

Editorial

Developing New Monoclonal Antibodies for Aggressive Lymphoma: A Challenging Road in the Rituximab Era

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Non-Hodgkin's lymphoma is the fifth most common and sixth most fatal cancer in the United States and has increased significantly in incidence over the past 30 years. The National Cancer Institute estimates that >60,000 new cases of non-Hodgkin's lymphoma will be diagnosed in the United States this year; the most common of which is diffuse large B-cell non-Hodgkin's lymphoma (1). Diffuse large B-cell non-Hodgkin's lymphoma is a curable disease with combination chemotherapy. The majority of randomized clinical trials have not found a significant treatment advantage for any particular chemotherapy program, and CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone), a 30-year-old regimen, remains the standard chemotherapy treatment of *de novo* large B-cell non-Hodgkin's lymphoma in the United States (2).

Few advances in the treatment of aggressive non-Hodgkin's lymphoma have had such dramatic clinical impact as the anti-CD20 monoclonal antibody rituximab (Rituxan; BiogenIdec, Cambridge, MA, and Genentech Inc., South San Francisco, CA). Rituximab is a "chimeric" anti-CD20 monoclonal antibody with both murine and human components. The mechanism of cytotoxicity in humans induced by rituximab therapy as a single agent or in combination with chemotherapy is not completely understood (3). Both complement-mediated cytotoxicity and antibody-dependent cell-mediated cytotoxicity have been demonstrated *in vitro*. In addition, direct apoptosis due to cross-linking of CD20 and cell signaling has been observed in some malignant cell lines.

When rituximab is given as a single agent to patients with relapsed or refractory aggressive large B-cell non-Hodgkin's lymphoma, the response rate is 30% with minimal toxicity (4). Given this activity and supportive Phase II trials the Groupe d'Etudes des Lymphomes de l'Adulte group randomized 399 previously untreated patients with diffuse large B-cell non-Hodgkin's lymphoma, 60–80 years old, to receive either eight cycles of CHOP every 3 weeks or eight cycles of CHOP plus rituximab (5). With a median follow-up of 2 years, the CHOP plus rituximab regimen increased significantly the complete response rate and prolonged both event-free and overall survival in these patients without a clinically significant increase in

toxicity. A larger ($n = 632$) intergroup United States study randomized patients to CHOP *versus* CHOP plus rituximab (with rituximab given on a different schedule) followed by a second randomization to rituximab maintenance therapy (4 doses every 6 months \times 2 years) or no maintenance (6). Preliminary results suggest a progression-free survival benefit to CHOP plus rituximab; however, no overall survival benefit is yet apparent. Based largely on the published results from Groupe d'Etudes des Lymphomes de l'Adulte, CHOP plus rituximab has emerged to become the standard initial treatment for most patients with advanced stage diffuse large B-cell non-Hodgkin's lymphoma in the United States.

Unlike CD20, CD22 is a separate antigen on the surface of malignant and normal B-cells, which is rapidly internalized and results in a potent costimulatory signal in primary B cells. It is a phosphoglycoprotein expressed by pre-B and mature normal B cells and by $\sim 90\%$ of diffuse large B-cell non-Hodgkin's lymphomas. When the CD22 antigen cross-links with ligand, the resulting complex is rapidly internalized and produces a potent costimulatory signal in primary B cells. The antigen is subsequently re-expressed on the cell surface. Epratuzumab (Immunomedics, Morris Plains, NJ) is a humanized version of the murine anti-CD22 LL2 antibody under development for the treatment of non-Hodgkin's lymphoma (7). Pharmacokinetics analyses show that the half-time of epratuzumab (mean of 23 days) is consistent with the half-life of a human IgG1 antibody (21 days). To date, epratuzumab has been administered to >250 subjects with non-Hodgkin's lymphoma, with the majority receiving the 360 mg/m² weekly \times 4 doses schedule.¹ No dose-limiting toxicities have been observed in Phase I studies, and most adverse events were mild or moderate in severity and generally decreased with subsequent infusions. Like rituximab, there is no clinically meaningful effect on hematologic parameters (except for an expected transient decrease in B-cell count) and remarkably no increased incidence of infection. Additionally, the treatment has been associated with low antigenicity as would be expected for a humanized antibody.

In the current issue of *Clinical Cancer Research*, Leonard et al. (8) describe the Phase I/II experience of escalating doses of single-agent epratuzumab in a cohort of aggressive non-Hodgkin's lymphoma patients who relapsed after chemotherapy. No dose-limiting toxicity was observed, and 5 of 52 patients treated at 240–600 mg/m²/week dose levels have had objective responses including 3 patients with complete responses. An additional 6 patients had "minor" responses, with some documented tumor shrinkage. In the diffuse large B-cell non-Hodgkin's lymphoma subset, the objective response rate

Received 5/10/04; accepted 5/11/04.

Grant support: Career development award from the National Cancer Institute (CA-102216–01).

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¹ Personal communication, Amgen Inc.

was 15% (5 of 33). The most frequently reported adverse events associated with epratuzumab in this trial were related to the first infusion and included nausea and flushing. Although these response rates appear to be modest and inferior to single-agent rituximab, it is important to realize many of these patients had received extensive prior therapy: the majority had received rituximab, and 25% received prior high-dose therapy and autologous stem cell transplantation. The results in this trial clearly suggest clinical activity, with negligible toxicity, in a disease setting with few other options and support additional development of epratuzumab in aggressive non-Hodgkin's lymphoma.

Because CD22 is an internalizing antigen, epratuzumab should have no cross-reactivity with rituximab, and presumably has a different mechanism of action. Therefore, there has been considerable enthusiasm to combine epratuzumab with rituximab. In 20 rituximab-naïve non-Hodgkin's lymphoma patients, the combination of epratuzumab 360 mg/m² with rituximab has resulted in a response rate of 63% for indolent patients (56% complete response/complete response unconfirmed; 6% partial response), suggesting possible synergistic activity (9). Three of 4 patients with diffuse large B-cell lymphoma in this study responded (2 complete response; 1 partial response). Toxicity in this study was comparable with what has been observed with single-agent monoclonal antibody therapy. A subsequent multicenter trial of rituximab-sensitive patients with indolent lymphoma resulted in an overall response rate of 58%, with 28% complete response (10). Despite this relatively high complete response rate, the time to progression was somewhat disappointing in this trial. Additional studies of combination therapy in a variety of histologies are planned.

Given the success of CHOP plus rituximab in the setting of *de novo* aggressive large B-cell non-Hodgkin's lymphoma, the Eastern Cooperative Oncology Group has conducted a pilot study of CHOP plus rituximab with epratuzumab every 21 days for newly diagnosed patients with diffuse large B-cell lymphoma and demonstrated the safety of this regimen. A phase II study in Eastern Cooperative Oncology Group is planned to assess the efficacy of CHOP plus rituximab with epratuzumab in newly diagnosed patients with diffuse large B-cell lymphoma. If promising, a Phase III randomized trial will be required to confirm superiority over CHOP plus rituximab.

Since the approval of rituximab, the clinical development of monoclonal antibodies for non-Hodgkin's lymphoma has become far more complex. Routine use of rituximab/chemotherapy combinations has rendered the antibody-naïve patient an endangered species in the United States, and defining antibody sensitivity is difficult when the agents are combined with chemotherapy. Additionally, our increasing understanding of subgroups of patients who benefit from antibody-based interventions should impact future clinical trial design. For example, an unplanned subgroup analysis of the Groupe d'Etudes des Lymphomes de l'Adulte CHOP plus rituximab trial demonstrated that the benefit of rituximab appeared limited to patients with lymphoma that overexpressed bcl-2 on immunohistochemistry (11). There is evolving evidence that in certain clinical situations, the genotype of the natural killer cell IgG receptor FcγRIIIa predicts response to anti-CD20 therapy (12). This suggests that the relative contribution of antibody-dependent cell-mediated

cytotoxicity (where the polymorphism is expected to be predictive of response) *versus* other mechanisms might vary in different disease states.

The impact of the FcγRIIIa genotype and the bcl-2 status of lymphoma on response to anti-CD22 therapy is currently unknown and may be critical to defining groups of patients who may benefit from this agent. Other possible biomarkers of anti-CD22 efficacy, including the intensity and pattern of CD22 staining of lymphoma specimens using immunohistochemistry techniques, need to be correlated with clinical responses (13). Leonard *et al.* (8) have demonstrated clinical activity, the critical first step in developing a novel antibody therapy. However, only through detailed translational research, including correlative studies incorporating molecular diagnostics of both the lymphoma and the patient, will we learn the optimal time and place for this agent in the growing armamentarium of biologics targeting non-Hodgkin's lymphoma.

REFERENCES

1. Armitage JO, Weisenburger DD. New approach to classifying non-Hodgkin's lymphomas: clinical features of the major histologic subtypes. Non-Hodgkin's Lymphoma Classification Project. *J Clin Oncol* 1998;16:2780-95.
2. Fisher RI, Gaynor ER, Dahlborg S, et al. Comparison of a standard regimen (CHOP) with three intensive chemotherapy regimens for advanced non-Hodgkin's lymphoma. *N Engl J Med* 1993;328:1002-6.
3. Rastetter W, Molina A, White CA. Rituximab: expanding role in therapy for lymphomas and autoimmune diseases. *Annu Rev Med* 2004;55:477-503.
4. Coiffier B, Haioun C, Ketterer N, et al. Rituximab (anti-CD20 monoclonal antibody) for the treatment of patients with relapsing or refractory aggressive lymphoma: a multicenter phase II study. *Blood* 1998;92:1927-32.
5. Coiffier B, Lepage E, Briere J, et al. CHOP chemotherapy plus rituximab compared with CHOP alone in elderly patients with diffuse large-B-cell lymphoma. *N Engl J Med* 2002;346:235-42.
6. Haberman TM, Weller EA, Morrison VA, et al. Phase III trial of rituximab-CHOP vs. CHOP with a second randomization to maintenance rituximab or observation in patients 60 years of age and older with diffuse large B cell lymphoma. *Blood* 2003;102:6a.
7. Coleman M, Goldenberg DM, Siegel AB, et al. Epratuzumab: targeting B-cell malignancies through CD22. *Clin Cancer Res* 2003;9:3991S-4S.
8. Leonard JP, Coleman M, Ketas JC, et al. Epratuzumab (Humanized anti-Cd22 antibody) in aggressive non-Hodgkin's lymphoma: phase 1/2 clinical trial results. *Clin Cancer Res* 2004;10:5327-34.
9. Leonard J, Coleman M, Matthews J, et al. High complete response rate following epratuzumab (anti-CD22) and rituximab (anti-CD20) combination antibody therapy in follicular non-Hodgkin's lymphoma. *Ann Oncol* 2002;13:38.
10. Emmanouilides C, Leonard JP, Schuster SJ, et al. Multi-center, Phase 2 study of combination antibody therapy with epratuzumab plus rituximab in recurring low-grade NHL. *Blood* 2003;102:69a.
11. Mounier N, Briere J, Gisselbrecht C, et al. Rituximab plus CHOP (R-CHOP) overcomes bcl-2-associated resistance to chemotherapy in elderly patients with diffuse large B-cell lymphoma (DLBCL). *Blood* 2003;101:4279-84.
12. Weng WK, Levy R. Two immunoglobulin G fragment C receptor polymorphisms independently predict response to rituximab in patients with follicular lymphoma. *J Clin Oncol* 2003;21:3940-7.
13. Cesano A, Gayko U, Brannan C, Kapushoc H, Fields SZ, Perkins SL. Differential expression of CD22 in indolent and aggressive non-Hodgkin's lymphoma: Implications for targeted immunotherapy. *Blood* 2002;100:350a.