

# New Agents and Future Directions in Biotherapy

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The area of biologic therapy has been undergoing numerous changes as new agents and combinations of chemotherapy and biotherapy are investigated. This article reviews several new biotherapy agents and describes the results of clinical trials evaluating these agents.

## Rituximab

Rituximab, a chimeric anti-CD20 monoclonal antibody (MOAB), is indicated in the treatment of patients with relapsed or refractory low-grade or follicular, CD20+, B cell non-Hodgkin's lymphoma (NHL) (O'Neal, 2001). In April 2001, the U.S. Food and Drug Administration (FDA) approved rituximab (Rituxan®, Genentech, Inc. and IDEC Pharmaceuticals Corporation, South San Francisco, CA) as a treatment for bulky disease and approved dosing schedules of eight weekly doses as initial treatment and four weekly doses for retreatment (Genentech, Inc., 2001). Combining rituximab with other approved agents or regimens for the treatment of NHL is being explored. For example, the use of a combination of cyclophosphamide, doxorubicin, vincristine, prednisone (the "CHOP" regimen), and rituximab resulted in a 95% response rate in 40 patients with low-grade B cell lymphoma (Czuczman et al., 1999). Another multicenter trial combined rituximab with interferon. The overall response rate in 38 patients with relapsed or refractory low-grade or follicular NHL was 45%. Long-term follow-up in this group of patients may determine whether this treatment combination leads to

Many new biotherapy agents to treat cancer are being studied as single agents and in combination with conventional cancer therapy, such as chemotherapy. These agents include the monoclonal antibodies, rituximab, trastuzumab, alemtuzumab, and IMC-C225. Radioimmunotherapy, a type of biotherapy that combines a radioactive isotope with a monoclonal antibody, also is being studied and has shown promise in the treatment of lymphoma. A tyrosine kinase inhibitor, STI 571, has been approved recently by the U.S. Food and Drug Administration. Several vaccines as cancer treatment are currently under investigation. Other biotherapy agents being investigated include angiogenesis inhibitors, such as endostatin, antivascular endothelial cell growth factor, and thalidomide, an agent that inhibits the formation of blood vessels that supply tumors.

a significantly longer time to progression than with single-agent rituximab (Davis, Maloney, et al., 2000).

Retreatment with rituximab as a single agent in patients who relapsed after a response to rituximab therapy was studied in 58 patients. The overall response rate to retreatment was 40%. Median time to progression in responders and median duration of response were estimated to be 17.8 months and 16.3 months, respectively. This finding is significant, as the estimated time intervals are greater than those achieved in patients' prior courses of rituximab therapy (Davis, Grillo-Lopez, et al., 2000).

Clinical trials for patients with NHL with bulky disease (lesions > 10 cm) are under way. These patients usually do not respond well to other therapies and have a poorer prognosis. In a study of 31 patients who received a course of rituximab, the overall response rate was 43%, with a median duration of response of 5.9 months and a median

time to progression of disease of 8.1 months (Genentech, Inc., 2001).

Clinical trials are exploring prolonged dosing with rituximab. In one study, patients with low-grade or follicular B cell NHL who had relapsed or failed primary therapy received eight weekly doses of rituximab instead of the usual four weekly doses. An overall response rate to this dosing regimen was 57%. The median time to progression and the median response duration have not yet been reached after 19.4+ months and 13.4+ months, respectively (Piro et al., 1999).

Rituximab is being investigated as an option for patients with cancers or disorders other than NHL, such as chronic lymphocytic leukemia (CLL). In a small Italian study of seven patients with refractory or relapsed CLL, rituximab was administered using schedules designed for patients with follicle cell lymphoma and was well tolerated. Although rituximab was not effective in treating nodal and splenic disease, all patients experienced a significant reduction in their peripheral blood (PB) lymphocyte count. Based on the responses

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