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New Therapeutic Approaches for Lymphoma and Chronic Lymphocytic Leukemia with Monoclonal Antibodies

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After 15-20 years of development, the potential for antibodies as targeted cancer therapy has been realized following the approval of several monoclonal antibody products for the treatment of human malignancy. These products include murine ("momabs"), chimeric ("ximabs") and humanized ("zumabs") antibodies. All were originally developed by immunizing rodents. Chimeric antibodies retain the rodent peptide sequences for the variable region while humanized antibodies retain only the hypervariable peptide sequences of the original antibody. Four monoclonal antibody products have been approved for B-cell malignancies.

Rituximab (Rituxan™)

Rituximab became the first monoclonal antibody approved for treatment of human malignancy in November 1997. It is a mouse/human chimeric antibody (ximab) consisting of variable regions from ibritumomab and constant regions of human IgG1. It targets the CD20 molecule which is expressed on normal and malignant B-lymphocytes, but not B-cell progenitors, plasma cells, T-lymphocytes, monocytes, dendritic cells, stem cells, or non-hematopoietic tissue. It is cytotoxic against CD20-positive cells in the presence of human complement and human effector cells, but also has regulatory effects on B cells by promoting apoptosis. Rituximab enhances the effects of chemotherapy agents and helps overcome resistance to many cytotoxic agents.

Single Agent Rituximab. In recurrent follicular lymphoma, four weekly infusions

of rituximab at 375 mg/m² produces response rates of 50-60% with median response durations of more than a year. As initial treatment of follicular lymphoma, response rates range from 60-70% with median durations of about 1.5 years. Giving additional courses of rituximab is associated with response rates in the range of 70-80% and median response durations beyond two years. In patients with follicular lymphoma who relapse after a response lasting at least 6 months, retreatment with rituximab results in response rates of 40-50% with a median response duration of 1.5 years. Response rates and duration of response are related to achieving and sustaining prolonged serum concentrations of rituximab, which in turn relates to antigen burden and rate of antigen production. Giving additional doses to sustain detectable serum levels results in higher response rates and longer progression-free survival in indolent lymphoma.

In other lymphomas, in the relapsed setting, rituximab has produced response rates of 40-50% in lymphoplasmacytic lymphomas, 35-40% in large B cell and mantle cell lymphomas, 50-60% in hairy cell leukemia, but only 10-15% in small lymphocytic lymphoma (SLL) and chronic lymphocytic leukemia (CLL). However, higher and/or more frequent doses of rituximab have yielded response rates of 35-45% in patients with relapsed CLL. When used as initial therapy in CLL or SLL, and followed by planned retreatment with additional rituximab, response rates of 50-60% have been achieved.

Rituximab with Chemotherapy.

Concurrent administration of rituximab with chemotherapy has produced response rates of 90-100% in follicular lymphoma, large B cell lymphoma, mantle cell lymphoma, and CLL. Randomized trials have confirmed the superiority of concurrent rituximab plus chemotherapy over chemotherapy alone, and over chemotherapy followed by rituximab. Although rates of neutropenia are somewhat higher with combination therapy, rates of infection have been the same. In one study of CHOP + rituximab in low-grade lymphoma, median progression free survival was almost seven years, but only four years for partial responders compared to more than 10 years for complete responders. In large B cell lymphoma CHOP + rituximab became the new standard treatment after a French randomized trial showed superior response rates, complete response rates, longer progression-free and overall survival compared to CHOP alone. A US trial did not confirm the differences in response rates, but did confirm the differences in progression free and overall survival. There does not appear to be an advantage to give additional rituximab to a patient who has achieved a complete response with rituximab plus chemotherapy for either indolent or aggressive lymphoma. There is increasing evidence that rituximab is particularly beneficial in the setting of tumors that over express markers associated with resistance to chemotherapy induced apoptosis.

Alemtuzumab (Campath™)

Alemtuzumab (Campath™) is a humanized MoAb that reacts with the CD52 molecule found on both B and T lymphocytes. It was approved in May 2001 based on results in patients with CLL that had recurred or been refractory to fludarabine. This zumab consists of rat hypervariable regions and human IgG1. Response rates of 30-40% were observed in patients with fludarabine-resistant CLL, with duration of response of 7-11 months. Because it reacts with both B and T cells, alemtuzumab produces significant infusion reactions in most patients. For this reason it is initially escalated from 3 to 10 to 30 mg during the first week, and then administered as 2-hour infusions of 30 mg thrice weekly for an additional 11 weeks.

The prolonged T-cell suppression that results from treatment with alemtuzumab is associated with an increased risk of opportunistic infections; so prophylaxis is recommended for pneumocystis and viruses. Because of the rather low doses that are used, sustained serum levels and good penetration of large tumor masses is unreliable; therefore, the best results have been in blood and bone marrow rather than large lymph nodes. Therapy for a more extended time period yields better results in large tumor masses, but is associated with more prolonged suppression of cell-mediated immunity. Subcutaneous administration for 18 weeks is associated with equivalent or superior response rates and is less toxic in terms of infusion reactions. That route causes significant, but manageable, local irritation. Alemtuzumab is also active in T cell and B cell lymphomas. There has been less interest in its role in B cell lymphomas because of the increased toxicity and infection rates compared to rituximab. Trials investigating alemtuzumab in combination with chemotherapy or rituximab are in progress. It is also being investigated in allogeneic stem cell transplants because of its immunosuppressive effects.

Y-90 Ibritumomab tiuxetan (Zevalin™)

The radiolabeled antibody 90-Yttrium ibritumomab tiuxetan was approved for the radioimmunotherapy of relapsed low grade and follicular or transformed lymphoma including rituximab-refractory, in February 2002. Ibritumomab is the momab that was modified with human IgG1 to create rituximab. Y-90 emits only beta radiation with a path length of 5mm. Only minimal radiation safety measures are needed because only beta radiation is emitted. In low-grade lymphoma patients with adequate marrow reserve, less than 25% bone marrow involvement with lymphoma, and a platelet count $>150,000/\text{mm}^3$, 0.4 mCi/kg (maximum of 32 mCi) produced response rates of 70-85% with a median duration of more than one year. About 25% of patients had durable complete responses that last a median of more than two years. Treatment requires coordination with nuclear medicine and/or radiation oncology specialists, who in turn have to schedule with

a radiopharmacy for delivery of Indium-111 ibritumomab tiuxetan for imaging, and Y-90 ibritumomab tiuxetan 7-9 days later for the radioimmunotherapy. Both radiolabeled antibody infusions are preceded by infusion of 250 mg/m² of rituximab. The major toxicity is reversible bone marrow suppression associated with grade III or IV neutropenia and/or thrombocytopenia in 60% of patients. Marrow counts typically nadir in the second month after treatment but recover to normal levels in the third month. Randomized trials showed Zevalin produced a higher response rate than standard dose rituximab (80% vs 56%). Response rates of 80% were seen with a 0.3 mCi/kg dose in indolent lymphoma patients who were mildly thrombocytopenic. Rituximab-refractory patients had a response rate of 74%. Clinical trials are exploring Zevalin in bone marrow transplantation instead of using total body irradiation.

rather than rituximab, is given prior to each radiolabeled antibody infusion, and 5 mCi of I-131 tositumomab is used to determine the therapeutic dose estimated to deliver 75 cGy of total body radiation 1-2 weeks later. The addition of I-131 tositumomab after CHOP chemotherapy increased the response rate of patients with low grade lymphoma. By historical comparisons Bexxar was superior to total body irradiation as part of marrow ablative therapy and stem cell rescue. As initial treatment indolent lymphoma patients, Bexxar produced responses in 90% of patients, and median progression free survival of more than three years. This trial is being closely monitored because of long-term safety issues related to radioactive iodine.

I-131 Tositumomab (Bexxar™)

I-131 tositumomab, which also reacts with CD20, was approved for use in the treatment of relapsed lymphoma in June 2003. Phase I trials established a non-marrow ablative maximum tolerated dose of 75 cGy of total body radiation and response rates of 40-80% were reported in patients with relapsed low grade or transformed B-cell lymphomas. Bexxar produced higher responses than tositumomab alone and response rates of about 70% in patients considered refractory to rituximab. Efficacy and toxicity results are virtually identical to those reported for Zevalin radioimmunotherapy. Bexxar may be somewhat less marrow suppressive than Zevalin, but it requires more complex radiation safety measures because of emission of gamma radiation in addition to the beta radiation. Free iodine released from the antibody is cleared through the urinary tract; so, patients must have an unobstructed urinary system, and dosimetric calculations are needed for every patient to calculate a therapeutic dose because of inter patient variability in retention and clearance of the iodine. Eligibility criteria and schedule of administration are similar to those for Y-90 ibritumomab tiuxetan, except that a 450 mg dose of the momab tositumomab,