

REVIEW ARTICLE

DRUG THERAPY

Monoclonal Antibody Therapy for B-Cell Non-Hodgkin's Lymphoma

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NON-HODGKIN'S LYMPHOMA IS THE MOST COMMON HEMATOLOGIC CANCER in adults, with more than 66,000 incident cases anticipated in the United States in 2008.¹ Approximately 85% of non-Hodgkin's lymphomas in adults are of B cell origin.² Some B-cell non-Hodgkin's lymphomas are indolent, or slow-growing, yet incurable. In contrast, others are aggressive or very aggressive, and may be rapidly fatal, yet are often curable.

There has been a revolution in the treatment of B-cell non-Hodgkin's lymphomas, owing largely to the availability of therapeutic monoclonal antibodies. The concept that antibodies might be effective for the treatment of cancers originated more than a century ago with Paul Ehrlich's hypothesis that it would someday be feasible to develop a "magic bullet" that has an affinity for "parasites" but that spares normal tissues³; 100 years elapsed, however, before antibodies were developed as effective agents for the treatment of cancer. The first step was the development of hybridoma technology capable of producing adequate quantities of monoclonal antibodies for clinical use.⁴ The next step was to identify tumor-specific cell antigens as targets.⁵ Finally, on November 26, 1997, rituximab became the first monoclonal antibody approved by the Food and Drug Administration (FDA) for the treatment of a human cancer — relapsed or refractory, low-grade (indolent) or follicular, CD20+ non-Hodgkin's lymphoma. In the ensuing decade, considerable effort has been focused on improving the effectiveness of this agent, identifying other therapeutic monoclonal antibodies (Table 1), and integrating antibodies into standard treatment regimens.

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Table 1. Unconjugated Monoclonal Antibodies for B-Cell Cancers.*

Antibody	Target	Status in the United States
Rituximab (Rituxan, Genentech or Biogen Idec)	CD20	Commercially available
Alemtuzumab (Campath, Bayer HealthCare Pharmaceuticals)	CD52	Commercially available
Human or humanized anti-CD20 antibodies	CD20	Phase 1–2 investigation
Lumiliximab (Biogen Idec)	CD23	Phase 3 investigation
Anti-TRAIL (Human Genome Sciences)	DRD	Phase 1–2 investigation
Bevacizumab (Avastin, Genentech)	VEGF	Phase 3 investigation
Galiximab (Biogen Idec)	CD80	Phase 2–3 investigation
Epratuzumab (Immunomedics)	CD22	Phase 2 investigation
SGN-40 (Seattle Genetics)	CD40	Phase 2–3 investigation
Anti-CD74 (milatuzumab, Immunomedics)	CD74	Phase 1 investigation

* DRD denotes death receptor domains, TRAIL tumor necrosis factor–related apoptosis-inducing ligand, and VEGF vascular endothelial growth factor.

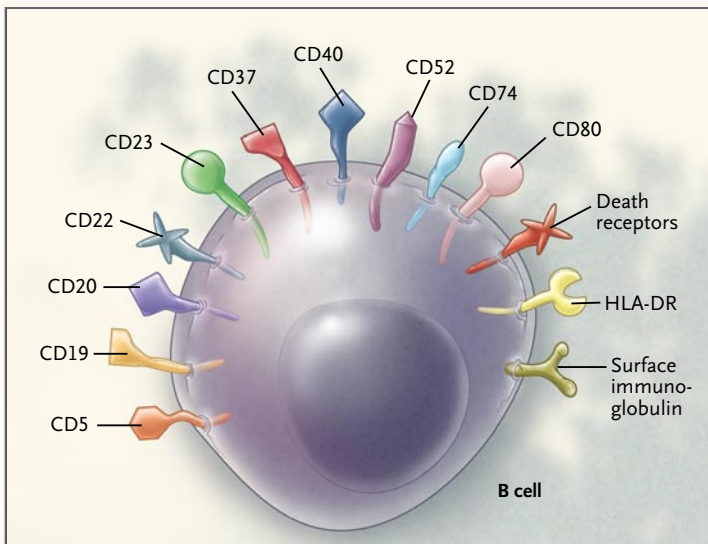


Figure 1. Cell-Surface Antigens on the B Cell.

The B cell has a large number of associated cell-surface antigens that can be exploited as targets for monoclonal-antibody therapy. The presence of CD5 on the surface of B cells varies according to histologic type.

RATIONALE FOR THE USE OF MONOCLONAL ANTIBODIES IN B-CELL LYMPHOMAS

A suitable target antigen requires expression that is largely restricted to the malignant cells, with sufficient expression on those cells for antibody binding (Fig. 1). Furthermore, the target antigen should not be internalized by the cells, nor should it be soluble, to ensure that the antibody reaches the tumor cells. Maturing B cells acquire specific surface antigens that are lost during terminal differentiation. Cell-surface antigens expressed on lymphoma cells are virtually always expressed on their nonmalignant counterparts as well. For example, CD20, a transmembrane calcium channel that is believed to play a role in B-cell activation, proliferation, and differentiation, is first expressed on pre-B cells and persists until later in differentiation but is absent on terminally differentiated plasma cells. This characteristic of B cells allows physiologic antibody production to be maintained and facilitates the regeneration of normal B cells after anti-B-cell therapy, thus mitigating the effects of immunosuppression.

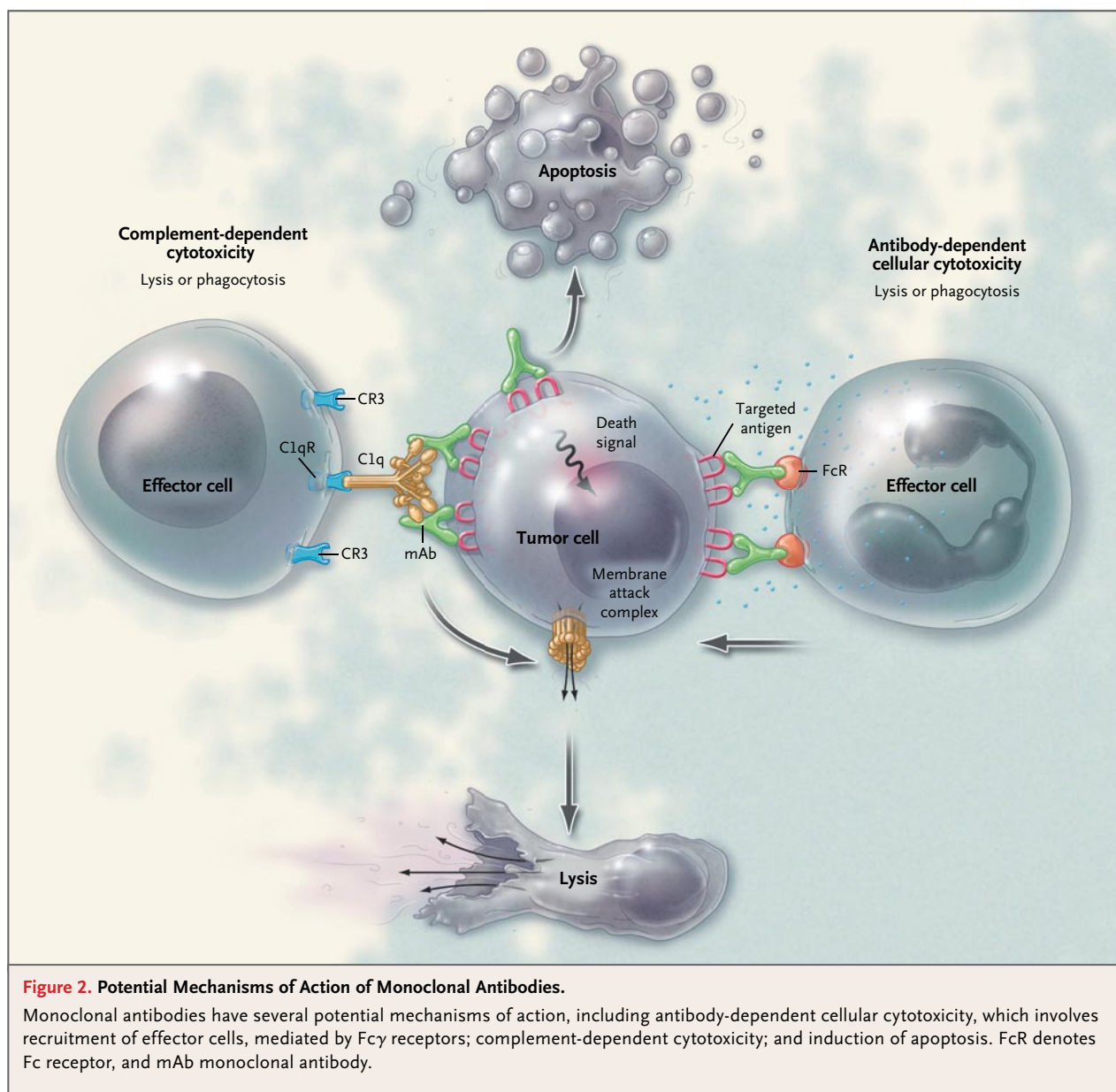
MECHANISMS OF ACTION

Antibodies kill tumor cells through complement-dependent cytotoxicity, antibody-dependent cellu-

lar cytotoxicity, and induction of apoptosis. When conjugated to a radioactive or toxic molecule, antibodies deliver the radiation or toxin to the target cell. Antibodies may also work by priming antigen-specific T cells through the cross-presentation of tumor antigens released by dying cells, a mechanism that is termed a “vaccinal effect.” Antibodies may also inhibit cytokines or other factors that are necessary for cell survival (Fig. 2). The relative importance of each mechanism varies with the type of tumor and the treatment administered. For example, the likelihood of a response to rituximab in patients with follicular lymphoma who have not previously received treatment may be correlated with the presence of an Fc-receptor polymorphism (valine at position 158) that is associated with improved antibody binding, suggesting the importance of antibody-dependent cellular cytotoxicity.⁶ Similar data have been generated from the results of chemotherapy in patients with diffuse large-B-cell lymphoma, although not in patients with chronic lymphocytic leukemia.^{7,8} The importance of complement-dependent cytotoxicity for the effectiveness of rituximab has been assessed by correlating the treatment response with the presence of complement-resistance proteins such as CD55 and CD59 on tumor cells; the results have been inconsistent.⁹ Preclinical studies suggest that rituximab and other monoclonal antibodies directly induce apoptosis or sensitize cells to proapoptotic stimuli, possibly accounting for the potential benefits of combining antibody therapy with chemotherapy.¹⁰

RESISTANCE TO MONOCLONAL ANTIBODIES

Despite the expression of antigens such as CD20, patients may not have a response to antibody therapy or resistance to the therapy may develop. Mechanisms of resistance potentially include impaired antibody-dependent cellular toxicity or complement-dependent cytotoxicity, limited effects on signaling and induction of apoptosis, and inadequate blood levels.¹¹ Laboratory assays are being developed to identify patients who are likely to have a response to therapy with monoclonal antibodies; such assays include the identification of FcγIII-receptor polymorphisms, representing the binding site of rituximab on immune effector cells, and DNA microarray signatures.^{12,13} Correlations between the assays that are currently available and the response to antibody therapy



vary among lymphoma subtypes and may depend on whether antibody therapy is used alone or in combination with chemotherapy.⁸ Some, but not all, studies involving patients with diffuse large-B-cell non-Hodgkin's lymphoma suggest an increased benefit of rituximab therapy in patients whose lymphomas overexpress the Bcl-2 protein but are negative for Bcl-6.^{14,15} Most analyses that have used assays that might predict responses have been retrospective, so the clinical usefulness of these assays is still uncertain.

ANTIIDIOTYPE ANTIBODIES

The first clinically active monoclonal antibodies for patients with B-cell lymphoma were directed at the idiotype, the hypervariable region of the immunoglobulin molecule, and the only specific clonal marker on these tumors.^{16,17} The surface immunoglobulin idiotype in the B-cell receptor appears to be important in B-cell survival. The first patient who was treated with antiidiotype antibodies for progressive "diffuse poorly differ-

entiated lymphocytic lymphoma" had a durable, complete remission without apparent toxic effects.¹⁶ A subsequent report included data on this patient and on 10 additional patients; all but 1 of these 11 patients had received extensive prior therapy. The patients were treated with patient-specific antiidiotype antibodies of murine origin; immune responses against the murine antibody limited repeated dosing.¹⁸ Five patients had transient partial responses; the initial patient remained in complete remission for more than 42 months.¹⁸ The generation of a unique tumor-specific antibody was needed for every patient in those studies, since lymphoma cells from only 6.2% of the patients shared idiotypes.¹⁹ In multicenter trials, about 25% of the patients had responses to antiidiotype antibodies; however, antiidiotype antibody therapy has been virtually abandoned because of its cumbersome technology, immune responses against the antibody, the emergence of idiotype-negative cells as the disease progressed, and the prohibitive expenses engendered by regulatory requirements.²⁰

RITUXIMAB FOR FOLLICULAR AND LOW-GRADE LYMPHOMA

Rituximab is a chimeric monoclonal antibody composed of murine variable regions from the anti-CD20 antibody 2B8 that are linked to a human Fc component directed against CD20 on B cells. Unfortunately, the optimal dose of rituximab has never been defined. Phase 1 studies of doses ranging from 10 to 500 mg per square meter of body-surface area, administered once, and of doses ranging from 125 to 375 mg per square meter, administered weekly for 4 weeks, identified no dose-limiting toxic effects.^{21,22} Although fever, chills, nausea, vomiting, urticaria, orthostatic hypotension, and bronchospasm occur in more than 80% of patients and are moderate to severe in about 15% of patients, these problems are generally limited to the infusion period. The regimen of 375 mg per square meter weekly for 4 weeks was selected for further testing on the basis of pharmacokinetic and pharmacodynamic data, the supply of the drug, and the feasibility of outpatient administration of the drug.²³⁻²⁵

Rituximab was initially approved by the FDA largely on the basis of a study involving 166 patients with relapsed or refractory, follicular or low-grade non-Hodgkin's lymphoma.²⁴ The over-

all response rate was 48%, with 6% of the patients having complete remissions; better response rates correlated with fewer previous treatments. The median duration of the response was about a year. The response rate among patients with bulky disease (nodes larger than 10 cm in diameter) was 43%, with 4% having complete remissions that lasted for a median of 5.9 months; the median time to progression among patients with a response was 8.1 months.²⁶ Responses lasting from 1 to 2.5 years have been reported in about 70% of patients with previously untreated, indolent non-Hodgkin's lymphoma and a low tumor burden.²⁷⁻²⁹

Until recently, no chemotherapeutic regimen provided a survival benefit superior to that of chlorambucil and prednisone in patients with indolent lymphomas.³⁰ However, single-group trials have suggested that adding rituximab to chemotherapy improves the rate and the duration of the response.^{31,32} Several randomized studies in which rituximab was added to various chemotherapy regimens showed not only increased rates of complete response but also prolonged survival as compared with chemotherapy alone (Table 2).^{33,34,41} Such results supported broadening the indications for rituximab in combination with chemotherapy to include its use as an initial treatment.

Rituximab is also effective against other indolent B-cell cancers, including marginal-zone lymphoma, lymphoplasmacytic lymphoma (also called Waldenström's macroglobulinemia), and small lymphocytic lymphoma.^{42,43} Response rates among patients with relapsed or refractory chronic lymphocytic leukemia or small lymphocytic lymphoma have been 10 to 15% but increased to 50 to 70% when rituximab alone was the initial therapy.^{23,28,44-46} A comparison with historical data suggests that response rates are increased and survival is prolonged among patients with chronic lymphocytic leukemia who are treated with chemotherapy plus rituximab.^{47,48}

ANTIBODIES AS MAINTENANCE THERAPY

Maintenance therapy with the use of monoclonal antibodies has been evaluated to determine whether this strategy prolongs the duration of the response and, possibly, survival (Table 3). Among patients with indolent non-Hodgkin's

Table 2. Randomized Trials of Chemotherapy plus Rituximab versus Chemotherapy Alone in B-Cell Lymphoma.*

Lymphoma Subtype	Prior Treatment	Treatment	Result	Reference
Follicular	No	R-CVP vs. CVP	Time to treatment failure, 27 mo vs. 7 mo; P<0.001	Marcus et al. ³³
Follicular	No	R-CHOP vs. CHOP	Treatment failure, 28/233 patients vs. 61/205 patients; P<0.001	Hiddemann et al. ³⁴
Follicular	Yes	R-CHOP vs. CHOP	Response rate, 85.1% vs. 72.3%; P<0.001	van Oers et al. ^{35,†}
Follicular or mantle cell	Yes	R-FCM vs. FCM	Response rate, 79% vs. 58%; P=0.001	Forstpointner et al. ³⁶
Diffuse large B-cell	No	R-CHOP vs. CHOP	Median event-free survival, 3.8 yr vs. 1.1 yr; P<0.001	Coiffier et al. ³⁷
Diffuse large B-cell	No	R-CHOP vs. CHOP	3-yr event-free survival rate, 79% vs. 59%; P<0.001	Pfreundschuh et al. ³⁸
Diffuse large B-cell	No	R-CHOP vs. CHOP	3-yr failure-free survival rate, 54% vs. 46%; P=0.04	Habermann et al. ³⁹
Mantle cell	No	R-CHOP vs. CHOP	Median time to treatment failure, 21 mo vs. 14 mo; P=0.01	Lenz et al. ⁴⁰
Follicular	No	R-MCP vs. MCP	4-yr overall survival rate, 87% vs. 74%; P=0.01	Herold et al. ⁴¹

* CHOP denotes cyclophosphamide, doxorubicin, vincristine, and prednisone; CVP cyclophosphamide, vincristine, and prednisone; FCM fludarabine, cyclophosphamide, and mitoxantrone; MCP mitoxantrone, chlorambucil, and prednisone; R-CHOP rituximab plus CHOP; R-CVP rituximab plus CVP; and R-FCM rituximab plus FCM.

† The ClinicalTrials.gov number for this study is NCT00004179.

lymphoma, maintenance therapy with antibodies after induction therapy with rituximab or cyclophosphamide, vincristine, and prednisone prolongs the time to progression but does not prolong survival.⁴⁹⁻⁵² In contrast, maintenance therapy with rituximab after chemotherapy or chemoimmunotherapy in patients with previously treated follicular lymphoma has been reported to improve progression-free and overall survival.³⁵ It is unclear whether maintenance therapy or retreatment after relapse is a better strategy, since 40% of patients with indolent non-Hodgkin's lymphoma who initially have a response to rituximab will also have a response after a relapse.^{52,53} Such responses generally last at least as long as the initial response.^{52,53} An Eastern Cooperative Oncology Group trial involving previously untreated patients with follicular non-Hodgkin's lymphoma is currently comparing treatment with rituximab that is continued until disease progression with retreatment at the time of recurrence and is evaluating the effect on the long-term outcome, as well as the toxic effects, of prolonged treatment with rituximab. No consensus exists concerning the optimal maintenance regimen.^{35,36,49,51,54}

CHEMOIMMUNOTHERAPY FOR DIFFUSE LARGE-B-CELL NON- HODGKIN'S LYMPHOMA

For decades, the combination of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) was the standard regimen for patients with diffuse large-B-cell non-Hodgkin's lymphoma, curing about 30% of the patients; no advantage was observed with more intensive combinations.⁵⁵ Since rituximab monotherapy induces brief responses in almost a third of patients with relapsed or refractory diffuse large-B-cell lymphoma,⁵⁶ it was incorporated into the CHOP regimen and similar regimens.⁵⁷ A marked shift in practice followed the report on the Groupe d'Etude des Lymphomes de l'Adulte study, in which 399 patients with diffuse large-B-cell non-Hodgkin's lymphoma (age range, 60 to 80 years) were randomly assigned to treatment with either CHOP or CHOP plus rituximab.³⁷ The complete response rate and the event-free and overall survival were significantly better in the group that received CHOP plus rituximab than in the group that received CHOP alone (complete response rate, 76%

Table 3. Randomized Trials of Maintenance Treatment with Rituximab versus Observation.

Lymphoma Subtype	Prior Treatment	Induction	Maintenance Treatment	Result	Reference
Follicular	Untreated and treated	Rx4	R every 2 mo for 8 mo	Event-free survival, 23.2 mo vs. 11.8 mo; P=0.02	Ghielmini et al. ⁴⁹
Follicular	Yes	R-CHOP vs. CHOP	R every 3 mo for 2 yr	Median progression-free survival, 51.5 mo vs. 14.9 mo; P<0.001	van Oers et al. ^{35†}
Follicular or mantle cell	Yes	R-FCM vs. FCM	Rx4 at months 3 and 9	Response duration, not reached vs. 17 mo; P<0.001	Forstpointner et al. ³⁶
Indolent	No	CVP	Rx4 at months 3 and 9	4-yr progression-free survival rate, 56% vs. 33%; P<0.001	Hochster et al. ⁵⁰
Diffuse large B-cell	No	R-CHOP vs. CHOP	Rx4 every 6 mo for 2 yr	Hazard ratio for failure-free survival at 3 yr, 0.63; P=0.009	Habermann et al. ³⁹

* CHOP denotes cyclophosphamide, doxorubicin, vincristine, and prednisone; CVP cyclophosphamide, vincristine, and prednisone; FCM fludarabine, cyclophosphamide, and mitoxantrone; R rituximab at a dose of 375 mg per square meter of body-surface area; R-CHOP rituximab at a dose of 375 mg per square meter plus CHOP; R-FCM rituximab at a dose of 375 mg per square meter plus FCM; and Rx4 rituximab, at a dose of 375 mg per square meter, weekly for 4 weeks.

† The ClinicalTrials.gov number for this study is NCT00004179.

for rituximab with CHOP vs. 64% for CHOP alone). These results have been confirmed after longer follow-up of this cohort and in other studies.^{38,39,58,59} These data and those from other trials supported the FDA approval of rituximab combined with CHOP for previously untreated diffuse large-B-cell lymphoma; this combination therapy is now the standard initial therapy. A U.S. intergroup study did not show a benefit from maintenance therapy with rituximab after initial therapy with rituximab and CHOP.³⁹

Treatment with rituximab before and after autologous stem-cell transplantation may prolong progression-free and overall survival, although most of the data are based on the responses of patients who were not previously treated with rituximab.⁶⁰ An ongoing trial (ClinicalTrials.gov number, NCT00137995) is evaluating the outcome with rituximab therapy as compared with observation in patients who have undergone transplantation.⁶¹

Studies exploring whether genetic factors predict a response to rituximab in patients with diffuse large-B-cell non-Hodgkin's lymphoma have shown variable results. Gene-expression profiles appear to identify a germinal-center subtype and an activated B-cell subtype of diffuse large-B-cell lymphomas, with the latter subtype having a less favorable outcome. The addition of rituximab to CHOP appears to overcome the difference in the outcomes of these subtypes.^{62,63} Another study suggested that overexpression of Bcl-2, which is important in regulating apopto-

sis, was associated with a poor prognosis and that rituximab-based immunochemotherapy might improve the outcome.¹⁴ However, Winter et al.¹⁵ were unable to confirm this observation and suggested that patients with tumors that are positive for Bcl-6, a follicular-center cell marker, did not benefit from the addition of rituximab to chemotherapy. Thus, the question of whether genetic profiles should or will direct treatment decisions remains unanswered.

COMBINATIONS OF ANTIBODY THERAPY AND CHEMOTHERAPY IN MANTLE-CELL LYMPHOMA

Mantle-cell lymphoma is rapidly progressive and generally considered to be incurable. Although this type of lymphoma has unique immunophenotypic and genetic features, patients with mantle-cell lymphoma are often given the same therapy as that given to patients with other aggressive non-Hodgkin's lymphomas. Rituximab is only modestly effective in the treatment of mantle-cell lymphoma, less so than in the treatment of other histologic types of non-Hodgkin's lymphomas.^{56,64,65} Yet an analysis based on historical data suggests that the addition of rituximab to intensive chemotherapy improves the outcome of mantle-cell lymphoma.⁶⁶ The German Low Grade Lymphoma Study Group randomly assigned previously untreated patients with mantle-cell lymphoma to treatment with either CHOP alone or CHOP with rituximab.⁴⁰ The response rates and the time to

progression were better with the combination therapy, but survival was not improved. In contrast, rituximab in combination with chemotherapy may benefit patients with relapsed or refractory disease and may be beneficial as maintenance therapy.⁶⁷

RADIOIMMUNOTHERAPY

Radioimmunotherapy involves the administration of an antibody linked to a radioisotope. Such agents “home” to antigen-presenting cells, to which the antibody binds. In addition, while bound to such cells, the radioactive component kills neighboring cells that either are inaccessible to the antibody or express insufficient antigen for antibody binding. The pioneering work of DeNardo et al. provides an early example of this concept; that work targeted HLA antigens in aggressive non-Hodgkin’s lymphoma with the use of radiolabeled monoclonal antibodies against Lym-1 and showed some complete responses.⁶⁸

Two commercially available and similar radioimmunoconjugates that target CD20 — yttrium-90 (⁹⁰Y)-labeled ibritumomab tiuxetan (Zevalin, Cell Therapeutics) and iodine-131 (¹³¹I)-labeled tositumomab (Bexxar, GlaxoSmithKline) — are approved for use in patients with relapsed or refractory follicular or low-grade lymphoma.

⁹⁰Y-LABELED IBRITUMOMAB TIUXETAN

A murine variant of rituximab, ⁹⁰Y-labeled ibritumomab tiuxetan, is conjugated to ⁹⁰Y. A course of therapy involves administering a dose of unlabeled rituximab on the first day of therapy to saturate nontumor CD20 sites and to facilitate the biodistribution of the radioimmunoconjugate. Because ⁹⁰Y is a beta emitter and cannot be used for imaging, a tracer amount of indium-111 (¹¹¹In)-labeled ibritumomab is administered to assess the biodistribution and to ensure the appropriate localization of the isotope. About a week later, a low dose of rituximab is administered, followed by the administration of 0.4 mCi of intravenous ⁹⁰Y-labeled ibritumomab tiuxetan per kilogram of body weight. The dose must be decreased to 0.3 mCi per kilogram in patients who have platelet counts of 100,000 to 149,000 per cubic millimeter. Patients who have more marked cytopenias or compromised bone marrow are not candidates for therapy with this agent because of the risk of excessive hematologic toxic effects.⁶⁹

About 80% of patients with follicular or low-grade lymphomas have a response to treatment with ⁹⁰Y-labeled ibritumomab tiuxetan, including 20 to 30% who have a complete response. Most responses last about a year, but the duration of the response has exceeded 3 years in about 25% of patients.⁷⁰⁻⁷³ The benefit of adding a radioisotope to the antibody was confirmed in a study that involved the administration of ⁹⁰Y-labeled ibritumomab tiuxetan in patients with indolent lymphoma that was refractory to rituximab. This strategy resulted in a 74% response rate; 15% had a complete response.⁷¹ In addition, the use of ⁹⁰Y-labeled ibritumomab tiuxetan, as compared with rituximab, resulted in higher response rates among patients with follicular or low-grade lymphoma who had not previously received treatment with antibodies.⁷² In a recent study, consolidation of an initial response to chemotherapy with treatment with ⁹⁰Y-labeled ibritumomab tiuxetan improved the rate of complete remission and prolonged progression-free survival, with an apparently favorable toxicity profile.⁷⁴ ⁹⁰Y-labeled ibritumomab tiuxetan also appears to be effective against some diffuse large-B-cell lymphomas and mantle-cell lymphomas when it is used in sequence with chemotherapy.⁷⁵

¹³¹I-LABELED TOSITUMOMAB

A conjugate of the murine anti-CD20 antibody tositumomab and iodine-131, ¹³¹I-labeled tositumomab is also administered over the course of about a week, along with drugs to protect the thyroid (given the glandular avidity of iodine). Because ¹³¹I is a gamma emitter, direct imaging is possible, with dosimetry providing patient-specific dosing. In one study, two thirds of patients with non-Hodgkin’s lymphoma that was refractory to chemotherapy had a response; 20% had complete remissions.⁷⁶ The rate of response to ¹³¹I-labeled tositumomab among patients with rituximab-refractory lymphoma has been 63%, with 29% having complete remissions.⁷⁷

In one study, 95% of patients with non-Hodgkin’s lymphoma had responses to ¹³¹I-labeled tositumomab used as initial treatment, including 75% who had complete remissions.⁷⁸ At 5 years, 59% of the patients were free from progression of the disease; the median progression-free survival was 6.1 years.⁷⁸ This regimen has also been administered after chemotherapy, resulting in durable responses and conversion of partial re-

mission to complete remission without serious toxic effects.⁷⁹ The results of a recently completed study (ClinicalTrials.gov number, NCT00006721) of CHOP followed by ¹³¹I-labeled tositumomab as compared with rituximab plus CHOP as the initial treatment of follicular lymphoma may ultimately redefine standard therapy.

TOXICITY OF RADIOIMMUNOTHERAPY

Major complications of radioimmunotherapy include infusion reactions from the antibody without its radioactive moiety and radiation-related myelosuppression, which is generally delayed for about 6 to 9 weeks. Because of the low incidence of mucositis, febrile neutropenia, and infections, hospitalization is uncommon. Alopecia, nausea, and vomiting are rare. Treatment with ¹³¹I-labeled tositumomab is associated with hypothyroidism in about 10% of patients. Among previously treated patients, human antimurine antibodies have been reported to develop in 2% of patients receiving ⁹⁰Y-labeled ibritumomab tiuxetan and in 9% of those receiving ¹³¹I-labeled tositumomab, with the rate increasing to 65% when these agents are used as the initial therapy.^{71,78,80} However, to date, the development of human antimurine antibodies has not limited this approach.

An important question when using this approach is whether secondary acute myelogenous leukemia or myelodysplastic syndrome might develop as a result of irradiation; this risk appears to be about 1.5% after treatment with ⁹⁰Y-labeled ibritumomab tiuxetan and 6.3% after treatment with ¹³¹I-labeled tositumomab. Relevant factors include the type and extent of prior treatments and the presence or absence, before the initiation of radioimmunotherapy, of cytogenetic abnormalities suggestive of myelodysplasia. The magnitude of the risk depends on the patient population, prior therapies, and the duration of follow-up. However, the risks may be no greater than those seen with chemotherapy alone in similar patients,^{81,82} a supposition supported by the absence of the myelodysplastic syndrome among patients in a trial in which radioimmunotherapy was used as the initial treatment.⁷⁸

Strict exclusion criteria have been developed for initiating radioimmunotherapy; these include more than 25% involvement of bone marrow with lymphoma, less than 15% bone marrow cellularity, a platelet count of less than 100,000

per cubic millimeter or a neutrophil count of less than 1500 per cubic millimeter, extensive prior radiation therapy, pregnancy or lactation, and prior stem-cell transplantation, the last because of unknown safety. Thus, evaluation of a bone marrow–biopsy specimen before radioimmunotherapy is initiated is mandatory.

Current research in this area is directed at combining or sequencing radioimmunotherapy with chemotherapy and other biologic agents.⁸³ Preliminary reports concerning ⁹⁰Y-labeled ibritumomab tiuxetan and ¹³¹I-labeled tositumomab suggest that a variety of other therapies can be administered subsequently without undue risk; however, a full understanding of this issue is complicated by variables such as patient selection.⁸⁴

Early studies indicate that radioimmunotherapy with either ⁹⁰Y-labeled ibritumomab tiuxetan or high-dose ¹³¹I-labeled tositumomab can be incorporated into a high-dose approach with autologous stem-cell rescue for patients with relapsed or refractory lymphomas. Results to date suggest that radioimmunotherapy may prolong progression-free and overall survival, with fewer toxic effects, as compared with high-dose chemotherapy.⁸⁵⁻⁸⁷

OTHER ANTIBODIES

There are a number of other antibodies that show some promise (Table 1).

ANTI-CD20 ANTIBODIES IN DEVELOPMENT

Ongoing attempts to improve on the rituximab molecule include modifications that permit binding to a better epitope, binding more tightly to CD20, increasing activation of antibody-dependent cellular cytotoxicity, and facilitating apoptosis (Fig. 2). The product furthest along in clinical development is ofatumumab (HuMax-CD20, Genmab), a fully human IgG1κ monoclonal antibody that targets a novel epitope of CD20. Preclinical studies indicate that ofatumumab is associated with greater complement-dependent cytotoxicity than rituximab, presumably because of a slower rate of dissociation from its antigen (“off rate”) and greater interaction with the complement component C1q. In clinical trials, patients with follicular lymphoma and chronic lymphocytic leukemia had responses to ofatumumab, which profoundly depleted CD19+CD5+ B cells and had a toxicity profile similar to that of rituximab.⁸⁸⁻⁹⁰

Another humanized antibody, hA20 (IMMU-106), induces apoptosis of B cells in vitro and mediates antibody-dependent cellular cytotoxicity and complement-dependent cytotoxicity.⁹¹ Early clinical trials suggest that patients have objective responses to this antibody.^{91,92} PRO131921, a third-generation rituximab product, is also being investigated in early clinical trials. Additional anti-CD20 antibodies under development include some with enhanced binding to Fc receptors and augmented antibody-dependent cellular cytotoxicity. Given the substantial activity and relative safety of rituximab, it will be challenging to show whether other anti-CD20 antibodies have an advantage when they are compared with rituximab and whether they will be effective in patients whose lymphoma is resistant to rituximab.

ALEMTUZUMAB

Alemtuzumab (Campath, Bayer HealthCare Pharmaceuticals) is a humanized anti-CD52 monoclonal antibody that has been approved by the FDA for the treatment of chronic lymphocytic leukemia. The recommended schedule for the administration of alemtuzumab is a dose of 3 mg on day 1 and 10 mg on day 2, followed by 30 mg three times weekly, as tolerated, for up to 12 weeks. About 30% of patients with chronic lymphocytic leukemia whose disease progressed after they received alkylating agents and fludarabine have had a response to alemtuzumab.⁹³⁻⁹⁵ When alemtuzumab is used as the initial therapy, the response rate is about 80%.⁹³⁻⁹⁵ Infusion-related rigors occur in about 90% of patients (14% of whom have moderate-to-severe reactions), fever in 85% (moderate to severe in 20%), mild-to-moderate nausea in 53%, vomiting in 38%, and rash in approximately 33%. These adverse events generally decrease in frequency and severity over the course of treatments. Subcutaneous administration has fewer toxic effects than intravenous administration but has similar efficacy and is now more widely used.⁹⁶

Infections develop in more than 50% of patients who receive alemtuzumab; these infections are severe to life-threatening in 25% of the patients. Alemtuzumab has been associated with an increased risk of *Pneumocystis jiroveci* and herpesvirus infections; thus, antimicrobial prophylaxis and close monitoring for infection are essential. A reactivation of cytomegalovirus occurs in ap-

proximately 25% of patients, necessitating weekly polymerase-chain-reaction monitoring.

GALIXIMAB

CD80 is an immune costimulatory molecule that is present on B cells.⁹⁷ Galiximab (Biogen Idec) is a macaque-human chimeric anti-CD80 antibody with antilymphoma properties in vivo. About 15% of patients with recurrent follicular non-Hodgkin's lymphoma appear to have positive responses with galiximab, some of which occur as late as a year after treatment. Galiximab is reported to cause minimal adverse events — primarily mild fatigue, nausea, and headaches.⁹⁸ On the basis of preclinical data suggesting synergy, a phase 1-2 study of galiximab together with rituximab was performed, and the results suggested that the combination therapy was superior to therapy with the single agents⁹⁹; a randomized trial of rituximab as compared with galiximab plus rituximab in patients who have had a relapse is under way. The Cancer and Leukemia Group B (CALGB) recently studied the combination of galiximab and rituximab as the initial therapy for follicular lymphoma and reported a response in 69% of the study participants, including 41% with complete remissions.¹⁰⁰

ANTI-CD40 ANTIBODIES

CD40, a member of the tumor necrosis factor-receptor family, is expressed on the surface of B cells from the pro-B stage to plasma cells. Preclinical studies of two anti-CD40 antibodies (SGN-40 [Seattle Genetics] and CHIR-12.12 [Novartis]) showed apoptotic effects and antibody-dependent cellular cytotoxicity. Durable, complete responses in patients with diffuse large-B-cell lymphoma in a phase 1 trial with SGN-40 stimulated further study of SGN-40 as a single agent and in combination with chemotherapy.¹⁰¹

EPRATUZUMAB

CD22 is widely expressed on B cells and may be important in B-cell activation, modulation of antigen-receptor signaling, and cell-surface-receptor circulation. Epratuzumab (Immuno-medics), a humanized IgG1 anti-CD22 monoclonal antibody, has induced responses in 24% of patients with follicular lymphoma and in 15% of patients with recurrent diffuse large-B-cell lymphoma, without dose-limiting toxic effects.^{102,103} Results of treatment with a combination of ritux-

imab and epratuzumab suggested at least an additive benefit, a finding that requires confirmation in a randomized study.¹⁰⁴ Epratuzumab is also being evaluated as a treatment in combination with rituximab plus CHOP and as a therapy in other B-cell cancers and autoimmune disease.¹⁰⁵

LUMILIXIMAB

Chronic lymphocytic leukemia cells express the CD23 antigen, a target for the anti-CD23 antibody, lumiliximab (Biogen Idec), a macaque-human chimeric monoclonal antibody that inhibits IgE secretion in vitro and induces apoptosis of lymphoma cell lines. Lumiliximab binds complement and mediates antibody-dependent cellular cytotoxicity by binding FcγRI and RII receptors. It appears to have limited effectiveness as a single agent among patients with chronic lymphocytic leukemia.¹⁰⁶ However, in vitro data suggest that it has synergy with fludarabine and rituximab.¹⁰⁷ When lumiliximab is added to the combination therapy of fludarabine, cyclophosphamide, and rituximab, the rates of response appear to be similar to those seen with the combination therapy without lumiliximab, but the proportion of complete responses is higher when lumiliximab is added.¹⁰⁸ An international randomized study comparing fludarabine, cyclophosphamide, and rituximab with and without lumiliximab is under way.

Hu1D10

HLA class II antigens are expressed on B cells throughout differentiation and play a key role in cell cycling and proliferation. Anti-class II antibodies inhibit B-cell proliferation and induce apoptosis, at least in part through induction of the Fas-Fas ligand pathway or activation of Akt. Apolizumab (Hu1D10), a humanized anti-HLA-DR antibody capable of inducing complement-dependent cytotoxicity, antibody-dependent cellular cytotoxicity, and programmed cell death, has limited activity.¹⁰⁹ Nevertheless, other anti-HLA-DR antibodies, including the anti-CD74 antibody milatuzumab (Immunomedics), are currently being studied for the treatment of non-Hodgkin's lymphoma, chronic lymphocytic leukemia, and multiple myeloma.¹¹⁰

OTHER ANTIBODY APPROACHES

Bispecific antibodies bind cytokines or immune effector cells along with tumor cells, potential-

ly enhancing cytotoxicity.¹¹¹ Small, modular immunopharmaceutical agents link an antigen-binding domain with the IgG1 hinge and the CH2 and CH3 domains. A CD20 antibody that is being developed as a small, modular immunopharmaceutical agent has been shown to have the capability of depleting B cells in patients with rheumatoid arthritis, and the effect of an anti-CD37 small, modular immunopharmaceutical agent against B-cell cancers is being investigated in a clinical trial (ClinicalTrials.gov number, NCT00614042).¹¹²

FUTURE DIRECTIONS

Therapies for B-cell cancers that are based on the use of monoclonal antibodies may avoid the toxic effects of chemotherapy, improve the outcomes when combined with chemotherapy, and provide options for patients with refractory disease. Given the heterogeneity of lymphomas and the array of treatment options available, it is challenging to integrate new compounds with traditional approaches. New immunotherapy targets are constantly emerging, and other antibodies against tumor vasculature (e.g., bevacizumab) and stroma also warrant evaluation. The CALGB is evaluating the use of antibody-based combination biologic therapy as an initial treatment of follicular lymphoma in order to potentially delay the initiation of chemotherapy, with its associated toxic effects. Investigation is ongoing to determine whether early and extensive use of antibody therapy is associated with long-term benefits or adverse consequences. Other strategies include the integration of radioimmunotherapy as part of the initial therapy. Newer antibodies may have the potential for enhanced efficacy or the capability of overcoming resistance to current therapies. Finally, the identification of patient subgroups that can optimally benefit from these agents is a priority. Despite these challenges, emerging evidence suggests that antibody-based treatments are improving the outcomes for patients with B-cell cancers.^{113,114}

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