disease as precursor B-cell or T-cell ALL based on the lineage of specific cell surface antigens found on these cells during normal maturation (see Table 46-7). T-cell ALL represents 15% to 25% of ALL diagnoses. More than 50% of T-cell ALL cases have activating mutations in NOTCH1, a key regulator of T-cell fate. One third of adult and 20% of pediatric B-cell ALL cases are associated with detection of the Philadelphia chromosome, t(9;22).

Clinical Presentation

Clinical and biologic features, particularly cytogenetics, at diagnosis have been identified as important prognostic factors (see Table 46-10).

Treatment

Treatment of ALL is lengthy and involves multiple chemotherapeutic agents given over 2 to 3 years. Induction chemotherapy typically includes vincristine, corticosteroids, and L-asparaginase with the addition of an anthracycline, cytarabine, or cyclophosphamide (or a combination) for adult patients. Given the propensity of ALL cells to reside in the CNS and testes (so-called sanctuaries for leukemia cells because standard systemic chemotherapy does not penetrate into these sites), most ALL patients undergo lumbar puncture at the time of diagnosis, followed by routine administration of intrathecal methotrexate or whole brain irradiation, or both, as a necessary adjunct to systemic induction and consolidation chemotherapy. Complete remission rates are 97% to 99% for children and 75% to 90% for adults.

After normal hematopoiesis returns, patients undergo consolidation and intensification therapy with multiple drugs to eradicate disease. For unknown reasons, ALL tends to relapse several months to years after initial remission. Studies have shown that the frequency of relapse is reduced by maintenance chemotherapy given for 2 to 3 years after initial remission achievement. Prolonged treatment may eliminate slow-growing leukemic clones, prevent further transformation, or destroy occult disease in other sites, particularly the CNS.

Progress in the understanding and treatment of this disease in the 1990s led to cure rates of up to 90% for children with ALL. Despite this success, only 20% to 40% of adult patients with ALL achieve cure. The poorer outcomes for adults are attributed to differences in the biologic mechanisms of disease in the different age groups and the inability of older patients to tolerate the intensive chemotherapy or transplantation procedures required to achieve long-term responses. Moreover, Philadelphia chromosome–expressing ALL, which is much more common in older individuals, is notoriously chemoresistant, has an increased risk of CNS involvement, and has an overall 5-year survival rate of less than 10%. Patients with Philadelphia chromosome–positive ALL routinely receive therapy with the oral BCR/ABL TKIs (i.e., imatinib and dasatinib) used in CML in addition to conventional chemotherapy. High-risk young patients with B-cell ALL may benefit from anti-CD20 antibodies (i.e., rituximab) directed against B-cell antigens on abnormal lymphoblasts.

In ALL, as in AML, the worse the prognosis, the earlier transplantation should be offered. Studies have shown that high-risk ALL patients (i.e., as older patients, Philadelphia chromosome–positive disease, high white blood cell count at presentation, or prolonged time to first remission) clearly benefit from SCT, preferably from an HLA-matched sibling, during the first remission. Early transplantation in adults has achieved 5-year survival rates of 40% to 44%, compared with 20% with other therapies.

Unfortunately, outcomes for high-risk ALL patients without an available HLA-matched donor are poor, and these individuals should pursue HLA-matched unrelated donor allogeneic SCT or experimental therapies. No significant benefit has been seen with autologous transplantation over standard chemotherapy for these patients. Standard-risk ALL patients, particularly pediatric patients, with high long-term remission rates after conventional chemotherapy and maintenance need not undergo allogeneic SCT unless disease recurs.

Most ALL relapses arise within 2 years of the initial diagnosis, with recurrence of leukemic cells in the bone marrow, CNS, or testes. Although relapsed disease may respond to further chemotherapy and local irradiation, the duration of second remissions is usually less than 6 months. All patients with relapsed ALL should be considered for allogeneic SCT (which represents the only known cure for disease) or experimental treatment. Autologous SCT for refractory or relapsed ALL is not routinely recommended because ALL blasts appear to be more chemoresistant, and failure rates after treatment are higher.

For relapsed ALL patients not eligible for SCT, several novel therapeutic approaches are available. The newest BCR/ABL inhibitor, ponatinib, is being investigated in combination with chemotherapy for Philadelphia chromosome–positive ALL. Toxin-containing antibodies targeting the B-cell markers CD19 and CD52 in relapsed ALL patients are also being explored. Marqibo, a liposomal formulation of vincristine and a standard chemotherapy drug used in initial ALL therapy, has induced clinical responses in 35% of refractory or relapsed ALL patients as a single agent with tolerable toxicities.

Perhaps the most exciting strategies for ALL therapy involve technologies specifically exploiting patient host immune responses to affect long-term cure. Blinatumomab (BiTE) is a bispecific single-chain antibody that binds the T-cell receptor CD3 on T cells and the B-cell antigen CD19 expressed by malignant lymphoblasts. Dual binding of CD3 and CD19 by BiTE brings reactive T cells close to tumor cells, redirects T cell lysis, and eliminates disease. Administration of BiTE to ALL patients in clinical remission but with evidence of minimal residual disease after standard chemotherapy resulted in eradication of detectable persistent disease in 76% of patients. Ongoing trials evaluating BiTE in relapsed or refractory ALL patients with much higher tumor burdens and in combination with chemotherapy regimens are ongoing.

An alternative approach has been to genetically modify autologous T cells from ALL patients with CD19-expressing chimeric antigen receptors, effectively reprogramming them to recognize and destroy CD19-expressing tumor cells. Reinfusion of these cells after lymphodepleting chemotherapy resulted in the complete eradication of ALL disease in 80% to 90% of individuals and some long-term disease control alone and when followed by SCT. Whether these engineered T-cell strategies will be broadly applicable for most patients with ALL outside of clinical trials at major academic centers remains to be determined.