associated with MOPP (level I evidence). Roughly 60% of patients with stage III or IV disease are cured with six cycles (months) of ABVD.

The intensive regimen of BEACOPP (i.e., bleomycin, etoposide, Adriamycin, cyclophosphamide, vincristine, prednisolone, and procarbazine) has been associated with higher rates of complete response and freedom from treatment failure compared with ABVD-based regimens used for patients with advanced disease, although overall survival has not been increased in all studies (level I evidence). BEACOPP is used increasingly in selected patients with high-risk features. Gonadal toxicity with permanent infertility is common after BEACOPP, and an increased risk of secondary leukemia has been reported. Late sequelae and acute toxicities must be considered when choosing this regimen.

Radiation therapy in combination with chemotherapy is typically not used to treat advanced-stage disease. However, in patients with bulky mediastinal disease, consolidative irradiation to the mediastinum after completion of chemotherapy has decreased the rate of relapse.

Evaluating the response to therapy involves repetition of the staging evaluation (i.e., physical examination, CT, and PET) during and at the completion of treatment. A mid-treatment PET scan after two cycles of ABVD for advanced disease is prognostically informative because persistent metabolic activity seen on PET highly correlates with resistance or subsequent relapse of disease. Conversely, patients may be cured despite the finding of a residual abnormality on CT (e.g., enlarged nodes, residual mediastinal mass) when residual disease is not found on PET imaging. A persistently positive PET scan after treatment of patients with residual radiographic abnormalities is associated with a high rate of subsequent relapse, and these patients should be monitored closely or considered for immediate repeat biopsy or salvage therapy. Most patients destined to relapse do so within 2 years; relapses after 5 years are rare except for patients with the NLP variant.

Patients who relapse or fail to respond after initial therapy should be offered salvage therapy because many can be cured if treated with high-dose chemotherapy and autologous hematopoietic cell transplantation (level I evidence). Patients who relapse after autologous transplantation usually are incurable, although a subset of young and medically fit patients can be considered for potentially curative allogeneic transplantation.

Palliation of refractory Hodgkin's lymphoma can be achieved with radiation therapy, salvage chemotherapy regimens, or with brentuximab vedotin, an immunotoxin composed of a CD30-directed antibody linked to an antitubulin agent. The latter agent is associated with high response rates, including complete responses in more than 30% of patients with relapsed disease after autologous transplantation (level II-1 evidence).

### Prognosis

Approximately 80% of patients with Hodgkin's lymphoma are cured. Prognostic factors that influence risk of relapse or survival include MC or LD histology, male sex, large numbers of involved nodal sites, age older than 40 years, B symptoms, high ESR, and bulky disease (i.e., mediastinum widening by more than one third or a mass larger than 10 cm). The International Prognostic Score, based on seven variables at diagnosis, is a validated predictor of outcome in advanced disease.

## Lymphoid Leukemias

### Acute Lymphocytic Leukemias

The acute lymphocytic leukemias that arise from precursor B or T cells are described in detail in Chapter 48.

### Chronic Lymphocytic Leukemia and Small Lymphocytic Lymphoma

#### Definition and Epidemiology

B-cell CLL is a malignant disorder of lymphocytes characterized by expansion and accumulation of small lymphocytes of B-cell origin. CLL is essentially identical to B-cell small lymphocytic lymphoma but represents the leukemic form of the disease. CLL is the most common form of leukemia in the United States and affects twice as many men as women. Although it can occur at any stage of life, the incidence increases with age, and more than 90% of cases are diagnosed in adults older than 50 years of age.

The cause of CLL is unknown. Familial clustering of CLL suggests a genetic basis in some cases. Radiation and common carcinogen exposures have not been associated with an increased risk of CLL.

#### Pathology

The common form of CLL is a clonal proliferation of mature B cells expressing characteristic mature B-cell markers and low levels of surface immunoglobulin M (IgM) that is light chain restricted, reflecting the clonal origin of this malignancy. Smears of the bone marrow or peripheral blood reveal a predominance of small lymphocytes with inconspicuous nucleoli; ruptured cells (i.e., smudge cells) are often observed. Examination of involved lymph nodes reveals a diffuse infiltrate of small lymphocytes ablating the normal architecture.

The diagnostic immunophenotype of CLL is unique, with expression of CD5 and CD23 along with the mature B-cell markers CD19, CD20 (dim expression), and CD21. Although a pathognomonic chromosomal abnormality has not been identified in CLL, 30% to 50% of patients have cytogenetic abnormalities, more so if sensitive assays such as fluorescence in situ hybridization (FISH) are employed. The most frequent abnormalities involve chromosome 12 (often trisomy 12), 13, and 14. Cytogenetic abnormalities of chromosomes 17 and 11 are associated with a very poor prognosis.

#### Diagnosis and Differential Diagnosis

The diagnosis of CLL is often made incidentally on a routine blood cell count that shows a leukocytosis with a predominance of small lymphocytes. Flow cytometric analysis of peripheral blood or a bone marrow aspirate reveals the characteristic clonal B-cell population that is CD5 and CD23 positive.

CLL must be distinguished from reactive causes of lymphocytosis and other forms of lymphoma or leukemia. Mantle cell lymphoma may appear similar morphologically and with a similar immunophenotype, although CD23 is typically absent and cyclin D1 expression is detected. An absolute lymphocytosis of more than 5000 cells/μL is required for the diagnosis of CLL.