What Is New in Lymphoma?

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ABSTRACT The lymphomas are a diverse group of malignant disorders that vary with respect to their molecular features, genetics, clinical presentation, treatment approaches, and outcome. Over the past few years, there have been major advances in our understanding of the biology of these diseases, leading to a universally adopted World Health Organization classification system. New therapies are now available with the potential to improve patient outcome, and the International Prognostic Index and standardized response criteria help make clinical trials interpretable. Most notably, the chimeric antiCD20 monoclonal antibody rituximab has altered our therapeutic paradigms for B-cell disorders. Combinations of this antibody with chemotherapy and other biologic agents have shown promise in treating lymphoma. Other antibodies, radioimmunoconjugates (such as Y-90 ibritumomab tiuxetan and I-131 tositumomab), and oblimerson sodium (a BCL-2 antisense oligonucleotide) have all shown promise. New chemotherapy regimens such as bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone (BEACOPP), agents such as gemcitabine, and monoclonal antibodies directed against CD30 are also being studied in Hodgkin Lymphoma. The challenge of clinical research is to optimize the use of these agents, select patients most likely to respond, and develop multitargeted strategies based on sound scientific rational, with the potential to increase the cure rate of patients with lymphomas. (CA Cancer J Clin 2004;54:260–272.) © American Cancer Society, Inc., 2004.

Lymphomas represent about 4% of the new cases of cancer diagnosed in the United States each year, making them the fifth most common cancer diagnosis and the fifth leading cause of cancer death. An estimated 62,250 people will be diagnosed with lymphoma in 2004, of which 54,370 are non-Hodgkin Lymphomas (NHLs), with the remainder being Hodgkin Lymphoma (HL). In fact, while the incidence of most cancers is decreasing, lymphoma is one of only two tumors increasing in frequency, although the cause for this increase is unknown.

NON-HODGKIN LYMPHOMA

Classification

The NHLs represent a clinically diverse group of diseases of either B-cell or T-cell origin. For several decades, they were classified according to the International Working Formulation which was primarily based on morphologic appearance and, to a lesser extent, clinical behavior. In 1994, the Revised European–American Lymphoma (REAL) Classification distinguished lymphomas not only by histology, but by immunophenotypic, genetic, and clinical characteristics. This system was further modified as the now universally accepted World Health Organization (WHO) classification (Tables 1, 2).

Prognosis

In general, the NHLs are divided into diseases that are indolent, aggressive, and very aggressive. However, even within histologic subtypes, patients vary considerably with regard to outcome. In 1993, the International Prognostic Index (IPI) was published, which was developed using data from a large number of similarly treated patients with diffuse large B-cell NHL. Based on age, performance status, serum lactate dehydrogenase (LDH), number of
extranodal sites of involvement, and stage, patients could be separated into clinically distinct groups. More recently, a similar system has been developed for follicular lymphomas, referred to as the Follicular Lymphoma IPI (FLIPI). Newer technologies, such as DNA microarray analyses that identify genes that are either overexpressed or underexpressed by the malignant cells, have further distinguished patients into distinct risk groups even within histology. For example, there appear to be at least two subcategories of diffuse large B-cell NHL, a germinal center B-cell type and a less favorable activated B-cell type that behave very differently, even within IPI categories.

**TABLE 1** World Health Organization Classification of B-Lymphoid Neoplasms

| Precursor B-cell neoplasms |
|----------------------------|
| Precursor B-lymphoblastic leukemia/lymphoma |
| Mature (peripheral) B-cell neoplasms |
| B-cell chronic lymphocytic leukemia/small lymphocytic lymphoma |
| B-cell prolymphocytic leukemia |
| Lymphoplasmacytic lymphoma |
| Splenic marginal zone B-cell lymphoma |
| Hairy cell leukemia |
| Plasma cell myeloma/plasmacytoma |
| Extramedullary plasmacytoma |
| Extramedullary plasmacytoma of MALT type |
| Nodal marginal zone B-cell lymphoma |
| Follicular lymphoma |
| Mantle-cell lymphoma |
| Diffuse large B-cell lymphoma |
| Burkitt’s lymphoma |

*Common entities are shown in boldface type.

**TABLE 2** World Health Organization Classification of T- and NK-Lymphoid Neoplasms

| Precursor T-cell neoplasm |
|----------------------------|
| Precursor T-lymphoblastic lymphoma/leukemia |
| Mature (peripheral) T-cell neoplasms |
| T-cell prolymphocytic leukemia |
| T-cell granular lymphocytic leukemia |
| Aggressive NK-cell leukemia |
| Adult T-cell lymphoma/leukemia |
| Extramedullary NK/T-cell lymphoma, nasal type |
| Enteropathy-type T-cell lymphoma |
| Hepatosplenic gamma-delta T-cell lymphoma |
| Subcutaneous panniculitis-like T-cell lymphoma |
| Mycosis fungoides/Sezary syndrome |
| Peripheral T-cell lymphoma, not otherwise characterized |
| Angioimmunoblastic T-cell lymphoma |
| Anaplastic large-cell lymphoma |

*Common entities are shown in boldface type.

**Advances in the Treatment of Follicular NHL**

The follicular lymphomas are the most common subtype of indolent NHL, representing about 30% of NHLs. They are characterized by an indolent clinical course with a median survival of 6 to 10 years. Only about 10 to 15% of patients present with limited (Stage I or nonbulky Stage II) disease. For those patients, radiation therapy may result in prolonged disease-free survival. Whether or not they are cured is controversial since relapses occur even after 10 to 20 years.

Until recently, no particular treatment clearly prolonged the survival of patients with advanced stage follicular NHL. As a result, a watch-and-wait approach was routinely recommended until treatment was clinically indicated because of disease-related symptoms, massive lymphadenopathy or hepatosplenomegaly, potential organ compromise, or peripheral blood cytopenias related to bone marrow involvement.

Despite decades of clinical research, there is still no consensus as to the optimal initial therapy for follicular and low-grade NHL. Neither an alkylating agent alone or combined with vincristine and prednisone (eg, CVP), CVP with doxorubicin (CHOP), nor fludarabine-based regimens produce a clear survival advantage over any other.

**Rituximab**

The availability of active monoclonal antibodies has revolutionized our approach to indolent B-cell malignancies (Table 3). Rituximab, a chimeric anti-CD20 monoclonal antibody was originally studied in patients with relapsed and refractory follicular and low-grade NHL. In the pivotal trial of 166 patients, a dose of 375 mg/m² weekly for four weeks was associated with responses in almost half of patients (including 6% complete remissions) with a duration of response of about 11 months. This antibody has been widely adopted because of its activity and favorable toxicity profile. Most adverse reactions occur during the infusion and consist primarily of fever and chills, with occasional hypotension.
Recent clinical trials have attempted to improve on the activity of rituximab. Increasing the number of weekly infusions from four to eight, delivery of higher doses, and increased dose density have all been unsuccessful in this regard. Higher overall response rates have been observed with rituximab as initial therapy, however, the duration of response has been disappointing.

The possible benefit of maintenance therapy has also been evaluated in an attempt at prolonging the time to disease progression. Hainsworth et al. treated 62 patients with follicular and low grade NHL using four weekly doses of rituximab followed by four additional doses every six months for two years. The time to progression of 32 months was longer than expected. In a randomized trial, Ghielmini et al. reported previously treated and previously untreated patients who received four weekly doses of rituximab, followed by a randomization to no further therapy or maintenance consisting of a single infusion of rituximab every two months for a total of eight months. The time to progression was significantly longer in the group that received maintenance; however, this benefit was primarily restricted to the previously untreated group.

The role of maintenance is confounded by the observation that 40% of patients who have experienced an initial response lasting at least six months will respond a second time, with a duration of response at least as long as the initial response. Therefore, an important question is whether it is preferable to deliver maintenance or to treat disease progression instead. Hainsworth et al. attempted to answer this issue in a study in which patients who were treated with an initial four weeks of rituximab were then randomized to maintenance therapy, as previously published, or to retreatment on recurrence. Although response rates and time to progression favored the maintenance arm, the time to which another treatment other than rituximab was required was similar (31 months versus 27 months). The Eastern Cooperative Oncology Group (ECOG) rituximab extended schedule or retreatment trial is comparing treatment until relapse with retreatment at the time of recurrence. Therefore, at the present time, the preferable approach is not clear.

In vitro studies suggest that monoclonal antibodies such as rituximab can sensitize lymphoma cells to the effects of subsequent chemotherapy. These observations have been supported by numerous reports in which results with rituximab plus chemotherapy appear superior to what would be expected with chemotherapy alone. The first of these regimens was reported by Czuczman et al. in which 38 patients, 31 of whom were previously untreated, received CHOP plus rituximab. The overall response rate was 100%, with 58% complete remissions and a median time to progression of 8.3 years. Comparable response rates can be achieved with a variety of other rituximab–based chemotherapy regimens (Table 3). For example, Czuczman et al. have also reported on the combination of fludarabine plus rituximab with a response rate of 93% and 80% complete responses. However, any differences in complete or overall response rates among the various regimens may be related to patient selection or the point in time when response is assessed, as maximal responses may occur several months following therapy.

Recent randomized trials have shown superiority for rituximab-containing regimens over chemotherapy alone. The German Low Grade Lymphoma Study Group conducted a randomized study of 394 patients who were allocated to either CHOP or R-CHOP, with a secondary randomization to a variety of postremission therapies. There was no advantage from rituximab in response rate (97% versus 93%), but the combination was associated with longer...
event-free survival and a trend toward longer overall survival. The variety of postremission therapies makes these data difficult to interpret.

Marcus and coworkers reported on 322 patients with either intermediate or poor risk follicular NHL who received CVP either alone or with rituximab (R-CVP). The overall response rate and complete response rates for the combined modality therapy were 81% and 40%, respectively, versus 57% and 10% for CVP alone. With a median follow-up of 18 months, the R-CVP patients had a significantly longer median time to treatment failure of 27 months, versus 7 months for CVP. In addition, the median time to treatment progression was not reached for R-CVP, compared with 113 months for CVP alone. Whether an eventual prolongation in survival will be achieved with any of these regimens remains to be demonstrated by longer follow up. Thus, a clinical trial remains the preferred option for the initial therapy for patients with follicular or low-grade NHL. In the future, the optimal treatment may be determined by clinical and biological characteristics of individual patients.

However, it is clear that not all patients respond to rituximab nor benefit from the addition of that antibody to chemotherapy regimens. Patients most likely to respond can be predicted by polymorphisms for FcR gamma III, which represent the binding site for the rituximab antibody, and DNA microarray signatures. Moreover, the benefit of rituximab appears to be limited to patients whose tumors overexpress the BCL-2 gene. Whether these observations will determine which patients will receive rituximab remains to be seen.

Other Monoclonal Antibodies

Other unconjugated antibodies being evaluated include epratuzumab, apolizumab, alemtuzumab, galiximab, and several humanized anti-CD20 antibodies; however, a major role for any of these in NHL is uncertain at present. Alemtuzumab (Campath-1H) is a humanized monoclonal antibody directed against the CD52 antigen, whose exact function remains unknown; it is expressed on the surface of all lymphocytes, monocytes, macrophages and eosinophils. Although alemtuzumab appears to be very active in chronic lymphocytic leukemia as well as T-cell lymphomas, its activity in B-cell NHL is disappointing with partial responses of 14%. Epratuzumab is a humanized IgG1 monoclonal antibody directed against the CD22 antigen, expressed in a variety of lymphomas. In a dose escalation study of epratuzumab in 55 patients with indolent NHL, no dose limiting toxicities were identified. The overall response rate was 24% in patients with follicular histologies. However, results from a subsequent trial designed to evaluate the combination of rituximab and epratuzumab was disappointing, suggesting that a suboptimal dose and schedule of these agents was selected.

Apolizumab (Hu1D10, Remitogen) is a humanized monoclonal antibody directed against a polymorphic determinant of HLA-DR, found on both normal B cells and in about half of patients with lymphoid malignancies. Although Phase I data revealed activity in patients with relapsed or refractory indolent NHL, the Phase II data were disappointing. Furthermore, toxicities including thromboses and hemolytic uremic syndrome have hindered its development.

CD80 is an immune costimulatory molecule present on the surface of NHL cells. Galiximab is a macaque-human chimeric anti-CD80 antibody with in vivo antilymphoma properties, which is actively being studied in patients with refractory NHL. The antibody is well tolerated except for mild fatigue, nausea, and headaches, and has single agent activity of about 15%. Based on preclinical data suggesting synergy, a Phase I/II study of the combination of galiximab and rituximab has recently been completed and is undergoing analysis.

Radioimmunotherapy

Despite the encouraging results with rituximab, all patients eventually become resistant to this agent. A number of reasons have been proposed including inadequate serum concentrations, loss of expression of CD20, and inaccessibility of the tumor cells to the antibody. One attempt to overcome these problems is the use of radioimmunotherapy (RIT), in which a
monoclonal antibody is conjugated to a radioisotope. RIT kills not only cells to which the antibody is bound, but as a result of a cross fire effect, also kills neighboring cells that may not express the antigen or which are inaccessible to the monoclonal antibody.

Two radioimmunoconjugates are currently commercially available. Y-90 ibritumomab tiuxetan (Zevalin) is a murine rituximab conjugated to Y-90. The Zevalin regimen takes about eight days to administer. On the first day, a dose of cold (nonradioactive) anti-CD20 antibody is administered to bind nontumor CD20 sites and to facilitate better biodistribution. Because Y-90 is a beta emitter, it cannot be used for imaging; thus, indium-111 labeled ibritumomab is substituted. Two to three sets of imaging studies are performed at days 0, 2 to 3, and 6 to 7 to ensure appropriate biodistribution. On day 7 to 8, another dose of cold antibody is delivered, followed by 0.4 mCi/kg of Zevalin (not to exceed 32 mCi) for patients with platelet counts of at least 150,000/mm³. The dose is reduced to 0.3 mCi in patients with a platelet count of 100 to 149,000/mm³. The clinical trials thus far conducted with radioimmunoconjugates have demonstrated that they are active (more active than their cold antibody) and are useful in patients who have relapsed after, or who are refractory to, rituximab. The response rate with Zevalin in rituximab failures is reported to be 74% with 15% complete remissions. In a randomized trial, 143 patients with relapsed CD20 positive NHL, without previous rituximab exposure, received either rituximab or Zevalin. Response rates were higher in the Zevalin arm at 80% compared with 56% in the rituximab arm, supporting the additive benefit of the radioisotope. However, there was no difference between the arms in time to disease progression. Responses can also be safely achieved in patients who have mild thrombocytopenia (100 to 149,000/mm³) using a lower dose of Zevalin.

The major complications following Zevalin therapy relate to its myelosuppression which occurs later than with chemotherapy, at around 7 to 9 weeks following treatment. As a result, exclusionary criteria for the use of Zevalin therapy include greater than 25% bone marrow involvement, a hypocellular bone marrow (<15% cellular), platelets <100,000/mm³, neutrophils <1,500/mm³, extensive prior radiation therapy, and prior stem cell transplantation—the latter because the safety in this setting is unknown.

Bexxar is a conjugate of the murine anti-CD20 antibody tositumomab and I-131. Since I-131 is a gamma emitter, dosimetry can be performed to provide patient-specific dosing. As with Zevalin, treatment occurs over about a week. In contrast, thyroid protection is required with Bexxar because of the radioactive iodine. In a multicenter pivotal trial, 60 heavily pretreated patients with NHL received Bexxar, with response rates of 65% with 20% complete response for the group as a whole. Patients with follicular histologies fared better, with an overall response rate of 81%. Response rates and response duration were significantly higher than with their last chemotherapy. In rituximab refractory patients, the response rate has been 63% with 29% complete response. Bexxar was subsequently approved for use in patients with relapsed/refractory follicular or transformed NHL. It has also been safely administered to previously untreated patients, with a response rate of 97% and 63% complete responses. The major toxicity is myelosuppression. Bexxar can be safely administered after CHOP chemotherapy, and converts some partial responses to complete responses. A randomized Phase III of a CHOP followed by Bexxar regimen versus R-CHOP is ongoing within the Southwest Oncology Group (SWOG) and the Cancer and Leukemia Group B (CALGB).

One of the major concerns with RIT is the development of secondary acute myeloid leukemia (AML)/myelodysplastic syndrome (MDS). Published data suggest that the risk is about 1.5% with Zevalin and 6.3% with Bexxar. However, the development of this secondary malignancy likely relates to the prior treatment and may not be greater than expected from chemotherapy alone. Preliminary reports with both Zevalin and Bexxar suggest that patients can tolerate additional therapies; however, the response and toxicity data are not yet available. RIT may also be useful in the stem cell transplant setting. Gopal and coworkers compared their results with follicular lymphoma patients...
who received high dose I-131 tositumomab with those treated using various high dose chemotherapy regimens. They found better overall survival and progression free survival, with lower toxicity in the RIT-treated population.53

Zevalin and Bexxar appear to have comparable activity, and their relative toxicity is being tested in a large Phase III trial. Current research is directed at trying to combine or sequence radioimmunotherapy with chemotherapy and other biologicals.

Other New Agents

**Antisense Oligonucleotides**

Antisense oligonucleotides are chemically modified single-strand DNA molecules that have a nucleotide sequence that is complementary to the target mRNA; therefore, they are capable of inhibiting expression of the target gene. The BCL-2 gene is a potentially important target because it is overexpressed in most follicular B-cell NHLs and chronic lymphocytic leukemias, and in about a quarter of large B-cell NHL. BCL-2 upregulation is thought to be responsible for maintaining the viability of tumor cells, as well as inducing a form of multidrug resistance. Elevated BCL-2 also correlates with poor response to therapy in NHL. These observations, and others, have stimulated interest in exploring an antisense strategy against BCL-2 and other genes important to tumor survival (Table 4).

To inhibit the target mRNA, antisense oligonucleotides must first be incorporated into cells by endocytosis. The oligonucleotide then inhibits gene expression by hybridization with the mRNA, followed by cleavage of the mRNA by recruitment of RNase-H and other endonucleases.

G3,139 (oblimersen sodium; Genasense, Genta Incorporated, Berkeley Heights, NJ) is the first antisense molecule to be widely tested in the clinic for the treatment of human NHLs. G3,139 is a phosphorothioate oligonucleotide consisting of 18 modified DNA bases (ie, 18-mer) that targets the first 6 codons of BCL-2 mRNA to form a DNA/RNA duplex.

In the first Phase I study of G3,139 in 21 patients with NHL,54 one patient with low-grade lymphoma who had progressive disease in nodes and bone marrow after two prior regimens attained a complete response, which has been maintained for longer than three years. Subjective improvement was also noted in the majority of patients who entered the study with tumor-related symptoms.

This BCL-2 antisense is also active in relapsed/refractory patients with mantle cell lymphoma (MCL).55 Side effects primarily include neutropenia, thrombocytopenia, and fatigue. Although the response rate to the single agent is modest, it augments the activity of other agents, such as rituximab, fludarabine and cyclophosphamide; therefore, this drug will have its greatest impact in combination strategies. Such multiagent regimens are currently under clinical investigation.

**Vaccines**

Lymphomas are characterized by their own unique idiotype, the variable region of the immunoglobulin light chain, providing the pos-
sibility for a lymphoma vaccine. In a study from Stanford, 49% of follicular NHL patients treated with this protein, conjugated to an adjuvant such as keyhole limpet hemocyanin (KLH), reacted with a cellular and humoral immune response. The ability to generate such a response appears to correlate with time to tumor progression (7.9 years versus 1.3 years). Three randomized studies are evaluating the clinical benefit of the antidiotype vaccine. In two of these, patients receive chemotherapy, followed by a rest period, and subsequently a series of vaccinations with either antidiotype vaccine plus GM-CSF and KLH, or GM-CSF and KLH alone. In the third trial, rituximab is used as initial treatment, followed by GM-CSF and KLH with or without the antidiotype vaccine.

**Advances in the Treatment of Aggressive NHL**

For decades, CHOP remained the standard regimen for patients with diffuse large B-cell NHL. Using this relatively well-tolerated regimen, about 40% of patients were cured with prolonged follow up. More intensive and aggressive regimens failed to demonstrate an advantage in randomized trials. Rituximab as a single agent was shown to have a response rate of 33% leading to interest in combining this antibody with chemotherapy. In initial studies by Vose and coworkers, the complete and overall response rates to R-CHOP were higher than would be expected with CHOP alone. A marked paradigm shift followed the 2002 publication by the Groupe d’Etude des Lymphomes Agressifs (GELA) group of their randomized trial in 399 patients between the ages of 60 to 80 years with diffuse large B-cell NHL (DLBCL), who received either CHOP alone or R-CHOP given on day 1 of each cycle. The complete response rate (76% versus 63%), as well as event-free and overall survival, significantly favored the combination arm. Although the difference in event-free and overall persists, there is some convergence of the overall survival curves over time. An ECOG, CALGB, and SWOG intergroup study compared CHOP with R-CHOP in 632 patients with diffuse large B-cell NHL over the age of 60 years. The study design also included a secondary randomization to rituximab maintenance or observation. In contrast to the previously published GELA study, there was no difference in response rates, time to treatment failure (TTF) or survival by induction regimen. An unplanned analysis performed to remove the confounding effect of rituximab maintenance suggested a benefit for R-CHOP with respect to TTF and survival noted only in patients who did not receive rituximab during induction. Thus, these studies support R-CHOP as the new standard for patients with diffuse large B-cell NHL.

**Other Drugs for Non-Hodgkin Lymphoma in Clinical Trials**

**Gallium Nitrate**

Gallium nitrate, the salt of the element gallium, was one of the elements tested in the National Cancer Institute (NCI) screening system found to have anticancer activity. Human clinical trials were started in 1976; the drug was found to have a profound hypocalcemic effect and was approved by the Food and Drug Administration for the treatment of hypercalcemia. Gallium has been shown to be a targeted therapy as it localizes to tumor sites, and this finding has been exploited in gallium scans. Initial Phase I and II clinical trials in a variety of malignant lymphomas used brief infusions of the drug and were associated with excessive toxicity, including optic neuritis. As a result, lower doses of the drug were delivered by continuous infusion, with responses in 43% of patients with relapsed and refractory disease. A multicenter Phase II confirmatory trial using contemporary diagnostic and response criteria has just been completed in the United States and is undergoing analysis.

**Bendamustine**

Bendamustine is a bifunctional compound with both an alkylating nitrogen mustard group and a purine-like benzimidazole ring. It was first synthesized in 1963 in the German Democratic
Republic and has been used extensively in Germany since. Bendamustine has demonstrated activity in indolent and aggressive NHL, HL, chronic lymphocytic leukemia, and multiple myeloma. In vitro and clinical data also support a beneficial interaction with rituximab. In a study of 63 patients with relapsed or refractory indolent NHL or mantle cell lymphoma (MCL), the response rate to this combination was 94% with 71% complete remissions. This combination was extremely well tolerated. To better characterize the activity of this agent and to provide broader experience with the agent, it is now being studied alone and in combination with rituximab in Phase II trials in the United States.

**Bortezomib**

Bortezomib (PS-341; Velcade) is a potent, reversible inhibitor of the 26S proteasome, an enzyme important in the intracellular degradation of proteins including those involved in cell cycle regulation, transcription factor activation, apoptosis, and cell trafficking. Notable among these is NF-κB. Bortezomib is the first proteasome inhibitor to be clinically studied and has recently been approved by the Food and Drug Administration for the treatment of relapsed/refractory multiple myeloma. The rationale for a study in NHL is that NF-κB is overexpressed in a number of histologies. In a report from Goy et al. including 51 evaluable patients with a median of 3.5 prior treatment regimens (including eight patients with a prior autologous stem cell transplant), the response rate was 48% in those 23 evaluable patients with MCL, with 26% complete responses. A lower level of 16% was reported in small numbers of patients with other histologies. Toxicities attributed to bortezomib included anemia, leukopenia, neutropenia, thrombocytopenia, fatigue, anorexia, nausea, vomiting, elevated alanine aminotransferase/aspartate aminotransferase, increased creatine phosphokinase (CPK), hypocalcemia, asymptomatic EKG changes (ST-T wave flattening and inverted T waves), and supraventricular arrhythmias (SVT/atrial fibrillation/flutter). A Phase II trial at the NCI is ongoing.

Another histone deacetylase inhibitor, suberoylanilide hydroxamic acid (SAHA), has demonstrated activity in NHL in Phase I trials and is now undergoing Phase II testing.

**Rapamycin Analog**

The macrolide rapamycin (sirolimus, Rapamune, Wyeth-Ayerst, Princeton, NJ) and its derivatives inhibit the mammalian target of rapamycin (mTOR), downregulating translation of specific mRNAs required for cell cycle progression from G1 to S phase. Preclinically, mTOR inhibitors potently suppress growth and proliferation of lymphocytes and tumor cell lines. Today, rapamycin is approved as an immunosuppressive drug for renal transplant
recipients. A related compound, CCI-779 (Wyeth-Ayerst, Princeton NJ) is being developed as a cancer therapeutic. In early studies, activity has been seen in mantle cell lymphoma, but with considerable myelotoxicity. Studies are being designed to explore this agent at more tolerable doses.

HODGKIN LYMPHOMA

HL accounts for 14% of lymphomas with an estimated 7,880 new cases in 2004. Although the etiology of HL is not known, people with a history of infectious mononucleosis have a threefold increased likelihood of developing HL, supporting a role for the Epstein-Barr virus.

Classification

The WHO classification of 1999 recommended changing the name to Hodgkin Lymphoma and proposed two categories: classical HL and nodular lymphocyte predominant HL. Classical HL is subdivided into nodular sclerosis (NS) HL, lymphocyte-rich classical (LRC) HL, mixed cellularity (MC) HL, and lymphocyte depletion (LD) HL. Nodular lymphocyte predominant HL is a unique form of HL that accounts for only 3 to 8% of cases of HL and generally exhibits a nodular growth pattern, with or without diffuse areas, and with rare Reed-Sternberg cells. The atypical lymphocytic and histiocytic (L&H) cells express B-cell antigens such as CD20, but rarely express CD15 or CD30, which are usually found in Classical HL. LPHL is more often localized than disseminated at diagnosis (>70% Stages I or II), exhibits a slowly progressive course, and has an extremely favorable outcome. Mediastinal masses are noted in fewer than 20% of cases. Although survival tends to be long, late relapses are more common than in other histologies, and 35% progress to a large B-cell NHL. Recent reports suggest activity for rituximab in patients with relapsed NLPHL with response rates up to 86% in one series, half of which are complete and many appear to be durable. However, while investigators from Stanford reported a high response rate of 100% with 46% complete remissions in previously treated and untreated patients, at a median follow-up of 13 months, 9 of the 22 patients had already relapsed.

Treatment

Early Stage Disease

Radiation therapy (RT) has been the standard approach for patients with nonbulky Stage IA/IIB disease. RT achieves complete remissions in more than 95% of patients with limited disease, and the failure-free survival and overall survival rates are 75% and greater than 90%, respectively, beyond 20 years. However, radiation is associated with a number of unwanted effects, including an increased incidence of secondary malignancies. Therefore, goals of recent studies have been to determine the lowest effective dose of RT. In low risk patients, involved field irradiation has been shown to be comparable to total lymphoid irradiation. Current trials are seeking to determine whether chemotherapy can replace RT altogether. A recent randomized study compared six cycles of doxorubicin, bleomycin, vinblastine, dacarbazine (ABVD) plus involved field with four cycles and radiation, with a similar outcome. In another study, patients were treated with either four to six cycles of ABVD or standard therapy (subtotal nodal irradiation, with or without two cycles). The standard therapy produced a small but significant increase in time to progression, but with no difference in overall survival at the present time.

Advanced Disease

Patients with advanced stage disease are those with Stages III or IV, the presence of B symptoms, and/or bulky disease (>10 cm at any site, >1/3 thoracic diameter). ABVD has become the standard chemotherapy because of a number of advantages; it is all-intravenous (providing better compliance), has less cumulative myelotoxicity, a lower risk of secondary malignancies (AML or solid tumors), and a lower rate of infertility compared with previous regimens (eg, mechlorethamine, vincristine,
procarbazine, and prednisone). This regimen can induce complete remissions in 80 to 85% of patients, with five-year freedom from progression of 61% and an overall five-year survival of 73%.76

New Treatments for Hodgkin Lymphoma

The German Hodgkin Lymphoma Group developed the intensive bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone (BEACOPP) regimen to improve on the outcome of patients with high-risk disease. Escalated BEACOPP improved failure-free survival compared with cyclophosphamide, vincristine, procarbazine, and prednisone/ABVD, but with an increased risk of secondary AML/MDS.77 The rate of progression during treatment was only 2%, with a relapse rate of 5%, a time to treatment failure of 88% at three years and overall survival of almost 95% at five years. Current studies are looking at a regimen of four cycles of escalated BEACOPP followed by four cycles of standard BEACOPP in an attempt at reducing toxicities. Another European trial is comparing escalated BEACOPP with ABVD.

Gemcitabine

Gemcitabine is a deoxycytidine analog with single agent activity in HL. When tested in a multicenter study in 23 patients with relapsed or refractory HL, excluding patients who had undergone autologous stem-cell transplantation, the toxicity was found to be manageable, with 9% complete response and 30% partial response.78 Pulmonary toxicity of gemcitabine is uncommon and usually mild when given as a single agent, but can be unacceptably severe when used in combinations, such as being substituted for dacarbazine in ABVD or for etoposide in BEACOPP.

Nevertheless, other combinations including gemcitabine have been tolerable with high response rates, such as the CALGB regimen of gemcitabine, navelbine, and doxil initially studied in relapsed and refractory patients. An upfront trial of doxorubicin, vinblastine, and gemcitabine in the initial treatment of low-risk patients is now active.

Anti-CD30 Monoclonal Antibodies

The CD30 antigen expressed on both Reed-Sternberg cells in HL and the malignant cells of anaplastic large cell NHL provides an excellent target for antibody therapy. Several anti-CD30 antibodies are currently being studied in clinical trials. They have been well tolerated, but the dose and schedule need to be optimized for greater activity.79

Assessment of Response

Standardized guidelines for response assessment facilitate interpretation of data, comparisons of the results among various clinical trials, and identification of new agents with promising activity, and also provide a framework on which to evaluate new biologic and immunologic insights into the diseases being studied.

Some of the differences among response criteria may appear subtle but have enormous implications. For a patient to be considered as having a complete response, a protocol generally requires that all lymph nodes that were involved with NHL return to normal size. However, what is considered “normal” varies among studies. Before treatment, a normal node is 1.0 cm in diameter. Nevertheless, following treatment, nodes rarely shrink below 1.0 cm, not because they are necessarily involved with tumor, but as the result of the presence of necrosis or fibrosis. In a study using the database generated from the 166 patient rituximab pivotal trial, the complete response rate was calculated using a bidimensional normal node size of 2.0 × 2.0 cm, 1.5 × 1.5 cm, or 1.0 × 1.0 cm. Whereas the overall response rate did not change appreciably (approximately 48%), the complete response rate significantly decreased from 28% to 18% to 6%.80

Recently published standardized response criteria have now been incorporated into lymphoma studies and are being used by regulatory agencies to evaluate new agents.81 Nevertheless, these recommendations were based pri-
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This is an exciting time for the management of patients with lymphomas. Therapies are moving away from the nonspecific cytotoxic agents and toward more targeted approaches, especially in the NHLs where the malignant cells are more reliably targeted. New classification schemes based on genetics and biology, and technologies such as genomics and proteomics, provide the opportunity to develop disease-specific and even patient-specific therapies. Not only have DNA microarrays identified different prognostic subsets, but also these subsets of patients may well be treated differently. Various approaches may be used to identify antibody-sensitive patients. At the same time, there is a growing list of new biologic and targeted chemotherapy agents. The challenge is to develop rational combinations and introduce these to patients who are most likely to benefit. The future lies in combining biologic therapies in a manner that will optimize their activity (with reduced dependence on the more toxic and nonspecific cytotoxic drugs), identifying those patients most likely to respond to those therapies, monitoring disease status, and preventing recurrence. Through these new technologies and with these unique agents, we will be able to improve the cure rate of patients with lymphomas.

FUTURE DIRECTIONS

This is an exciting time for the management of patients with lymphomas. Therapies are moving away from the nonspecific cytotoxic agents and toward more targeted approaches, especially in the NHLs where the malignant cells are more reliably targeted. New classification schemes based on genetics and biology, and technologies such as genomics and proteomics, provide the opportunity to develop disease-specific and even patient-specific therapies. Not only have DNA microarrays identified different prognostic subsets, but also these subsets of patients may well be treated differently. Various approaches may be used to identify antibody-sensitive patients. At the same time, there is a growing list of new biologic and targeted chemotherapy agents. The challenge is to develop rational combinations and introduce these to patients who are most likely to benefit. The future lies in combining biologic therapies in a manner that will optimize their activity (with reduced dependence on the more toxic and nonspecific cytotoxic drugs), identifying those patients most likely to respond to those therapies, monitoring disease status, and preventing recurrence. Through these new technologies and with these unique agents, we will be able to improve the cure rate of patients with lymphomas.

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