expression is said to be low in the better-prognosis patients expressing mutated immunoglobulin and high in poorer-prognosis patients expressing unmutated immunoglobulin, but this test has not been confirmed as a reliable means of distinguishing the two groups. ZAP-70 expression correlates with the presence of unmutated immunoglobulin genes, but the assay is not yet standardized and widely available.

TREATMENT B-CELL CHRONIC LYMPHOID LEUKEMIA/ SMALL LYMPHOCYTIC LYMPHOMA

Patients whose presentation is typical B-cell CLL with no manifestations of the disease other than bone marrow involvement and lymphocytosis (i.e., Rai stage 0 and Binet stage A; Table 134-7) can be followed without specific therapy for their malignancy. These patients have a median survival >10 years, and some will never require therapy for this disorder. If the patient has an adequate number of circulating normal blood cells and is asymptomatic, many physicians would not initiate therapy for patients in the intermediate stage of the disease manifested by lymphadenopathy and/or hepatosplenomegaly. However, the median survival for these patients is ~7 years, and most will require treatment in the first few years of follow-up. Patients who present with bone marrow failure (i.e., Rai stage III or IV or Binet stage C) will require initial therapy in almost all cases. These patients have a serious disorder with a median survival of only 1.5 years. It must be remembered that immune manifestations of typical B-cell CLL should be managed independently of specific antileukemia therapy. For example, glucocorticoid therapy for autoimmune cytopenias and γ globulin replacement for patients with hypogammaglobulinemia should be used whether or not antileukemia therapy is given.

Patients who present primarily with lymphoma and have a low IPI score have a 5-year survival of ~75%, but those with a high IPI score have a 5-year survival of <40% and are more likely to require early therapy.

The most common treatments for patients with typical B-cell CLL/small lymphocytic lymphoma have been chlorambucil or fludarabine, alone or in combination. Chlorambucil can be administered orally with few immediate side effects, while fludarabine is administered IV and is associated with significant immune suppression. However, fludarabine is by far the more active agent and is the only drug associated with a significant incidence of complete remission. The combination of rituximab (375–500 mg/m^2 day 1), fludarabine (25 mg/m^2 days 2–4 on cycle 1 and days 1–3 in subsequent cycles), and cyclophosphamide (250 mg/m^2 with fludarabine) achieves complete responses in 69% of patients, and those responses are associated with molecular remissions in half of the cases. Half the patients experience grade III or IV neutropenia. For young patients presenting with leukemia requiring therapy, regimens containing fludarabine are the treatment of choice. Because fludarabine is an effective second-line agent in patients with tumors unresponsive to chlorambucil, the latter agent is often chosen in elderly patients who require therapy. Bendamustine, an alkylating agent structurally related to nitrogen mustard, is highly effective and is vying with fludarabine as the primary treatment of choice. Patients who present with lymphoma (rather than leukemia) are also highly responsive to bendamustine, and some patients will receive a combination chemotherapy regimen used in other lymphomas such as CVP (cyclophosphamide, vincristine, and prednisone) or CHOP plus rituximab. Alemtuzumab (anti-CD52) is an antibody with activity in the disease, but it kills both B and T cells and is associated with more immune compromise than rituximab. Young patients with this disease can be candidates for bone marrow transplantation. Allogeneic bone marrow transplantation can be curative but is associated with a significant treatment-related mortality rate. Mini-transplants using immunosuppressive rather than myeloablative doses of preparative drugs are being studied (Chap. 139e). The use of autologous transplantation in patients with this disorder has been discouraging.

At least two newer anti-CD20 monoclonal antibodies have become available, ofatumumab and obinutuzumab. Both have activity in previously treated patients. Agents targeting signaling pathways, such as ibrutinib, an irreversible inhibitor of Bruton's tyrosine kinase, and idelalisib, an inhibitor of phosphoinositide-3-kinase delta, also have antitumor effects. The ideal combination and sequence of these therapies have not been defined.

Extranodal Marginal Zone B-Cell Lymphoma of MALT Type Extranodal marginal zone B-cell lymphoma of MALT type (MALT lymphoma) makes up ~8% of non-Hodgkin's lymphomas. This small cell lymphoma presents in extranodal sites. It was previously considered a small lymphocytic lymphoma or sometimes a pseudolymphoma. The recognition that the gastric presentation of this lymphoma was associated with *H. pylori* infection was an important step in recognizing it as a separate entity. The clinical characteristics of MALT lymphoma are presented in Table 134-10.

The diagnosis of MALT lymphoma can be made accurately by an expert hematopathologist based on a characteristic pattern of infiltration of small lymphocytes that are monoclonal B cells and CD5 negative. In some cases, transformation to diffuse large B-cell lymphoma occurs, and both diagnoses may be made in the same biopsy. The differential diagnosis includes benign lymphocytic infiltration of extranodal organs and other small cell B-cell lymphomas.

MALT lymphoma may occur in the stomach, orbit, intestine, lung, thyroid, salivary gland, skin, soft tissues, bladder, kidney, and CNS. It may present as a new mass, be found on routine imaging studies, or be associated with local symptoms such as upper abdominal discomfort in gastric lymphoma. Most MALT lymphomas are gastric in origin. At least two genetic forms of gastric MALT exist: one (accounting for ~50% of cases) characterized by t(11;18)(q21;q21) that juxtaposes the amino terminal of the *API2* gene with the carboxy terminal of the *MALT1* gene creating an API2/MALT1 fusion product, and the other characterized by multiple sites of genetic instability including trisomies of chromosomes 3, 7, 12, and 18. About 95% of gastric MALT lymphomas are associated with *H. pylori* infection, and those that are do not usually express t(11;18). The t(11;18) usually results in activation of nuclear factor-κB (NF-κB), which acts as a survival factor for the cells. Lymphomas with t(11;18) translocations are genetically stable and do not evolve to diffuse large B-cell lymphoma. By contrast, t(11;18)-negative MALT lymphomas often acquire *BCL6* mutations and progress to aggressive histology lymphoma. MALT lymphomas are localized to the organ of origin in ~40% of cases and to the organ and regional lymph nodes in ~30% of patients. However, distant metastasis can occur—particularly with transformation to diffuse large B-cell lymphoma. Many patients who develop this lymphoma will have an autoimmune or inflammatory process such as Sjögren's syndrome (salivary gland MALT), Hashimoto's thyroiditis (thyroid MALT), *Helicobacter* gastritis (gastric MALT), *C. psittaci* conjunctivitis (ocular MALT), or *Borrelia* skin infections (cutaneous MALT).

Evaluation of patients with MALT lymphoma follows the pattern (Table 134-11) for staging a patient with non-Hodgkin's lymphoma. In particular, patients with gastric lymphoma need to have studies performed to document the presence or absence of *H. pylori* infection. Endoscopic studies including ultrasound can help define the extent of gastric involvement. Most patients with MALT lymphoma have a good prognosis, with a 5-year survival of ~75%. In patients with a low IPI score, the 5-year survival is ~90%, whereas it drops to ~40% in patients with a high IPI score.

TREATMENT MUCOSA-ASSOCIATED LYMPHOID TISSUE LYMPHOMA

MALT lymphoma is often localized. Patients with gastric MALT lymphomas who are infected with *H. pylori* can achieve remission in the 80% of cases with eradication of the infection. These remissions can be durable, but molecular evidence of persisting neoplasia is not