Indolent B-Cell Non-Hodgkin’s Lymphomas

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The indolent B-cell non-Hodgkin’s lymphomas are a diverse group of disorders that differ markedly with respect to presenting features and natural history. This article reviews entities that have generally been encompassed

Introduction

Non-Hodgkin’s lymphomas are a diverse group of malignancies that can behave either quite aggressively, as is the case with the intermediate- and high-grade histologies, or in a more indolent manner, as is the case with the indolent lymphomas.

The intermediate- and high-grade lymphomas have the potential for being cured even when in advanced stages. In contrast, although indolent lymphomas, or low-grade lymphomas as they were called in the Working Formulation, are generally highly responsive to a variety of therapies, there is little convincing evidence that any therapy is curative. The majority of patients with indolent lymphomas will relapse and suffer substantial morbidity as well as mortality related to the persistence or recurrence of their disease.

This article discusses various aspects of the natural history and current therapeutic approaches to the more indolent lymphomas, as defined in the recently proposed Revised European-American Lymphoma (REAL) classification.[1] The intent of this classification scheme was to place identifiable lymphoid malignancies into categories that are biologically similar, thus facilitating the study of these entities.

A major contribution of the REAL classification scheme is the incorporation of several recently described entities that have not had specified niches in previous classification schemes (eg, mantle cell lymphomas and marginal zone lymphomas, including the mucosa-associated lymphoid tissue [MALT] lymphomas). The REAL classification also utilizes information beyond pure histopathology, such as immunophenotyping, cytogenetics, and molecular characteristics, to help define the entities. Using this type of classification, studies leading to a greater understanding of more specific disease processes may be planned.

The classification schemes of lymphomas used most commonly in recent years have been the Kiel classification,[2] which is used predominantly in Europe, and the Working Formulation.[3] The Kiel classification originated from an attempt to classify lymphoid malignancies based on the normal counterpart or cell of origin, whereas the Working Formulation relied heavily on histology, resulting in a classification that correlates well with natural history and response to treatment. The Working Formulation also facilitated translation of tumor type among various classifications.

This article reviews entities that have generally been encompassed under the category of indolent lymphomas in various classifications, including the Working Formulation, although many were not specifically identified or labeled as separate entities. These include small-lymphocytic lymphoma (SLL), lymphoplasmacytoid lymphoma, the follicle center cell lymphomas, mantle cell lymphoma, and nodal and extranodal marginal zone lymphomas, including MALT lymphoma. Mantle cell lymphoma carries a poorer prognosis than most of the other disease processes discussed in this review and is not an indolent disease in the true sense. It has, however, been grouped with the other indolent or low-grade lymphomas in the past and is frequently confused with some of the other indolent entities. Table 1 provides information about immunophenotyping and the translation of histologic types between the REAL Classification and Working Formulation.[1]

Small Lymphocytic Lymphoma

Histology

The predominant cell type seen in SLL is a small, benign-appearing lymphocyte with a round nucleus, condensed chromatin, and sometimes a small nucleolus. Larger cells are present and pseudofollicles may be seen.
In the past, some MALT and mantle cell lymphomas were included in this classification, in part, because they were not recognized as distinct pathologic entities and, in part, because of similar histologic appearances. However, the International Lymphoma Study Group for the REAL Classification recommended that only those lymphomas with morphology and immunophenotyping similar to that of chronic lymphocytic leukemia (CLL) be included in this group.[1] Immunoglobulin gene rearrangements are seen in SLL, and trisomy 12 and abnormalities of chromosome 13 may be present. Selected immunophenotypic features of this entity are shown in Table 1.[1,3,4]

**Epidemiology**
Small lymphocytic lymphoma accounts for approximately 4% to 5% of the non-Hodgkin’s lymphomas.[4,5] The male-to-female ratio is approximately 1.3:1, and the median age at diagnosis is 60 years.[4-6] This disease is quite rare in patients under 30 years of age. Small lymphocytic lymphoma is the nodal counterpart of CLL, and patients with evidence of bone involvement are generally considered to have leukemia.[4-6]

**Clinical Features and Natural History**
The great majority (greater than 60% to 80%) of patients with SLL are diagnosed with stage IV disease, most often based on bone marrow involvement.[3,4,6] Over time, many patients also develop peripheral blood involvement, which, again, suggests the relationship to CLL. So-called B-symptoms (fever, weight loss, and night sweats) generally are not present but may be seen in 15% of cases.[6] Extranodal involvement of the liver, lung, spleen, gastrointestinal (GI) tract, and other sites may occur,[3] but clinical problems at these sites are unusual.

The disease process is generally indolent, median survival exceeds 5 to 8 years, and involved nodes may spontaneously regress and increase in size at various intervals.[3,4] Transformation to large-cell lymphoma does occur, and the prognosis in this situation is poor.[5]

**Management**
Few studies have specifically addressed the treatment of SLL, and therefore, most information is derived from studies of either CLL or indolent lymphomas in aggregate.

**Need for Early Treatment** Evidence from studies of CLL suggests that early treatment of patients at the presymptomatic stage does not prolong survival and may actually be associated with shorter overall survival.

Catovsky et al reviewed the results of a number of clinical trials initiated by the Medical Research Council Working Party on Leukemia in Adults.[7] Two randomized studies (CLL trials 1 and 2) compared treatment with chlorambucil (Leukeran) vs no initial therapy in a total of 306 patients with early-stage CLL. Results of both studies suggested that patients on the early-treatment arms experienced shorter overall survival.

The French Cooperative Group on Chronic Lymphocytic Leukemia conducted a randomized clinical trial comparing initial treatment with daily oral chlorambucil vs observation in 612 patients with early-stage CLL. This trial indicated that early treatment imparted no benefit in terms of patient survival.[8]

In one of the studies included in the review published by Catovsky et al, 61 patients were randomized to receive chlorambucil alone or one of two regimens of cyclophosphamide, vincristine, and prednisone (CVP); the CVP arms differed with respect to the cyclophosphamide dose.[7] Overall response rates were 61% to 63% for the chlorambucil arm and 53% to 73% for the CVP arm, with the higher response rate seen in the arm using the higher cyclophosphamide dose.

There appear to be no significant advantages to treating patients with CLL in the early stages, before symptoms develop and before there is evidence of real or threatened organ dysfunction. Patients treated earlier do not gain any survival benefit, and the natural history of the disease is such that treatment directed toward symptom relief or amelioration of organ dysfunction may not be necessary for months to years. Single-agent alkylator therapy is quite effective, as is other low-intensity therapy such as CVP, and these therapies carry lower risks of treatment-related morbidity than do higher-intensity regimens.

Similar trials have been conducted in patients with indolent B-cell non-Hodgkin’s lymphomas. Again, these studies generally showed no important advantages to the use of multiple agents in treating these diseases, although response rates may be higher with regimens of higher intensity. Presumably, the results described above, although not derived from patients with SLL, may be used to guide treatment choices.

**Fludarabine (Fludara)** may be a drug of special promise in CLL and, by extension, possibly in SLL as well. Several trials have confirmed the efficacy of fludarabine in the treatment of CLL.[9] Response rates of 20% to 70% have been seen in previously treated patients, and response rates of
70% to 100% have been reported in untreated patients. A large study of fludarabine vs chlorambucil in 233 previously untreated patients revealed an overall response rate of 71% with a complete response rate of 33% for fludarabine, as compared with an overall response rate of 43% with a complete response rate of 8% for chlorambucil.[10] No influence on survival was reported, but this may reflect the relatively short follow-up of less than 5 years in these patients. Thus, fludarabine has promise as a first-line agent in CLL, but it is not clear that its use prolongs survival. Moreover, there have been several reports of an increased incidence of opportunistic infections in patients treated with fludarabine.[9]

**Lymphoplasmacytoid Lymphoma/Immunocytoma**

**Histology**
The lymphomas described as lymphoplasmacytoid have a diffuse pattern of mature-appearing lymphocytes that demonstrate some differentiation toward plasma cells with the presence of a generous amount of basophilic cytoplasm but with nuclei that resemble those of mature lymphocytes. The nuclei are often eccentrically placed.[1,5] This category specifically excludes neoplasms containing cells with a plasmacytoid appearance but that otherwise fit well into other defined categories. Other entities that occasionally contain lymphocytes with lymphoplasmacytoid differentiation include small lymphocytic, mantle cell, follicle center, and marginal zone lymphomas. Under other classification schemes, lymphoplasmacytoid lymphoma falls into the category of small lymphocytic, plasmacytoid; diffuse mixed small cleaved and large cell (Working Formulation); or immunocytoma, lymphoplasmacytic type (Kiel classification). Table 1 lists selected immunophenotypic findings of lymphoplasmacytoid lymphoma.

**Epidemiology**
Lymphoplasmacytoid lymphoma represents only a very small portion of the total number of cases of non-Hodgkin’s lymphoma. In the National Cancer Institute (NCI)-sponsored study that reported on the Working Formulation, only 5% of lymphomas were lymphoplasmacytoid.[3] As noted above, some tumors that otherwise fit into other categories by immunophenotypic and molecular studies may have a plasmacytoid appearance. It is likely that the true proportion of lymphoplasmacytoid lymphoma is even somewhat lower than 5% if lymphomas that morphologically have a plasmacytoid component but otherwise fit well into other categories are excluded. Median age at diagnosis is approximately 55 to 65 years. The male-to-female ratio, approximately 1.2:1, is similar to that of SLL.[11]

**Clinical Features and Natural History**
Lymphoplasmacytoid lymphoma is a disease of older patients and occurs in the same population as does SLL. The clinical condition is called Waldenström’s macroglobulinemia when accompanied by the presence of high levels of circulating IgM,[12] but other lymphoplasmacytoid tumors may preferentially secrete IgG or IgA. Patients who have Waldenström’s macroglobulinemia often present with signs and symptoms attributable to hyperviscosity or paraproteinemia, including bleeding of the mucous membranes, fatigue, and confusion, and plasma volume expansion possibly resulting in congestive heart failure. At the time of initial evaluation, the disease is usually advanced, and clinically important involvement of extranodal sites, such as the liver, spleen, and bone marrow, is more common than in SLL. Patients often present with generalized lymphadenopathy, and peripheral blood lymphocytosis is seen in up to 30% of patients.

A recent study by Silvestri et al demonstrated evidence of hepatitis C in 30% of patients with lymphoplasmacytoid lymphoma.[13] It is currently not understood what role the hepatitis C virus plays in the disease process, although viral processes are known to be involved in or associated with the pathogenesis of other lymphomas.

Recent reports have linked the t(9;14)(p13;q32) chromosomal translocation to the lymphoplasmacytoid histology, and it appears that this translocation results in the transposition of the PAX-5 gene to a location in close proximity to the IgH locus.[14] The PAX-5 gene is a member of a family of genes that are transcription regulators and that may be involved in lymphomagenesis.

**Management**
Management of lymphoplasmacytoid lymphoma involves the treatment of both the neoplastic process and the associated paraproteinemia as necessary. Treatment of the paraproteinemia has recently been reviewed elsewhere, and treatment of the lymphoma is similar to that of the follicle...
center lymphomas (see discussion below).\[12\] Treatment of the underlying lymphoma is indicated if the associated paraproteinemia is causing a physiologic disturbance, or if the lymphoma is otherwise causing symptoms or organ dysfunction. No therapy has proven to be curative.

**Mantle Cell Lymphoma**

Mantle cell lymphoma is a recently described entity that has received a great deal of attention. In the 1970s, this entity was described as lymphocytic lymphoma of intermediate differentiation. In the 1980s, the term \[mantle zone lymphoma\] was coined, and in the REAL classification the term \[mantle cell lymphoma\] is used.\[1\] In the Working Formulation in the past, this disease has most commonly been included with diffuse small-cleaved, diffuse mixed, or small-lymphocytic lymphoma. In the Kiel classification, mantle cell lymphoma corresponds closely with centrocytic lymphoma.

**Histology**
The cells seen in mantle cell lymphoma are primarily small- to medium-sized, atypical lymphocytes with scant cytoplasm and nuclei that bear indentations and have moderately coarse chromatin. A small number of cases have a \[blastic\] morphology, which refers to larger cells with chromatin that is more open, more prominent nucleoli, and has a variable amount of cytoplasm. At the time of diagnosis, 30% to 50% of mantle cell lymphomas may exhibit nodularity.\[1,5,15\] The degree of nodularity varies, although this nodularity represents an expansion of the mantle zone rather than the germinal center. Cases with a more nodular appearance may represent an earlier stage of the disease process, as serial biopsies disclose a pattern of decreasing nodularity. Transformation to blastic histology may be seen on serial biopsy specimens, although this is different than the transformation to large cell lymphoma seen with other entities.\[1,5,15\] Selected immunophenotypic features of mantle cell lymphomas are given in **Table 1**.

**Epidemiology**
Mantle cell lymphoma represents 2% to 10% of non-Hodgkin's lymphomas. This is a disease of older patients, with a median age at diagnosis of approximately 60 to 70 years. Some of the variability in incidence in different reports may be due to difficulties in recognizing this entity and the previous absence of a specific category for mantle cell lymphoma, particularly in the Working Formulation. There is a male predominance of approximately 4:1. However, a wide range male-female ratios have been reported in numerous series.\[15-18\]

**Clinical Features and Natural History**
Mantle cell lymphoma carries a poorer prognosis than the other lymphomas described in this review, and, for that reason, it may not belong with the indolent lymphomas. However, since it has often been grouped with other indolent subtypes based on histology, it will be included in this discussion. The median survival of patients with mantle cell lymphoma ranges from 3 to 4 years in most series.\[15-18\] At presentation, 90% of patients have advanced (stage III or IV) disease and 40% have B-symptoms. Generalized lymphadenopathy and splenomegaly are commonly seen. In the spleen, the pattern is that of an expansion of the white pulp by the atypical lymphoid cells. Marrow involvement, usually with a diffuse interstitial or a paratrabecular nodular pattern, is present in 80% of cases, and there is a peripheral lymphocytosis in 30%. Approximately 20% of patients have gastrointestinal tract involvement, and 10% of patients have involvement of Waldeyer's ring. Mantle cell lymphoma may occasionally present as lymphomatous polyposis of the intestine.\[15\] Liver involvement is also seen frequently. Numerous studies have attempted to define prognostic factors. There is some evidence that a greater degree of nodularity confers a better prognosis. Also, overexpression of p53 appears to be associated with a significantly poorer prognosis.\[19\] The rarely seen \[blastic\] histology has been associated with a life expectancy of less than 2 years.\[15\] Other poor prognostic indicators include advanced age, presence of B-symptoms, elevated lactate dehydrogenase (LDH), high mitotic rate, and marked lymphocytosis.\[15-18\]

**Cytogenetics and Molecular Biology**
The hallmark genetic lesion is the t(11;14) translocation, which has been studied in great detail recently. This translocation results in the transposition of the bcl-1 locus on chromosome 11, which brings it into apposition with the IgH gene on chromosome 14, resulting in the overexpression of CCND1, the gene encoding for cyclin D1 protein.\[15\] Overexpression of this protein results in shortening of the G1 phase and continuation of cell cycling. This probably occurs through multiple mechanisms, some involving interactions between cyclin-dependent kinases and the tumor-suppressor retinoblastoma protein, the transcription-regulating effect of which is diminished by cyclin-dependent kinase phosphorylation.
Management

Chemotherapy
The results of treating mantle cell lymphoma are entirely unsatisfactory, and consequently, the treatment of choice is unsettled. Based on a retrospective review of two studies involving 562 patients, Teodorovic et al found 64 patients treated with one of four protocols designed for low- or intermediate-grade non-Hodgkin’s lymphomas.[20] Of these 64 cases, 29 were treated as intermediate- or high-grade lymphoma with aggressive combination chemotherapy and 35 were treated as low-grade lymphoma. The patients in the intermediate-grade study were treated with two separate combinations, each containing cyclophosphamide, doxorubicin, an epipodophyllotoxin, vincristine, and prednisone, plus various other drugs. The patients in the low-grade study were treated with CVP and those with responsive or stable disease were randomized to observation or to receive treatment with maintenance interferon. Some patients in both groups received irradiation.

The 29 patients treated on the intermediate/high-grade protocol had an initial response rate of 83%, median duration of response of 21 months, and median survival of 45 months. Patients treated on the low-grade lymphoma study with CVP with or without maintenance interferon had an overall response rate of 60%, an identical median duration of response (21 months), and a median survival of 45 months. The use of interferon did not enhance duration of response or median survival. This retrospective study suggests that aggressive multiagent chemotherapy does not improve outcome when compared with the lower-intensity CVP regimen.

This hypothesis was put to a more direct test by Meusers et al. They randomized 63 patients with centrocytic lymphoma to receive either cyclophosphamide, vincristine, and prednisone (CVP; 37 patients) or CVP plus doxorubicin (CHOP; 26 patients).[21] There were no significant differences between the CVP and CHOP arms with regard to complete response (41% vs 58%), partial response (43% vs 31%), or median survival (32 vs 37 months).

These investigators concluded that anthracycline-based therapy did not significantly improve overall response rate or survival when used as part of first-line treatment for this disease.

There are limited studies of new drugs in mantle cell lymphoma. The early results of small series indicate that fludarabine has some activity in this disease. Decaudin et al reported a response rate of 27% in a series of 15 patients, 13 of whom had received previous treatment.[22] Kaufman et al reported a response rate of 53% (3 complete and 5 partial responses) in a series of 15 previously untreated patients.[23]

Thus, it is not clear whether initial aggressive treatment of mantle cell lymphoma is more effective, but it is certainly more toxic. Although not extensively studied, survival data seem to indicate that treatment with less intense chemotherapy gives similar results to those obtained with higher-intensity regimens.

The issue of whether asymptomatic patients should merely be observed has not been directly addressed in the literature. However, anecdotal evidence suggests that this strategy may be of use in selected patients. Whichever course is chosen, patients with mantle cell lymphoma do not do well as a group, and to date no curative therapy has been discovered. In most cases, management will consist of a series of treatments repeated over the course of the disease. These patients, now generally recognized with ease, are good candidates for carefully planned clinical trials.

Bone Marrow Transplantation
Some patients with mantle cell lymphoma have been treated with autologous bone marrow transplantation. Early results of small series reveal good response rates, but cure or prolongation of survival has not been established. Nademanee et al reported on five patients treated with autologous transplantation as consolidation therapy during first remission. All patients were alive and disease free with follow-up of 2 to 24 months.[24]

In a series of 14 patients treated with autologous transplantation as consolidation therapy, Surbiguet et al obtained a 30-month overall survival rate of 80% and 30-month failure-free survival rate of 63%.[25] Of eight patients who had had a partial response prior to the procedure, seven achieved a complete response with high-dose therapy.

Thus, bone marrow transplantation holds some promise in mantle cell lymphoma, but patients offered a transplant should be treated on clinical trials.

Nodal and Extranodal Marginal Zone Lymphomas

Marginal zone B-cell lymphomas have generated a good deal of confusion recently with regard to classification. Monocytoid B-cell lymphoma and MALT lymphoma share a number of features, including histologic appearance and immunophenotypic characteristics, that would indicate that they may be different manifestations of similar disease processes. Accordingly, the REAL classification...
groups them together under one category, marginal zone lymphoma.[1] Within the Kiel classification, these would be classified under the monocytoid B-cell, immunocytoma, or centroblastic/centrocytic or centrocytic categories. Under the Working Formulation classification, these tumors would fall under the small lymphocytic or the diffuse or follicular small cleaved or mixed categories.[1-3,5]

**Histology**

There are two basic types of marginal zone lymphomas: extranodal and nodal.[1] The majority of the extranodal sites are associated with epithelial tissue and may properly be called MALT-type lymphoma. The most common epithelium-associated sites are the stomach, lung, salivary glands, and other areas of the upper aerodigestive tract.[26-29] Other marginal zone lymphomas may not be associated with epithelial tissue and may be best called extranodal marginal zone lymphomas. The provisional subtype of nodal (± monocytoid B-cells) may be employed if there is no associated extranodal component, but some of these nodal presentations may represent extension of primary extranodal disease. Both the nodal and extranodal marginal zone tumors are characterized by a good deal of cellular variability, with the presence of marginal zone cells, monocytoid B-cells, small lymphocytes, and plasma cells.[1,4,5] Occasional large cells are also seen. Follicular and diffuse patterns can be present, and some follicles are reactive, in which case, the neoplastic cells often inhabit the marginal zones and interfollicular areas. In epithelial tissues, invasion of the epithelium is seen, resulting in the typical lymphoepithelial lesion characteristic of the MALT lymphomas.[1,4,5] Immunophenotypic features are similar for the nodal and extranodal tumors. Selected specific features are presented in **Table 1**.

**Epidemiology**

The epidemiology of the MALT lymphomas is unique. Occurrence in the stomach is associated with **Helicobacter pylori**, and occurrence in other extranodal sites is often related to autoimmune disease.[16,26-29] Montalban et al reported on a series of 84 patients with low-grade gastric MALT lymphoma and found that 67% were male and the median age at diagnosis was 56 years.[26] In this series, 63% of patients had stage I disease and only 15% had marrow involvement. An association with **H pylori** was documented in 75% of these cases. Nongastric MALT lymphomas have a female predominance and have not been demonstrated to be associated with **H pylori**.

The epidemiology of the marginal zone lymphomas other than the gastric MALT type is somewhat different. Nongastric marginal zone lymphomas have been shown to be associated with autoimmune disease, in particular, Sjögren's syndrome, may have a lower male-to-female ratio (approximately 1:2), and may less commonly present at an early stage. Overall, the median age at diagnosis for the marginal zone lymphomas is the 50s and 60s.[16,27-29]

**Clinical Features and Natural History**

The natural history of the marginal zone B-cell lymphomas is generally indolent, particularly in the case of the gastric MALT lymphomas. In over 80% of cases, MALT lymphomas are stage I at presentation. Nodal marginal zone lymphomas are more often diagnosed at a more advanced stage, with only approximately 50% of these patients having stage I disease. In addition, up to 50% of patients with nodal marginal zone lymphomas will develop marrow involvement at some point during the course of their disease. However, overall, these patients are diagnosed at an advanced stage less commonly than others discussed in this review.

The 5-year survival rate for patients with early-stage MALT lymphoma is 80% to 100%, and a large proportion of treated patients remain disease free during this time. In contrast, the nodal marginal zone B-cell lymphomas which more commonly present in advanced stages have a worse outcome, with a 5-year survival rate of approximately 50%.[16,26-31]

**Management**

Gastrectomy, radiotherapy, and chemotherapy have all been used in the treatment of low-grade gastric lymphoma. New evidence dealing with the association of gastric MALT and **H pylori** has substantially changed the approach to treatment. As mentioned above, gastric MALT lymphomas are closely linked to the presence of **H pylori**, and this organism is present in the majority of cases. **Antibiotic Therapy** Based on reports of regression of lymphoma in association with the treatment of **H pylori** infection, Bayerdorffer et al initiated a study to determine the effects of eradication of **H pylori** on this disease.[32] In the original study, 33 patients with primary low-grade gastric MALT lymphoma were treated with omeperazole (Prilosec) and amoxicillin, resulting in the successful eradication of **H pylori**. All patients were stage I, 70% of patients had complete regression of tumor, and 12% had partial regression of tumor. Of the patients who did not respond, four were found to have a higher-grade histology at the time of resection. During median follow-up of 12.5 months, no
patients had a relapse of low-grade gastric MALT lymphoma, but one patient was found to have a high-grade lymphoma of the nasal concha.

An update of this study was presented recently, encompassing a total of 50 patients with a median follow-up of 1.5 years.[33] There have been no further histologic recurrences; however, molecular analysis has shown that a number of patients harbor residual monoclonal cells. Roggero et al also demonstrated the regression of H pylori-associated MALT lymphoma after treatment of the infectious agent.[34] Of 26 patients with low-grade gastric MALT lymphoma treated for H pylori, 60% responded with complete or near-complete regression of their tumors. Long-term follow-up was not included in this report.

These studies suggest that antibiotic therapy may be the initial treatment of choice for patients with Helicobacter-associated gastric MALT tumors in which rapid tumor regression is not necessary. The long-term results of this approach are not yet clear, however.

**Surgery or Chemotherapy** Patients with gastric MALT lymphomas may also be treated surgically or with chemotherapy. Ruskone-Fourmestreaux reported the results of a study of 28 patients with low-grade gastric lymphoma who initially underwent attempted resection, followed by 11 cycles of CVP therapy.[30] The overall 5-year survival rate was 81% and 4-year disease-free survival rate was 68%.

A recent study by Hammel et al compared the efficacy of low-intensity chemotherapy with single-agent cyclophosphamide or chlorambucil in low-grade gastric MALT lymphoma.[31] A total of 17 patients with stage I disease and 7 with stage IV disease were treated with daily low-dose chlorambucil or cyclophosphamide for 8 to 24 months. Responses were seen in 100% of the patients, and complete responses in 75%. During a median follow-up period of 45 months, five of these patients have relapsed. The fact that over 80% of these patients had evidence of H pylori infection indicates that low-intensity chemotherapy is effective in the setting of Helicobacter-associated MALT lymphomas as well.

Thus, antibiotic therapy appears to be effective for Helicobacter-associated MALT lymphoma. Low-intensity chemotherapy and resection are also effective, but surgery is certainly more invasive and not obviously superior to the other approaches. In asymptomatic patients with H pylori-associated gastric MALT tumors in whom there is no need for rapid response, an initial trial of antibiotic therapy under close monitoring is a reasonable approach. The long-term results of this treatment are unknown, however.

**Follicle Center Lymphoma**

**Histology**

The cells of follicle center lymphomas are derived from the germinal center cells of the normal lymph node. This category in the Working Formulation encompasses three different tumor types: follicular predominantly smallcleaved, follicular mixed small-cleaved and large-cell, and follicular predominantly large-cell.[2] In the Kiel classification, these tumors are included within the centroblastic/centrocytic and follicular centroblastic classifications.[3] The provisional subtype diffuse, predominantly small cell was added to the REAL classification because there are some tumors that contain cells that appear to be derived from the follicle center cells but do not have a follicular arrangement on biopsy. Despite this, immunophenotyping and molecular studies indicate a follicle center cell origin, and for now these tumors should be grouped with the other tumors of follicle center cell or germinal center origin.[1]

The follicle center cell lymphomas have been provisionally divided into grades. The term grade had different meanings in the context of previous discussions of the non-Hodgkin’s lymphomas, but in the context of the REAL classification, the term refers to cytologic grade only and is determined primarily by the relative proportions of centroblasts and centrocytes. Used in this sense, grade does not imply a general clinical course, as it does when used in the context of the Working Formulation. All follicle center cell lymphomas contain centrocytes, which are small, cleaved follicle center cells, and centroblasts, which are larger noncleaved cells. The centroblasts are usually in the minority; however, the variability seen in the proportions of cell types determines the grade of the tumor, as noted above.

At present, there are no universally accepted standards that define the three grades, although Harris and Ferry have recommended a method of grading these tumors that incorporates features of work previously published by Lennert [35] and by Mann and Berard.[36] Harris and Ferry recommend that the small cleaved cell grade include tumors in which the cleaved cells or centrocytes are £ 8 mm in size and that have an average of less than 5 large cells per high power field.[37] The mixed small
and large cell category includes tumors with 5 to 15 large cells per high power field, or tumors with centrocytes ≤ 8 mm. The large cell category includes tumors with greater than 15 large cells per high power field or the presence of small cleaved cells that are greater than 8 mm in size with atypical features. The cells generally demonstrate a follicular pattern on examination; however, there is variability in the degree of nodularity.[1,3-5,37] The extent to which the degree of nodularity is associated with prognosis is unsettled. Selected immunophenotypic findings are listed in Table 1.

Epidemiology

The follicular or follicle center cell histology accounts for up to 40% to 45% of non-Hodgkin’s lymphomas in North America. The frequency in considerably lower in Asia.[1,3-5,37] Follicle center cell lymphoma is a disease of adults, and incidence increases with age. Median age at diagnosis is approximately 55 years, but this is from treatment studies, and the actual median age is likely to be higher. The male-female ratio is approximately 1:1, but there may be a tendency for the predominantly large cell gradation to show a male preponderance.

Clinical Features and Natural History

Tumors comprised of small cleaved cells generally progress slowly, but tumors with predominantly large cell histology may be more rapidly progressive. The majority of patients present with advanced disease, and involvement of the marrow, either grossly or as detected by molecular techniques, is very common at the time of diagnosis. At presentation, 80% of patients have stage III or IV disease. The spleen, as well as other extranodal sites, may be involved.[1,3-5,37] Coiffier et al recently reviewed prognostic factors for the follicular lymphomas.[38] This paper discusses multiple characteristics that have a negative influence on prognosis, including advanced age or stage, poor performance status, B-symptoms, bulky tumor, number of extranodal sites, anemia, and high serum LDH, or beta-2-microglobulin. These are similar to prognostic factors identified for other types of non-Hodgkin’s lymphomas. In their long-term follow-up of patients included in the Working Formulation study, Simon et al noted that response to therapy was similar in patients with the three different subtypes of follicular lymphomas, but that patients with the follicular large cell subtype had a consistently decreased survival when compared with the other subtypes.[39] Median survival for the follicular small cleaved, follicular mixed, and follicular large cell subtypes in the original subjects of the Working Formulation study were 7, 5, and 3 years, respectively.[3]

Tumor bulk is associated with prognosis; however, there is currently no well-accepted measure of this parameter.[40] Massive marrow involvement with peripheral cytopenias and the presence of large numbers of circulating neoplastic cells denote a poorer prognosis. Most recent studies have shown a longer overall and progression-free survival in patients who achieve a complete response to therapy.[38] Whether this is an effect of chemotherapy or an inherent quality of tumors that respond better is unclear. It does not necessarily follow that increasing the intensity of chemotherapy to achieve a complete response will result in improved survival. Transformation to a more aggressive histology occurs with the follicular lymphomas, and 25% to 35% of patients exhibit transformation by 10 years.[41]

Cytogenetics and Molecular Biology

The cytogenetics and molecular biology of follicle center cell tumors have been the subject of a great deal of recent interest.[42] The t(14;18) translocation is seen in the majority of these cases. This translocation involves the rearrangement of the bcl-2 gene, bringing it into apposition with the IgH sequences, with resultant increased production of the Bcl-2 protein. The increased Bcl-2 protein levels presumably prevent apoptosis and allow accumulation of the neoplastic cells.

Management

The approach to managing patients with follicular lymphomas is dictated, to some extent, by the histology, including grade, and by the stage of disease at presentation. Multiple strategies have been used in the past, ranging from initial observation, with treatment reserved for symptomatic or threatening disease only, to treatment with high-dose chemotherapy and allogeneic or autologous transplantation.

Local Disease

Patients with stage I or II disease are uncommon, comprising less than 15% of all patients with follicular lymphomas. These patients with early-stage disease are often treated with radiation with or without additional chemotherapy. Radiation has been used less frequently in patients with stage III disease.[43,44] Although radiation appears to have a useful role in the setting of localized disease, especially stage I, no randomized trials have compared it with other forms of management. Thus, the relatively favorable outcomes could reflect the extreme indolence of stage I disease rather than the efficacy of treatment.
Indolent B-Cell Non-Hodgkin’s Lymphomas

MacManus and Hoppe retrospectively analyzed 177 patients with stage I or II follicular small cleaved or follicular mixed histology lymphoma who were treated with radiation; 9 of the patients also received chemotherapy.[45] The authors concluded that radiation therapy alone is the treatment of choice for these patients, and that this approach may be curative in a substantial number of cases. Median survival was 13.8 years, with actuarial survival rates of 64%, 44%, and 35% at 10, 15, and 20 years, respectively. Rates of freedom from relapse at 5, 10, and 20 years were 55%, 44%, and 37%, respectively. The continuing rate of relapse raises the possibility that, although these patients do well, many may not be cured.

Evidence from retrospective analyses suggests that the addition of chemotherapy to radiation in patients with early-stage disease may slightly lengthen failure-free survival but not overall survival.[45-47] This supposition was also tested in a randomized trial by Kelsey et al, in which patients with stage I or II indolent non-Hodgkin’s lymphoma were treated with irradiation alone (82 patients) or irradiation plus adjuvant chlorambucil, given over a period of 6 months (66 patients).[48] The two groups did not differ significantly with regard to the rate of relapse, relapse-free survival, or overall survival. The 10-year disease-free survival rate was 28% in the patients treated with radiation alone and 36% in those treated initially with adjuvant chemotherapy. Overall survival rates at 10 years were 52% and 42%, respectively.

**Advanced Disease** The vast majority of patients with follicular lymphomas present with advanced-stage disease, particularly if sensitive molecular techniques are used to analyze the bone marrow or blood. A wide variety of management options are available for these patients, and choosing among them may be difficult.

**Observation** Observation, as opposed to initial therapy, is advocated for many patients who are essentially asymptomatic at presentation, have no real or threatened organ dysfunction due to their lymphoma, and have advanced indolent B-cell non-Hodgkin’s lymphoma. The watch-and-wait strategy is based on the premise that the low-grade lymphomas of advanced stage are indolent and incurable, and that early intervention with chemotherapeutic agents does not improve quality of life or prolong survival. Certainly, it is difficult to demonstrate any survival advantage in disease processes that have such long natural histories and primarily affect an older population.

Horning and Rosenberg reported on 83 patients with follicular lymphoma or SLL who were managed initially with observation.[41] All of the patients had stage III or IV disease. Median follow-up was 50 months, and patients were treated as it became necessary. Of the 83 patients, 51 eventually required treatment, and median time to treatment was 16.5 months for patients with follicular mixed, 48 months for patients with follicular small cleaved, and 72 months for patients with small lymphocytic histology. Median actuarial survival for the entire group was 11 years, spontaneous regression was observed in 19 patients, and transformation to a more aggressive histology occurred in 10 patients. The patients in this study were compared with a population of patients derived from those treated on protocol with various regimens. Actuarial survival rates at 5 years were similar for patients managed with initial observation or early treatment, and there was no detectable difference in the rate of transformation. This study suggests that survival in patients who are observed initially is similar to that in patients treated with a variety of standard approaches, and that treatment may not be required for a substantial period of time from diagnosis. This conclusion was tested more directly in an NCI study involving 104 patients with stage III or IV indolent non-Hodgkin’s lymphoma.[49] This population included patients with indolent nodular and diffuse lymphoma, of whom 60% to 70% had a nodular histology. Forty-four of these patients were randomly assigned to the watch-and-wait arm, in which local radiation was used only as indicated to treat specific problems, and 45 patients were treated with ProMACE-MOPP (prednisone, methotrexate, Adriamycin, cyclophosphamide, etoposide, mechlorethamine, Oncovin, and procarbazine) followed by total nodal irradiation.

Overall survival at 5 years did not differ between the two groups. However, the rate of disease-free survival at 5 years was 51% for the patients treated aggressively vs 12% for the patients managed with initial observation. The median duration of initial remission was more than 45 months. This ongoing randomized study indicates that patients managed initially with close observation have survival patterns similar to those of patients given early aggressive therapy. Together, these studies suggest that there is no significant advantage to treating patients with advanced-stage low-grade B-cell lymphoma with chemotherapeutic agents or irradiation in the absence of symptoms or significant organ dysfunction attributable to the malignant process. More specifically, treatment early in the disease process does not prolong survival, and observation is a reasonable initial approach in these patients.
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Chemotherapy
Various single chemotherapeutic agents and combinations of agents have been tested for efficacy in the treatment of low-grade B-cell lymphomas. The alkylating agents chlorambucil and cyclophosphamide have been most widely studied. Vincristine is often used with cyclophosphamide and prednisone in the combinations of CVP or COP. Trials have also attempted to determine whether higher-intensity regimens are useful in this group of diseases. Some of these trials will be reviewed here.

Dana et al conducted a retrospective study of 415 patients with indolent non-Hodgkin’s lymphoma (83 patients with small lymphocytic histology and 312 patients with follicular small cleaved or follicular mixed histology) treated on three Southwestern Oncology Group (SWOG) protocols.[50] Patients treated with chlorambucil or CVP-based regimens were compared with those treated with a doxorubicin-containing regimen. No difference in survival was seen; overall median survival was approximately 7 years.

Hoppe et al published the results of a small randomized study in which single-agent chemotherapy was compared with combination chemotherapy and with whole-body irradiation in the treatment of advanced stage low-grade lymphoma.[51] A total of 51 patients with advanced indolent lymphoma were randomized to treatment with cyclophosphamide or chlorambucil, CVP, or whole-body irradiation. Patients were treated for at least 2 years and received additional maintenance therapy if they attained a complete response.

Overall, the complete response rate was very high, 64% to 88%, probably reflecting the duration of therapy. There was no difference between the groups with regard to response rate, duration of response, or survival. Actuarial survival at 4 years was 84%, but only 25% of patients did not suffer a relapse.

This relative small study suggests that a low-intensity combination, single-agent therapy, and whole-body irradiation have essentially equivalent efficacy.

Lepage and associates prospectively studied the efficacy of doxorubicin in the treatment of indolent lymphomas.[52] This study enrolled 113 patients, the majority of whom had stage III or IV disease and follicular histology. All patients received COPP (cyclophosphamide, Oncovin, procarbazine, prednisone), and some patients were randomly assigned to receive additional doxorubicin. In addition, patients were given maintenance therapy with CVP or chlorambucil.

The overall complete response rate was 45%. There was no significant difference between the groups with regard to survival (62% at 5 years), progression-free survival (39 months), or the rate of complete responses. This study suggests that the addition of doxorubicin to combination chemotherapy does not improve the outcome of indolent lymphoma, which is in contrast to the remarkable difference seen when doxorubicin is included in regimens to treat intermediate-grade lymphoma.

Response rates in follicle center lymphoma are good for both single-agent alkylator therapy or CVP-type regimens. Higher-intensity chemotherapeutic regimens, including those with doxorubicin, are effective in treating the low-grade B-cell lymphomas, but there is no evidence that their use prolongs survival, except possibly in patients with the follicular large cell and follicular mixed types. In addition, higher-intensity regimens are generally more toxic, and thus, their use as initial therapy is probably not indicated in this population of patients, who tend to be older.

Large Cell Histology
In the Working Formulation, follicular large cell lymphoma is classified among the intermediate-grade lymphomas, and many practitioners treat this disease with multiagent regimens containing doxorubicin, as is the case with other intermediate-grade lymphomas. Anderson et al published a study in which 107 patients with follicular predominantly large cell lymphoma were treated primarily with six to eight cycles of CAP/BOP (cyclophosphamide, Adriamycin or mitoxantrone, procarbazine, bleomycin, Oncovin, and prednisone or dexamethasone) for stage III or IV disease, or two to three cycles of the same combination therapy followed by involved-field radiation therapy for stage I or stage II disease.[53] The complete response rate was 88% for stage I and II patients, the rate of failure-free survival was estimated to be 61%, and the overall survival at 3 years was 76%. In the stage III or IV patients, the complete response rate was 49%. Failure-free survival for stage III or IV patients at 3 years was estimated to be 34% and overall survival at 3 years was estimated to be 61%.

At the NCI, 31 patients with follicular large cell histology were treated with aggressive combination chemotherapy, including 15 patients treated most recently with a Pro-MACE-based regimen.[54] All of these patients had stage III or IV disease, and the complete response rate was 87%. Disease-free survival at 5 years was 29%, and there have been no relapses after 5 years.

Long-term disease-free survival may be possible in patients with follicular large cell lymphoma, and multiagent regimens containing doxorubicin should be considered for patients with this disease.
entity. In addition, evidence from a Cancer and Leukemia Group B (CALGB) study suggests that patients with follicular mixed lymphoma derive a survival benefit from the use of CHOP-bleomycin chemotherapy, when compared with patients treated with single-agent cyclophosphamide.[55] Combination chemotherapy with doxorubicin should be considered for either of these entities.

New Treatment Approaches

**Interferon**
Interferon has some activity in indolent lymphomas, and interest in it increased as the recombinant product became available for clinical trials. The major focus of recent research, however, has been on the use of this agent in combination with chemotherapeutic agents, either as part of induction or maintenance therapy. Table 2 summarizes the results of studies of interferon used in combination with chemotherapeutic agents.[56-63]

As a group, these studies point to the conclusion that interferon maintenance therapy may prolong time to treatment failure, but an effect of this on overall survival remains to be seen. Interferon given in the induction phase of treatment in conjunction with cytotoxic therapy does not appear to greatly increase the response rate. Although studies by Solal-Celigny et al indicate that there may be some prolongation of survival if interferon is used as induction therapy for indolent lymphomas, this has yet to be confirmed in other studies.

**Purine Analogs**
The purine analogs cladribine (2'-chlorodeoxyadenosine, or 2-CDA [Leustatin]) and fludarabine have established efficacy in the treatment of relapsed indolent non-Hodgkin's lymphomas. In previously treated patients, cladribine therapy has produced overall response rates of 43% to 75% with complete response rates of 14% to 38%. Similarly, overall response rates of 39% to 72% with complete response rates up to 20% have been seen in patients treated with fludarabine.[9] The results of a small number of trials have been reported in which fludarabine or cladribine has been used as initial therapy in previously untreated patients.[64-67] As shown in Table 3, the results of these trials indicate good overall response rates with complete response rates of 18% to 37%. However, as seen in the last column of Table 3, the responses are not durable, and no impact on survival has been demonstrated. Thus, although the purine analogs have activity and can be used in the setting of resistant disease, their role has yet to be defined, and their use as first-line agents has not been established.

**Bone Marrow Transplantation**
Despite initial optimism, the role of bone marrow transplantation in indolent lymphoma has not been established. Bone marrow transplantation has been studied in the indolent B-cell malignancies, but the results of studies have not matured sufficiently in comparison to the long natural history and course of these diseases.

Schouten et al retrospectively analyzed 92 patients treated with autologous transplantation for whom median follow-up was 19 months.[68] The patients were treated with various conditioning regimens, and some patients received purged marrow. Overall, the progression-free survival rate was projected to be 52% at 5 years. In this group, there was no discernible effect of either marrow purging or mode of conditioning, but poorer results were seen in patients with resistant or refractory disease.

Rohatiner et al reported on a series of 121 patients with follicular lymphoma who were treated with autologous bone marrow transplantation as consolidation treatment during second or subsequent remission.[69] Median follow-up in this series was 2.5 years. There were four treatment-related deaths, and seven additional patients have been subsequently diagnosed with acute myelogenous leukemia (AML) or myelodysplastic syndrome (MDS).

The patients in this study were compared with historical controls. Patients treated with autologous bone marrow transplantation fared better with regard to freedom from progression; however, there was no difference in survival at this early point in analysis (median follow-up, 2.5 years).

Bierman et al described a series of 141 patients with relapsed or refractory follicular lymphoma or composite lymphoma who were treated with autologous transplantation.[70] Failure-free survival at 4 years is projected to be 40% to 45% for follicular small cleaved and follicular mixed histology and 14% for follicular large cell histology.

An update of this study that included 100 patients was recently published. These patients had follicular small cleaved cell and follicular mixed histology, with a few patients displaying some areas of diffuse involvement.[71] Median follow-up was 2.6 years, and overall survival at 4 years was estimated to be 65%, with a failure-free survival rate of 44%. A pattern of continuous relapse was
seen with no plateaus in the failure-free survival curve. Various other studies have shown that there is a high overall complete response rate with the high-dose therapy that can be delivered, as would be expected for these generally chemosensitive diseases. The early death rate from complications of autologous transplantation has been relatively low as well, generally in the 3% to 7% range. It is still unclear whether cure has been attained with this mode of therapy, however, as there have not been enough patients treated with sufficient follow-up to determine this.

Also, patients with indolent B-cell malignancy are generally elderly and may be less tolerant of aggressive therapy. It is becoming apparent that late effects of therapy, such as MDS and AML, may develop in a significant number of patients treated with high-dose chemotherapy and autologous bone marrow transplantation. Questions that remain to be answered include: (1) whether a substantial number of patients are cured with transplant; (2) what the optimal conditioning regimen may be; (3) what the best time for transplant may be; and (4) whether bone marrow purging is a beneficial procedure. Further clinical trials, as well as mature data from current trials, are needed before these questions can be answered.

There have also been a few patients with indolent lymphoma who have been treated with allogeneic bone marrow transplantation. The numbers of patients and length of follow-up make it difficult to assess the utility of this form of treatment. van Besien et al described a small series of 10 patients who underwent allogeneic HLA-identical sibling bone marrow transplantation.[72] Of these 10 patients, 8 achieved a complete response and 2 died of early complications. The responders have remained disease free with a median follow-up of 816 days.

**Conclusions**

The indolent non-Hodgkin’s B-cell lymphomas are a diverse group of disorders that vary substantially in presentation and natural history. There is still a great deal to be learned about the basic biology of these disorders, as well as the treatment options. A number of variables influence the type of management used for each individual case, including the disease entity and stage, symptoms and real or threatened organ dysfunction, patient age, and medical condition, as well as preferences of the patient and practitioner. Unfortunately, because of the inadequacy of current treatment, most patients will not be cured, and continued investigation in the laboratory and through carefully designed clinical trials is essential.

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