The proteosome inhibitor bortezomib is a novel nonchemotherapeutic agent with activity against mantle cell NHL. The Bruton tyrosine kinase inhibitor ibrutinib is a novel compound for the treatment of recurrent mantle cell lymphoma, and it represents a new class of targeted agents available for NHL treatment.

### High-Grade Non-Hodgkin's Lymphomas

The two high-grade subtypes, Burkitt's lymphoma and lymphoblastic lymphoma, are rare in the adult population. Nonetheless, these subtypes are important because they are potentially curable with appropriate therapy and often require urgent, inpatient treatment at the time of diagnosis due to their highly aggressive nature, rapid growth, and tendency to develop tumor lysis on initiation of therapy.

Lymphoblastic lymphoma in adults is an aggressive lymphoma that is usually considered the lymphomatous counterpart of acute T-cell lymphocytic leukemia. B-cell lymphoblastic lymphoma is less common. Lymphoblastic lymphoma usually afflicts young adult men and involves the mediastinum and bone marrow, with a propensity to relapse in the leptomeninges.

Burkitt's lymphoma is a rare B-cell lymphoma in adults that is highly aggressive, with a propensity to involve the bone marrow and central nervous system. Burkitt's lymphoma is characterized cytogenetically by the pathognomonic t(8;14) translocation that moves the *MYC* oncogene from chromosome 8 to a location close to the enhancers of the antibody heavy-chain genes (*IGH* locus) on chromosome 14. In central Africa, where Burkitt's lymphoma is endemic in children, it is usually associated with EBV. However, in the United States, it is uncommon for sporadic Burkitt's lymphoma to be EBV positive.

Burkitt's lymphoma and lymphoblastic lymphomas require treatment with intensive multiagent chemotherapy, including intrathecal chemotherapy to prevent leptomeningeal relapse. These lymphomas undergo rapid tumor lysis on initiation of chemotherapy, and all patients must receive prophylaxis against tumor lysis syndrome before and during their first course of chemotherapy. Prophylaxis includes hydration, alkalinization of the urine, allopurinol, and consideration of rasburicase therapy for rapid lowering of elevated uric acid levels.

### Prognosis

A variety of prognostic variables have been identified for NHL, and specific prognostic schemes have been devised for common diseases, including DLBCL, follicular NHL, and mantle cell lymphomas. The predictors for poor survival for most subtypes of NHL include advanced stage (III/IV) at onset, involvement of multiple extranodal sites of disease, elevated LDH levels, B symptoms (e.g., fever, night sweats, weight loss), and poor performance status.

The International Prognostic Index (IPI) stratifies patients based on age, performance status, stage, and number of extranodal sites. The likelihood of cure and long-term, disease-free survival ranges from more than 75% for patients with one or no adverse factors to less than 50% for patients with four or more adverse factors.

Factors associated with shortened survival in follicular NHL include older age, advanced stage, anemia, multiple lymph node sites (more than four), and elevated LDH levels. Patients with three or more of these factors have a median survival of 5 years, roughly one half of that of patients with zero or one risk factor. Aggressive T-cell lymphomas usually fare more poorly than B-cell NHL, and patients are typically considered candidates for investigational studies and transplantation therapies.

*For a deeper discussion of these topics, please see Chapter 185, "Non-Hodgkin's Lymphomas," in* Goldman-Cecil Medicine, *25th Edition.*

## Hodgkin's Lymphoma

Hodgkin's lymphoma is a node-based lymphoid malignancy characterized by the neoplastic Reed-Sternberg (RS) cell in an inflammatory background. Hodgkin's lymphoma accounts for 10% of lymphomas, with about 9000 new cases diagnosed in the United States annually, and it is the most common lymphoma among young adults. The age distribution in industrialized countries is bimodal, with the larger peak occurring between the ages of 15 and 35 and a smaller peak seen in patients older than 50 years.

The cause of Hodgkin's lymphoma remains enigmatic. Risk factors include a history of infectious mononucleosis, high socioeconomic status, immunosuppression (e.g., HIV infection, allograft transplantion, immunosuppressive drugs), and autoimmune disorders. Although EBV is frequently detected in patients, a direct casual role has not been established.

### Pathology

Hodgkin's lymphoma is diagnosed by identifying the RS cell in involved lymphoid tissue. The classic RS cell is large and binucleate, with each nucleus containing a prominent nucleolus, suggesting the appearance of owl eyes. Although the cellular origin of the RS cell was debated for decades, molecular studies have confirmed that RS cells are B cells with clonal rearrangement of the germline *IG* locus. Unlike NHL, the bulk of the infiltrate in lymph nodes involved with Hodgkin's lymphoma is usually composed of benign reactive inflammatory cells, and the RS cells often can be difficult to find. Immunophenotyping of classic RS cells reveals that they are CD30 (Ki-1) and CD15 positive and are negative for CD20, CD45, and cytoplasmic or surface immunoglobulin. EBV is identified in the RS cells in about 50% of cases.

The pathologic subtypes of classic Hodgkin's lymphoma include four variants—nodular sclerosing (NS), mixed cellularity (MC), lymphocyte depleted (LD), and lymphocyte rich (LR)—and the nonclassic variant, nodular lymphocyte-predominant (NLP). The NS form is the most common variant (60% to 80%) and is characterized by fibrous bands separating the node into nodules and by the lacunar type of RS cells. It is the predominant type encountered in adolescents and young adults and typically involves the mediastinum and supradiaphragmatic nodal sites. In the MC type (15%), band-forming sclerosis is absent, and RS cells are easily identified in a diffuse inflammatory infiltrate that is more heterogeneous than that seen in the NS variant. The LR variant (5%) is characterized by classic RS cells in a background composed predominantly of small lymphocytes. LD is a rare variant (<1%) that is associated with