The Important Role of Monoclonal Antibodies in the Treatment of Non-Hodgkin's Lymphomas

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ABSTRACT

Monoclonal antibodies for the treatment of non-Hodgkin's lymphoma (NHL) have been under clinical evaluation since the late 1970s. The first antibody to show significant efficacy and gain regulatory approval was rituximab. It was approved for the treatment of patients with low-grade or follicular, relapsed or refractory NHL in November 1997. Several other antibodies are undergoing clinical evaluation: Hu1D10, epratuzumab, and the radiolabeled antibodies ibritumomab and tositumomab. Antibodies can have significant clinical activity even as single agents in patients with poor prognostic factors. Antibodies are no longer for "mopping up" after chemotherapy; they have very significant therapeutic potential, particularly for the treatment of hematologic malignancies. Anticancer therapies, such as radiotherapy and chemotherapy, have served us well for many years; however, their toxicity was tolerated only because we lacked other options. This is the age of antibodies.

Oncology Spectrums *2001;2(10):700-705*

INTRODUCTION

Monoclonal antibodies were originally developed for use as diagnostic reagents.[1] The promise of specific targeting, decreased toxicity, and clinical activity led to numerous clinical trials to define their therapeutic utility. These efforts, up to 1992, were largely fruitless.[2] In contrast, monoclonal antibodies are now recognized as important additions to the therapeutic armamentarium for the treatment of non-Hodgkin's lymphoma (NHL).[3] The events surrounding this paradigm shift, from therapeutic nihilism to optimism, unfolded during the last 10 years (Table 1).

Pioneering developments were made during the early clinical trials with the chimeric, anti-CD20 antibody, rituximab. The first hints of efficacy were seen in the initial single-dose study where several patients had partial responses even at lower dose levels.[4] Rituximab went on to become the first antibody approved worldwide for the treatment of NHL.[5] More recently, data have shown that rituximab in combination with CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) chemotherapy prolongs event-free survival in patients with diffuse large-cell lymphoma versus CHOP alone.[6] If these findings hold up over longer observation, rituximab must be considered a curative therapy. Rituximab plus CHOP will become the new "gold standard."

Other unlabeled and radiolabeled antibodies have also been studied during this decade (Table 2). Alemtuzumab was approved for fludarabine-refractory chronic lymphocytic leukemia (CLL). Ibritumomab, which is labeled with yttrium 90 (^{90}Y), is awaiting approval. Others are under continuing evaluation (iodine 131[^{131}I]-labeled tositumomab). Several unlabeled antibodies are in Phase II clinical trials (eg, Hu1D10 and LL2). Clearly, monoclonal antibodies will play an important role in the treatment of NHL. We can truly say that, "Today, the armamentarium has radically changed. Now, monoclonal antibodies, gene therapies, genomics-based targeted therapies, vaccines, and other biologics are available, in addition to small molecule chemicals. It is possible that, right now, we may have at hand the ingredients necessary to cure more patients with diffuse large cell NHL…We could assemble the necessary ingredients for a combination regimen that could be curative for patients with low-grade NHL."[7]

UNLABELED ANTIBODIES

Anti-Idiotype Monoclonal Antibodies

The first approach to treating B-cell lymphomas with antibodies used murine anti-idiotype (id) antibodies (private anti-id antibodies) that were specific for the idiotype on the neoplastic B-cells in an individual patient.[8] Maloney et al have reviewed results from clinical trials including combinations with chlorambucil and interferon.[9] Patients had to have tumors that were accessible to biopsy, and the tumor cells had to express immunoglobulin (Ig) on their surfaces. Mice were immunized with the patients' tumor

TALKING POINTS Physicians Pharmacy Formulary Cancer Nurses

Several labeled and unlabeled antibodies are approved or in clinical trials for the treatment of non-Hodgkin's lymphoma (NHL).

Most antibodies are dosed on a mg/m^2 or mg/kg basis. Radioimmunotherapy dose is calculated based on dosimetry results except for ibritumomab, which is dosed on a mCi/kg basis.

The antibodies approved for cancer therapy are rituximab (NHL), trastuzumab (breast cancer), gemtuzumab (acute myelogenous leukemia), and alemtuzumab (chronic lymphocytic leukemia).

The adverse-event profile for unlabeled antibodies is different from that of chemotherapy; radiolabeled antibodies are myelosuppressive.

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cells. When sufficient amounts of the customized monoclonal antibodies (mAbs) were available, patients were re-evaluated and those with measurable disease and <100 mg/mL of circulating serum idiotype had a repeat biopsy. Those who showed >90% reactivity of tumor cells with the customized anti-id were treated. The time lag from biopsy to therapy could be several months long.

The results showed the potential for significant clinical efficacy with antibody therapy (response rates in the 60% range) as well as the possibility of synergism with chemotherapy and with other biologic agents (response rates in the 70% range). Additionally, these efforts provided information on the development of human antimurine antibody and the challenge of overcoming shed circulating antigen. However, the procedures for generating anti-id antibodies were cumbersome, costly, and time-consuming, and remain so today.

In an attempt to make this approach more practical and to enable a larger number of patients to be treated, idiotypes that are shared (shared anti-id antibodies) among

TABLE 1. IMPORTANT EVENTS IN THE DEVELOPMENT OF RITUXIMAB

Event	Date
Identification and characterization of the murine anti-CD20 antibody, IDEC-2B8 (parent antibody for rituximab)	January 1991
Construction of the chimeric antibody—murine variable and human constant regions (IgG1 isotype)	June 1991
Engineering of the vector needed for expression in CHO cells	August 1991
IND filed with the FDA—1st Phase I trial protocol submitted	December 1992
First patient treated with rituximab in the Phase I trial	February 1993
First patient treated on the 1st combination study—CHOP + rituximab in LG/NHL	April 1994
First patient treated on the Pivotal trial that led to the approval of rituximab in the USA and Europe	March 1995
Last patient entered on the pivotal trial	March 1996
Biologics Licence Application (BLA) filed with the FDA and simultaneous filing of the European dossier with the EMEA	February 1997
Biologics Response Modifiers Advisory Committee of the FDA recommends approval	July 1997
Rituximab approved in the USA by the FDA for LG/NHL	November 1997
Rituximab approved in Europe by the EMEA for LG/NHL	June 1998
GELA study results presented at ASH 2000 indicating superiority of CHOP + rituximab over CHOP alone in patients with Intermediate Grade NHL	December 2000
Committee for Proprietary Medicinal Products (CPMP) of the EMEA recommends approval of rituximab for patients with Intermediate Grade NHL	October 2001

CHO=Chinese hamster ovary cells; CHOP=Cyclophosphamide, hydroxydaunorubicin, vincristine, prednisone; LG/NHL=Low grade non-Hodgkin's lymphomas; IND=Investigational new drug application; FDA=Food and Drug Administration; EMEA=European Medicines Evaluation Agency; GELA=Groupe des Etudes Lymphomes de l'Adulte; ASH=American Society of Hematology; CDC=Complement dependent cytotoxicity; CRu=Complete response, unconfirmed; DR=Duration of response; TTP=time to progression; ORR=Overall response rate; IWRC=International Workshop Response Criteria

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Grillo-López, AJ. *Oncology Spectrums.* Vol 2. No 10. 2001.

TABLE 2. UNLABELED ANTIBODIES FOR NON-HODGKIN'S LYMPHOMA*

Antibody	Construct	Isotype
Anti-idiotype (private and shared)	Murine	IgG (1, 2a, or 2b)
Anti-CD19	Murine	IgG2a
Anti-CD21 (OKB7)	Murine	IgG2b
Anti-CD20 (1F5)	Murine	IgG2a
Anti-CD20 (rituximab)	Chimeric	IgG1 kappa
Anti-CD52 (alemtuzumab)	Humanized	IgG1
Anti-HLA-DR (1D10)	Humanized	IgG1 kappa
Anti-CD22 (epratuzumab)	Humanized	IgG1

*Not intended to be exhaustive.

Grillo-López, AJ. *Oncology Spectrums.* Vol 2. No 10. 2001.

lymphomas from different patients were identified.[10] The shared-id antibodies could be prepared in advance of treatment so that the mAb treatment could be initiated as soon as the patient's idiotypic phenotype has been identified. Early results from this group demonstrated that the approach seems feasible and more broadly applicable than the private anti-id approach.[11]

Nevertheless, a panel of 15 shared anti-id antibodies was required for about 25% of patients. This required the production, validation, large-scale manufacturing, and regulatory approval of 15 different products plus the associated diagnostic assays, making this approach not financially viable.

ANTIBODIES TO B-CELL ANTIGENS

Antigens on the surface of B cells are attractive targets for antibody therapy. These antibodies include OKB7 murine anti-CD21, murine anti-CD19, 1F5 murine anti-CD20, alemtuzumab humanized anti-CD52, 1D10 humanized anti-HLA-DR, epratuzumab humanized anti-CD22, and rituximab chimeric anti-CD20.

Murine OKB7 (IgG2b isotype) recognizes the Epstein-Barr virus receptor, CR2. OKB7 is not complement fixing and does not mediate antibody-dependent cellular cytotoxicity (ADCC). It was inactive in clinical trials.[12] However, the accurate determination of tumor uptake of OKB7 provided a basis for the design of future studies with murine IgG2b and other immunoglobulin subtypes. Further, the importance of complement-mediated cytotoxicity and of antibody-dependent, cell-mediated cytotoxicity for the activity of antibodies became evident. Murine anti-CD19 antibodies and the murine 1F5 anti-CD20 antibody (IgG2a isotype) were studied in patients with NHL and found to have some clinical activity (15–25% response rate) and an occasional long-lasting response.[13,14] The laboratory research for these clinical experiences yielded important information regarding pharmacokinetics, blood levels necessary to deplete circulating cells and to saturate antigenic sites, penetration into nodal compartments, and dose and schedule for antibody therapy. It became clear that antibodies should be dosed in grams or larger quantities to saturate antigenic sites within lymph nodes and to optimize efficacy.

The alemtuzumab-1 family of antibodies is prototypical for many reasons. It maps the evolution of therapeutic antibodies from IgM to IgG, from IgG2a to IgG2b rat antibody isotypes, and from rat to humanized IgG1 antibodies.[15] The alemtuzumab experience also yielded substantial information regarding the gamut of adverse events associated with antibody therapies (and the role of complement in their etiology) as well as pharmacologic maneuvers to ameliorate them. The role of antiglobulin responses, affecting tolerability and limiting efficacy, became better understood. In clinical trials, alemtuzumab-1H exhibited limited antilymphoma activity (20% response rate and 4 months median time to progression) and significant toxicity.[16] It has been effective in patients with CLL refractory to fludarabine and is now approved for that indication.

Hu1D10, a humanized antibody that recognizes the 1D10 antigen (a polymorphic determinant of HLA-DR expressed primarily on B cells, macrophages, dendritic cells, and other stromal cells), mediates complement dependent cytotoxicity (CDC) and ADCC and induces apoptosis in lymphoma cell lines.[17] The antigen has been detected on only 60% of all NHL specimens tested, which may limit its applicability. In a Phase I study in 20 patients with relapsed or refractory B-cell lymphoma, treatment consisted of four weekly intravenous infusions at doses ranging from 0.15 to 5.0 mg/kg (maximal tolerated dose). Grade 4 adverse events consisted of the following in one patient each: hypotension, nausea/vomiting, hypoxia, hypophosphatemia, lymphopenia, pleural effusion, and elevated liver enzymes. Responses were seen only in patients with follicular NHL: two unconfirmed complete responses and three partial responses.[18] A Phase II multicenter trial, in which Hu1D10 is being administered at 1.5 mg/kg, is ongoing. It will be important to know if Hu1D10 will synergize with other antibodies, particularly rituximab, with biologicals, or with chemotherapy.

Epratuzumab (hll2), a humanized antibody, recognizes the CD22 antigen on B cells. A Phase I/II clinical trial in 24 patients with relapsed or refractory DLCL was reported.[19,20] Patients received four weekly infusions of antibody at 240–1,000 mg/m^2/week. Objective responses were noted in 5 of 17 evaluable patients (11% complete responses and 18% partial responses) with response durations ranging from 3 to 24+ months. Treatment was well tolerated with no grade 3 or 4 toxicities reported. The initial clinical data are encouraging and suggest some similarity to rituximab. However, data are limited because of low patient numbers and only one investigational site is involved. Further data from more trials and centers are being generated.

Rituximab, a chimeric mouse-human antibody (IgG2 kappa isotype), recognizes the CD20 antigen on B cells (not present on stem cells, pro B cells, plasma, or dendritic cells). It has been shown (in vitro) to affect CDC, ADCC, and apoptosis and to sensitize chemo-resistant cells. Rituximab is currently approved for the treatment of relapsed or refractory, low-grade or follicular, B-cell NHL.[5] Recently its indication was expanded to include eight-infusion dosing in addition to the original four-infusion schedule.[21] The package insert now also includes information on the treatment of patients with bulky disease, re-treatment of patients previously treated with rituximab, and use in combination with CHOP. Single-agent rituximab therapy at the usual dose of 375 mg/m^2/week for four doses achieves response rates in the 50% range and durations (time to progression) in excess of a year.[22] Re-treatment achieves similar results.[23] Combinations with other biologicals, chemotherapy, and radioimmunotherapy are now being studied in Phase II and III trials in the US and Europe.

The combination of rituximab with CHOP chemotherapy was the first to be studied. In low-grade NHL, rituximab/

CHOP was reported to produce a 100% response rate with median duration of response (DR) and time to progression not reached at over 50 months observation time.[24-26] Subsequent studies in intermediate-grade NHL, particularly the Groupe des Etudes Lymphomes de l'Adulte (GELA) study, have yielded encouraging results. GELA, a randomized Phase III trial, showed a statistically significant increase in event-free survival for rituximab/CHOP versus CHOP alone in patients treated at frontline.[27] This is the first time that any combination regimen has been shown to improve on the results obtained in intermediate-grade NHL with CHOP, which, until now, has been the "gold standard." Multiple studies are ongoing in a variety of indications that will serve to clarify the role of rituximab, alone or in combination, in several other malignant and autoimmune diseases.[21]

RADIOLABELED ANTIBODIES

Ibritumomab and tositumomab are the furthest along in development (mostly in patients with relapsed low-grade NHL) and both are being reviewed by the FDA for approval. Ibritumomab was developed by IDEC Pharmaceuticals Corporation and tositumomab by Coulter Pharmaceuticals, which recently transferred the project to Coryxa. Both products are radiolabeled murine antibodies, require a cold antibody preceding the labeled antibody, and are myelosuppressive. Ibritumomab is labeled with ^{90}Y and tositumomab with ^{131}I; the cold antibody for ibritumomab is the chimeric rituximab, whereas tositumomab utilizes the murine anti-B1 antibody. Ibritumomab is dosed on a mCi/kg basis and tositumomab requires dosimetry to calculate each patient's dose.

Ibritumomab

Ibritumomab ^{90}Y is composed of ibritumomab covalently bound to tiuxetan and stably chelated to the radionuclide ^{90}Y.[28, 29]

TABLE 3. ANTIBODY THERAPY OF LOW-GRADE NHL: REPRESENTATIVE RESPONSE RATES AND DURATIONS

Antibody	Response Rate (%)	Duration (months)
Anti-idiotype[9]	66	4+
Anti-CD20 (1F5)[14]	25	1.5
Anti-CD20 (rituximab)[22]	48	13.2 (TTP)
Anti-CD52 (alemtuzumab)[16]	20	4 (TTP)
Anti-HLA-DR (1D10)[18]	25	N/A
Anti-CD22 (epratuzumab)[19,20]	29	N/A
Ibritumomab, radiolabeled*[30,31]	80	11.2 (TTP)
Tositumomab, radiolabeled*[33]	58	14.9+

*Relapsed or refractory, low-grade or transformed.
NHL=non-Hodgkin's lymphoma; TTP=time to progression.

Grillo-López, AJ. *Oncology Spectrums.* Vol 2. No 10. 2001.

In a Phase III study comparing ibritumomab to rituximab, the overall response rate (ORR) was significantly higher in the ibritumomab treatment arm (International Workshop Response Criteria: 80% versus 56%, P=.002). The estimated median time to progression was 11.2+ months for ibritumomab patients and 10.1+ months for rituximab patients.[30,31] In a Phase II rituximab-refractory study, ibritumomab induced responses in most patients (ORR=74%) with a significantly longer duration of response versus prior rituximab therapy.[31] Adverse events have been primarily hematologic, transient, and reversible. Grade 4 neutropenia, thrombocytopenia, and anemia occurred in 28.0%, 8.4%, and 4.2% of patients, respectively. Most nonhematologic adverse events were grade 1 and 2 and were related to accompanying rituximab infusions.

Tositumomab

Tositumomab ^{131}I is composed of the anti-B1 antibody radiolabeled with ^{131}I. In a multicenter Phase II rituximab-refractory study, patients with relapsed low-grade NHL received tositumomab at a total body dose of 75 cGy.[32] The response rate in 33 patients was 58% (21% complete response) and the median time to progression was 566 days. Data are available on 273 patients treated in a multicenter expanded-access study.[33] The response rate in relapsed low-grade or transformed NHL patients was 58% with a 14.9+ months duration of response. An analysis of 251 low-grade or transformed NHL patients with poor prognostic factors revealed a 74% ORR with a median duration of 11.3 months.[34] Of these patients, 24% had transformed and 76% had low-grade NHL. The ORRs were 54% and 80%, and the median durations were 11 and 11.7 months, respectively. Safety and tolerability data from a cohort of 215 patients were recently reported.[35] Grade 4 neutropenia occurred in 16% and thrombocytopenia in 2% of patients. Supportive care was as follows: platelet transfusions, 5–12%; granulocyte colony-stimulating factor, 8–12%; any supportive care, 12–20%.

DISCUSSION AND CONCLUSIONS

The CD20 antigen is the antigen of the decade. It possesses most of the characteristics of the ideal antigenic target for antibody therapy. CD20 is present on all B-cell lymphoma cells, does not internalize or shed, clusters (rafts) on the cell surface, and serves to transmit an apoptotic signal. It is present on normal cells but only on B cells, where its expression is limited to the range from pre-B cells to mature B cells. It is not expressed by dendritic cells, macrophages, or any other hematopoietic cells. CD20 is not found on stem cells, pro-B cells, or plasma cells.

All of this is critically important to the safety and efficacy of antibodies that target this antigen. In the case of a depleting antibody, such as rituximab, normal B cells will be specifically and severely depleted. However, plasma cells are unaffected and will continue to produce antibodies while B cells are regenerated from the equally unaffected stem cells. Lymphoma cells are killed and,

in responding patients, may only reappear from the remaining pool of minimal residual disease. Thus, retrospectively it might appear easy to state that CD20 was an ideal target and that anti-CD20 antibodies would prove to be successful therapeutic agents for NHL.

Scarcely 10 years ago this was all theoretical and not widely believed or understood. At that time there were many prevailing biases born of decades of disappointing results with antibody-based therapies. Many believed that antibodies would never work at all and if they did show any clinical activity it would be in the setting of minimal residual disease (mopping up after effective chemotherapy response). The rituximab experience has dispelled many of these biases. It proved to be effective as a single agent not only in patients with advanced relapsed or refractory disease but even in patients with bulky disease. This was the exact opposite of what most people expected. Rituximab was the first antibody approved for the treatment of cancer. It opened the gates for therapeutic research with monoclonal antibodies and led to a resurgence in this area that has extended beyond hematologic malignancies to solid tumors and even to nonmalignant disorders. A measure of the interest in this area of research is the sizable number of abstracts submitted to the last American Society of Hematology and American Society of Clinical Oncology meetings. The last few years have also marked the approval of other therapeutic antibodies such as trastuzumab (breast cancer) and gemtuzumab (acute myleogenous leukemia).

Further, the rituximab story is barely starting to unfold. This antibody, originally approved for relapsed or refractory low-grade or follicular NHL, is being studied in intemediate- and high-grade NHL, multiple myeloma, other B-cell malignancies, and autoimmune disorders (idiopathic thromobocytopenic purpura, autoimmune hemolytic leukemia, rheumatoid arthritis). There are several antibodies in development that may compete for the stature that rituximab has gained: Hu1D10, epratuzumab, and others. They need to show clinical activity similar to or greater than rituximab with equivalent or better safety or clinical activity in patients refractory to rituximab. Otherwise, they would be interesting only if they could synergize with rituximab or with chemotherapy. An important challenge is to generate the data necessary to gain approval from the FDA. For these reasons, most antibodies competing with rituximab are following one of three clinical development strategies: showing activity in rituximab-refractory patients, showing an additive or synergistic effect when combined with rituximab; or being compared in head-to-head randomized trials versus rituximab.

Beyond unlabeled antibodies, a variety of antibodies that are toxin-labeled, chemolabeled, and radiolabeled are in clinical trials. Ibritumomab and tositumomab are furthest along. Ibritumomab was presented to the FDA's Oncologic Drugs Advisory Committee in September, 2001. The committee recommended approval of ibritumomab, and final approval by the FDA is likely to occur before the end of 2001. If the Committee votes for approval, the FDA could grant final approval before the end of 2001. Tositumomab has recently filed additional data requested by the FDA and still has to file reports on some additional studies. It is unlikely that tositumomab will be scheduled for an Advisory Committee review this year.

All in all, the 1990s have yielded exciting new antibody-based therapies. Labeled and unlabeled antibodies have shown good clinical activity (Table 3). These antibodies operate via mechanisms that are entirely different from those of chemotherapeutic agents and thus are excellent agents for use in combination regimens. Further, they exhibit a safety profile that does not overlap with the toxic effects of chemotherapy. We are clearly at the beginning of a new era in the therapy of NHL. The possibility of improving the cure rate in intermediate-grade disease beyond that obtained with CHOP chemotherapy is now very real. The task now at hand is to determine if there is a regimen that can result in cures in low-grade lymphoma. Long-lasting remissions are being achieved and we may be very close to developing curative regimens with some combinations of these new therapeutics. OS

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