(i.e., cyclophosphamide, hydroxydaunorubicin [doxorubicin], Oncovin [vincristine], and prednisone) plus rituximab in a randomized trial with regard to toxicity, response rate, and progression-free survival (level 1 evidence).

Most patients respond to treatment, and at least one third achieve a clinical complete remission that may last 1 to 3 years. Treatment with cytotoxic agents is typically discontinued when the maximum response has been achieved, but rituximab may be continued on an intermittent schedule to maintain remission. It has been shown to prolong remission times in randomized studies (level 1 evidence). Risk of recurrence and cost considerations may influence the use of this therapy because rituximab may also be used at the time of recurrence with similar outcomes.

After a patient relapses, subsequent remissions may be achieved but are often less durable compared with the first remission. Therapeutic options for patients who relapse include retreatment with chemotherapy, often with a different drug or combination than that used initially. Patients in relapse can also be treated with rituximab as a single agent. Two radioactively labeled anti-CD20 antibodies, ibritumomab tiuxetan (yttrium labeled) and tositumomab (iodine 131 labeled), are also used for patients with relapsed or refractory follicular lymphoma, and they have been associated with a high response rate. For patients who have clinical or pathologic evidence of transformation to a higher grade of lymphoma, treatment that is appropriate for a diffuse, aggressive histology should be offered (discussed later).

High-dose chemotherapy with autologous or allogeneic stem cell transplantation for follicular NHLs may be appropriate for selected patients with recurrent or refractory disease. Long-term follow-up of patients undergoing allogeneic transplantation suggests that some patients are cured with this modality, but the morbidity associated with allogeneic transplantation has limited its widespread use for refractory indolent lymphomas.

In addition to the follicular NHLs, the MALT lymphomas and closely related marginal zone lymphomas are considered low-grade, indolent subtypes. Given the excellent prognosis, localized nature, and long natural history of the MALT lymphomas, they usually are managed conservatively with local treatment modalities (i.e., irradiation or surgery) and avoidance of systemic chemotherapy. The monoclonal antibody rituximab has activity against MALT lymphomas and may be used when systemic therapy is desired. The gastric MALT lymphomas are highly associated with *H. pylori* infection, and remissions can often be achieved with eradication of this infection. Antibiotic therapy is the first-line treatment for early *H. pylori*–positive gastric MALT lymphoma.

Aggressive Non-Hodgkin's Lymphomas

Aggressive NHLs include DLBCL, anaplastic large cell lymphoma, peripheral T-cell lymphomas, and the high-grade lymphomas, Burkitt's lymphoma and lymphoblastic lymphoma (see High-Grade Non-Hodgkin's Lymphomas). Most of the diffuse, aggressive large cell lymphomas are B cell in origin; aggressive T-cell lymphomas are managed similarly but have an overall worse prognosis compared with their B-cell counterparts.

DLBCL accounts for up to 40% of all NHL subtypes. In contrast to patients with low-grade follicular NHLs, all patients with diffuse, aggressive histology should be offered immediate therapy because these lymphomas are life-threatening but potentially curable. The standard initial therapy for all patients with diffuse, aggressive NHL, regardless of stage, is a multidrug chemotherapy regimen that includes an anthracycline in combination with the anti-CD20 monoclonal antibody rituximab.

For DLBCL, CHOP is the most widely used chemotherapy regimen. Patients with early-stage disease (I/nonbulky II) may be treated with local radiation therapy after a minimum of three cycles of CHOP plus rituximab if there is a need to limit exposure to chemotherapy. Patients with advanced-stage disease require six cycles of CHOP plus rituximab; the role of local radiation to sites of bulky disease in the setting of advanced-stage disease is not established. Complete remissions can be achieved with CHOP plus rituximab or similar regimens, and more than 50% of patients are cured.

Patients who experience relapse after achieving a remission may be cured with high-dose chemotherapy with autologous peripheral blood stem cell transplantation, particularly if their relapsed disease remains responsive to standard doses of chemotherapy. High-dose chemotherapy with autologous stem cell transplantation is superior to standard doses of salvage chemotherapy and is considered standard therapy for patients with chemosensitive diffuse, aggressive NHL that has relapsed.

Mantle Cell Lymphoma

Mantle cell lymphoma accounts for 5% to 8% of all NHLs and is most common in older male patients. Mantle cell lymphomas are mature B-cell neoplasms that appear to arise in the mantle zone of the lymphoid follicle and display a highly characteristic immunophenotype, expressing the CD5 antigen and other B-cell markers, but CD23 expression is absent, in contrast to CLL. Mantle cell lymphomas are also characterized by a pathognomonic t(11;14) chromosomal translocation that juxtaposes the immunoglobulin heavy chain gene (14q32 locus) with the *BCL1* gene, which encodes the growth-promoting protein cyclin D1. Demonstration of the translocation or expression of cyclin D1 protein by immunohistochemistry allows a definitive diagnosis in most cases. Pathologic classification as a blastoid or pleomorphic subtype and a high proliferation rate are features associated with more aggressive behavior and a poor outcome.

Mantle cell lymphomas are in many ways similar to indolent lymphomas in that patients usually have advanced-stage disease with frequent bone marrow involvement. These lymphomas have a peculiar propensity to involve the Waldeyer ring and gastrointestinal tract. As with the low-grade follicular lymphomas, mantle cell lymphomas are treatable but not typically curable. However, in contrast to the indolent lymphomas, these neoplasms may be biologically aggressive, with a median survival of only 3 years.

Patients are usually treated with systemic chemotherapy combined with rituximab at diagnosis, but durable remissions are difficult to achieve. High-dose chemotherapy and autologous stem cell transplantation are often applied during first remission for younger patients and have been associated with more durable remissions (level II-1 evidence). Multiple agents and regimens are available for those who are not candidates for transplantation and patients with recurrent disease.