the only known curative therapy for these patients. Blast phase CML patients often undergo induction chemotherapy with acute leukemia regimens followed by BCR/ABL inhibition and allogeneic SCT.

Prognosis

Overall, the transformation of CML from a progressively fatal cancer to one in which almost 90% of patients are alive with stable disease on oral kinase therapy after 5 years remains one of the crowning achievements in cancer therapy in the past decade. The median overall survival for chronic phase CML patients has risen dramatically from a few months to a few years in the first half of the 20th century to 6 years for interferon-treated patients. In the era of BCR/ABL inhibition therapy, it is expected to be almost normal for most patients on long-term TKI therapy.

The standard of care for CML patients who are responding optimally to treatment is to continue TKI therapy indefinitely. However, ongoing studies are examining the impact of discontinuing TKI in selected individuals whose disease has responded particularly well to therapy based on molecular criteria. Despite many therapeutic advances, a true cure for CML disease remains elusive and presents a therapeutic challenge for the years ahead.

ACUTE LEUKEMIAS

Definition and Epidemiology

The acute leukemias are clonal hematopoietic diseases that arise from the malignant transformation of an early hematopoietic stem cell. Leukemias occur in 8 to 10 of 100,000 people (compared with 42 of 100,000 for prostate cancer and 62 of 100,000 for breast cancer). Acute leukemias are classified by cell lineage as AML or ALL based on morphology, cytogenetics, cell surface and cytoplasmic markers, and molecular studies. Between 80% and 90% of adult leukemia diagnoses are AML (others are ALL), whereas most childhood leukemias are ALL (10% are AML).

Pathology

The pathogenesis of acute leukemia is under intense investigation. Many patients with acute leukemia have detectable characteristic clonal chromosomal abnormalities, but the role of all but a few of these aberrations in malignant transformation is unknown. Unregulated proliferation of immature cells incapable of further differentiation (i.e., blasts) results in marrow replacement and hematopoietic failure.

Known risk factors for leukemia are high-dose radiation exposure and occupational exposure to benzene. Patients with secondary AML after prior chemotherapy have usually received alkylating agents (e.g., chlorambucil, melphalan, nitrogen mustard) or topoisomerase II inhibitors (e.g., epipodophyllotoxins). Patients with chromosomal instability disorders such as Bloom's syndrome, Fanconi's anemia, Down syndrome, and ataxia telangiectasia also have an increased incidence of leukemia.

Diagnosis and Differential Diagnosis

The distinction between AML and ALL is crucial diagnostically, therapeutically, and prognostically. AML can be distinguished from ALL by cell morphology and the finding of Auer rods, which are formed by the aggregation of myeloid granules (E-Fig. 46-2). Further immunophenotyping of blast cells using cell surface antigens, cytochemistry, and immunohistochemistry confirms cells as having a myeloid or lymphoid origin (Table 46-7). Morphologic subgroups of ALL and AML were originally defined by the French-American-British (FAB) classification and then by the World Health Organization (WHO) classification, which incorporated newer biologic information (Table 46-8).

Clinical Presentation

Patients exhibit clinical evidence of bone marrow failure similar to other hematopoietic disorders. Complications of disease include anemia, infection, and bleeding from peripheral cytopenias. Proliferating blasts infiltrating the bone marrow may cause bone pain. Blasts also invade other organs and lead to peripheral, mediastinal, and abdominal lymphadenopathy, hepatosplenomegaly, skin infiltration, and meningeal involvement.

Treatment

Therapy for acute leukemias is divided into several stages. *Induction therapy* is directed at reducing the number of leukemic blasts to an undetectable level and restoring normal hematopoiesis (i.e.,