

# ADVANCES IN LLM

Current Developments in the Management of Leukemia, Lymphoma, and Myeloma

Section Editor: Clara D. Bloomfield, MD

## New Antibodies in the Treatment of Lymphoma

John P. Leonard, MD  
Associate Attending Physician  
New York Presbyterian Hospital  
Associate Professor of Medicine  
Clinical Director of the Center for  
Lymphoma and Myeloma  
Weill Cornell Medical College of Cornell University

### **H&O** How has rituximab been studied in lymphoma?

**JL** Rituximab (Rituxan, Genentech) was initially developed as a treatment for relapsed indolent lymphoma, and was approved by the US Food and Drug Administration (FDA) in this setting. Over the past several years, rituximab has been studied in virtually every context of indolent and aggressive B-cell lymphomas, both alone in a variety of treatment schedules and in combination with a multitude of chemotherapy agents. Data from these studies suggest that adding rituximab to chemotherapy in most settings does not result in major added toxicity, and does appear to improve outcomes. Depending on the specific situation, this benefit may be reflected by increases in response rates, time to progression, and overall survival.

### **H&O** Has enough time elapsed with these studies to gauge the benefit of rituximab in terms of long-term survival?

**JL** In the setting of diffuse large B-cell lymphoma (DLBCL), studies have evaluated rituximab combined with the standard chemotherapy regimen of cyclophosphamide/doxorubicin/vincristine/prednisone (CHOP). In several patient populations and variations on the standard CHOP regimen, virtually all studies have suggested a potential survival benefit with rituximab.

A number of phase II trials have explored adding rituximab to chemotherapy for the treatment of indolent lymphomas, and recent phase III studies suggest that

adding this antibody to chemotherapy either concurrently or sequentially can improve both response rates and time to progression. Recent presentations at the 2005 Annual Meeting of the American Society of Hematology preliminarily indicate that this approach might also be improving overall survival in some settings, which is the most important endpoint in assessing benefit.

### **H&O** Do all patients benefit from rituximab, or are specific subgroups more likely to respond?

**JL** Whether all patients or only certain subgroups respond can depend on the specific situation and lymphoma subtype. In general, most patients seem to have some benefit, and we are still learning about which subtypes benefit to greater or lesser degrees.

### **H&O** Is alemtuzumab being studied for the treatment of lymphoma?

**JL** Yes. Alemtuzumab (Campath-1H, Berlex) was approved by the FDA for the treatment of recurrent chronic lymphocytic leukemia (CLL). The target of alemtuzumab, CD52, is present not only on CLL cells but also on a variety of cells seen in B- and T-cell malignancies. Thus, it was logical to pursue the use of this agent in various types of lymphoma. Alemtuzumab has been demonstrated to be active in several B- and T-cell lymphoma subtypes, including peripheral T-cell lymphoma, cutaneous T-cell lymphoma, follicular lymphoma, and others.

The challenge with alemtuzumab is that the target is not selective for malignant cells. Whereas the target of rituximab, CD20, is present only on normal and malignant B cells, expression of CD52 is more widespread, including normal T cells. Thus this agent is associated with significant immunosuppression, and patients undergoing treatment with alemtuzumab are at risk for infectious complications, making the risk:benefit ratio different from that of rituximab. That being said, rituximab does not have a role in the treatment of T-cell malignancies, whereas alemtuzumab can be useful. Although the T-cell lymphomas represent only 10–15% of all lymphomas, the therapeutic options for these subtypes are relatively limited. Alemtuzumab is a modest but significant breakthrough for the treatment of these diseases.

### **H&O** What is epratuzumab?

**JL** Epratuzumab (Immunomedics) is a monoclonal antibody directed against CD22, an antigen present on B-cell malignancies. At Cornell, we have studied this antibody both alone and in combination with rituximab, and both approaches have shown activity in B-cell malignancies, particularly in the settings of follicular lymphoma and DLBCL. Whether epratuzumab truly enhances the effects of rituximab needs to be studied in the setting of a randomized trial. Epratuzumab is also being studied in combination with CHOP and rituximab, with encouraging results in initial reports.

### **H&O** Could you describe the anti-CD80 monoclonal antibody being studied in lymphoma?

**JL** Galiximab (Biogen Idec) has been demonstrated to have single-agent activity in follicular lymphoma, and has been combined safely with rituximab. Early studies have suggested that galiximab may enhance the activity of rituximab, in comparison to a historical cohort of patients treated with the single agent. This effect needs to be confirmed in a randomized trial, which is currently in the planning stages.

### **H&O** How are the radioimmunotherapy agents being used in the treatment of lymphoma?

**JL** There are two FDA-approved radioimmunotherapies: iodine-131 tositumomab (Bexxar, GlaxoSmithKline), and yttrium-90 ibritumomab tiuxetan (Zevalin, Biogen Idec). These agents have been studied primarily in relapsed indolent lymphomas, and are currently being evaluated in other types of lymphoma and in sequential combination with chemotherapy.

These agents appear to be effective in patients with indolent lymphoma that is resistant to rituximab and/or chemotherapy. One current key question is should these agents be used earlier in the course of disease? Also, can they be used in other lymphoma subtypes, either alone or in sequential combination with other treatments? Finally, do they enhance the activity of chemotherapy or chemotherapy plus rituximab-based regimens when they are given as consolidation after these treatments? These areas of research are all currently being investigated.

### **H&O** How common is resistance to rituximab?

**JL** Resistance to rituximab is relatively common. At least one third of patients are resistant at their first exposure and, with time, many additional patients develop resistant disease.

### **H&O** What is the mechanism behind this resistance?

**JL** This question is difficult to answer, as one must first fully understand how a treatment works in order to understand why a tumor might be resistant to it. We do not completely understand the dominant mechanism by which rituximab, or other antibodies, work. Antibody-dependent cellular cytotoxicity (ADCC) appears to be a major component of the activity of rituximab and perhaps some other antibodies as well. Fc-receptor polymorphisms can correlate with disease responsiveness to rituximab. This finding suggests that the immune status of the patient may have an impact on whether or not a treatment works and whether or not the disease will be resistant.

### **H&O** Are agents being developed to overcome this resistance?

**JL** Yes. New versions of anti-CD20 antibodies, both human and humanized, that may potentially overcome the mechanisms of resistance to rituximab are currently in clinical development. Early clinical trial findings are showing these agents, such as HuMax (Genmab), HA20 (Immunomedics), and ocrelizumab (Genentech/Roche), are well tolerated and have evidence of clinical activity. How they compare to rituximab remains to be determined.

### **H&O** Are these agents analogous to rituximab?

**JL** These agents are similar to rituximab, but with some differences. Whereas rituximab is chimeric, some of these agents are fully human or humanized. Some bind to the same place to which rituximab binds on the CD20 molecule, and some bind to a different area.

### **H&O** What other antibodies are being investigated in lymphoma?

**JL** There are two anti-CD30 antibodies currently being developed, one by Seattle Genetics and one by Medarex. These are being studied in Hodgkin's disease (HD) and in anaplastic large cell lymphoma (ALCL) a subtype of large cell lymphoma; investigations thus far show that these appear to be more active in ALCL and less active in HD. Antibodies against CD40 are also in development by Seattle Genetics and Chiron. Currently in phase I trials, these agents may potentially have activity in a wide variety of lymphoproliferative disorders. An antibody directed against TRAIL (tumor necrosis factor-related apoptosis-inducing ligand) being developed by Genentech is currently in phase I trials.

## H&O What themes have emerged regarding the clinical development of monoclonal antibodies for the treatment of lymphoma?

**JL** One of the predominant themes in the clinical development of antibodies for lymphoma is the challenge in introducing new agents. Because rituximab is already approved, and has been demonstrated to be effective in multiple settings, any new antibody must be compared to or combined with rituximab, or used in patients with rituximab-refractory disease. However, in a population of patients who have relapsed after treatment with rituximab but are not necessarily refractory to it, it is not possible to know how a new antibody compares with re-treatment with rituximab alone. It is therefore difficult to know whether a new agent represents an improvement over rituximab or adds to the benefit of rituximab if they are being studied in combination (in the absence of a control group for comparison).

Interestingly, the Cancer and Leukemia Group B is conducting a study in patients with follicular lymphoma relapsed after treatment with chemotherapy with rituximab that includes a rituximab-alone arm in order to establish baseline data with single-agent rituximab. Such data are needed in order to be able to accurately compare the activity of new agents, either alone or in combination with rituximab, with rituximab alone. We hope that these data will be valuable in the assessment of new agents being evaluated either singly or in combination with rituximab.

## Suggested Reading

Gordan LN, Grow WB, Pusateri A, et al. Phase II trial of individualized rituximab dosing for patients with CD20-positive lymphoproliferative disorders. *J Clin Oncol.* 2005;23:1056-1058.

Hainsworth JD, Litchy S, Burris HA 3rd, et al. Rituximab as first-line and maintenance therapy for patients with indolent non-Hodgkin's lymphoma. *J Clin Oncol.* 2002;20:4261-4267.

Ghielmini S, Schmitz H, Cogliatti S, et al. Prolonged treatment with rituximab significantly improves event-free survival and response duration compared with the standard weekly  $\times 4$  schedule. *Blood.* 2004;103:4416-4423.

Hainsworth JD, Litchy S, Shaffer DW, et al. Maximizing therapeutic benefit of rituximab: maintenance therapy versus retreatment at progression in patients with indolent non-Hodgkin's lymphoma—a randomized phase II trial of the Minnie Pearl Cancer Research Network. *J Clin Oncol.* 2005;23:1088-1095.

Vugmeyster Y, Beyer J, Howell K, et al. Depletion of B cells by a humanized anti-CD20 antibody PRO70769 in *Macaca fascicularis*. *J Immunother.* 2005;28:212-219.

Leonard JB, Coleman M, Ketas JC, et al. Phase I/II trial of epratuzumab (humanized anti-CD22 antibody) in indolent non-Hodgkin's lymphoma. *J Clin Oncol.* 2003;21:3051-3059.

Stein R, Qu Z, Chen S, et al. Characterization of a new humanized anti-CD20 monoclonal antibody, IMMU-106, and its use in combination with the humanized anti-CD22 antibody epratuzumab, for the therapy of non-Hodgkin's lymphoma. *Clin Cancer Res.* 2004;10:2868-2878.

Kaminski MS, Zelenetz AD, Press OW, et al. Pivotal study of iodine I 131 tositumomab for chemotherapy-refractory low-grade or transformed low-grade B-cell non-Hodgkin's lymphomas. *J Clin Oncol.* 2001;19:3918-3928.

Gordon LI, Molina A, Witzig T, et al. Durable responses after ibritumomab tiuxetan radioimmunotherapy for CD20+ B-cell lymphoma: long-term follow-up of a phase 1/2 study. *Blood.* 2004;103:4429-4431.

Horning SJ, Younes A, Jain V, et al. Efficacy and safety of tositumomab and iodine-131 tositumomab (Bexxar) in B-cell lymphoma, progressive after rituximab. *J Clin Oncol.* 2005;23:712-719.

Davies AJ, Rohatiner AZ, Howell S, et al. Tositumomab and iodine I 131 tositumomab for recurrent indolent and transformed B-cell non-Hodgkin's lymphoma. *J Clin Oncol.* 2004;22:1469-1479.

Kaminski MS, Tuck M, Estes J, et al. I-131 tositumomab therapy as initial treatment for follicular lymphoma. *N Engl J Med.* 2005;352:496-498.