Monoclonal antibodies (MoAbs) for cancer have been the subject of intense clinical investigation for nearly 2 decades.[1] Although the concept of MoAb therapy is simple, a host of unforeseen difficulties hindered the realization of clinical benefit from this therapeutic approach. The review by McLaughlin and colleagues of rituximab (Rituxan), the first MoAb approved for the treatment of cancer, describes one of the success stories in this field. Many other candidate antibodies have appeared to be equally promising during preclinical testing, only to fail during subsequent clinical trials. The lessons learned from these failures (eg, anti-B4-blocked ricin) and the successes, like rituximab, highlight the challenges involved in the development of an effective MoAb for cancer therapy.

**Obstacles to the Development of Effective MoAbs**

One challenge has been the selection of appropriate target antigens. Although hematologic malignancies are relatively unique in their expression of cell surface antigens not present on other tissues, not every antigen has proven to be an optimal target. Studies with antibodies targeting CD5,[2,3] CD19, and CD22[4] demonstrated that these antigens internalize upon antibody binding, making them poor targets for serotherapy with unconjugated antibodies. Furthermore, the tumor must persistently express antigen despite intense negative selection imposed by the antibody; otherwise, the tumor could escape therapy. Rituximab recognizes CD20, which remains stable in the face of antibody binding, making it a nearly ideal target antigen. Optimal dosing and adequate tissue penetration represent further stumbling blocks to effective serotherapy. Unlike studies with conventional cytotoxic agents, initial phase I studies with rituximab never reached a maximum tolerated dose. Some published studies have used larger doses than the currently approved 375 mg/m² weekly × 4 regimen. For example, Coiffier et al used doses up to 500 mg/m² in a weekly × 8 regimen in patients with intermediate- or high-grade lymphoma.[5] Thus, the best dose and schedule of rituximab remain to be established.[6,7]

Moreover, even when serum levels that correspond to effective in vitro cytotoxicity can be achieved, tissue levels may still be subtherapeutic, particularly within poorly vascularized lymphomatous nodes. Studies of the Campath-1H MoAb (anti-CD52) demonstrate effective penetration into bone marrow and spleen but not into lymph nodes and extranodal tissue sites.[8] In contrast, rituximab has shown efficacy even in bulky tumors. Whether its activity is augmented in the minimal disease setting requires further investigation.

As with all therapies, the potential toxicities of MoAbs must always be considered. Although acute reactions to all MoAbs are common, particularly during initial infusions, few patients require discontinuation of the agent. Subacute toxicities may vary considerably, depending on the particular antibody. Campath-1H induces significant T- and B-cell depletion, since it targets a cell surface antigen common to both lymphocyte lineages. The resulting profound lymphopenia significantly increases the risk of opportunistic infections.

To date, no major toxicity has been seen with rituximab, despite prolonged B-cell depletion following therapy. This minimal side effects profile therefore makes rituximab an attractive agent for combination therapies and as salvage therapy for patients who may have impaired marrow reserve and reduced tolerance for toxicity.

**Rituximab Combined With Chemotherapy**

In vitro data suggesting synergy of rituximab with conventional chemotherapy represent the most exciting potential for this agent.[9,10] A phase II trial of rituximab in combination with CHOP ...
(cyclophosphamide, doxorubicin HCl, Oncovin, and prednisone) chemotherapy in patients with previously untreated follicular or low-grade non-Hodgkin’s lymphoma reported a 100% response rate, with complete responses in approximately two-thirds of patients.[7] Furthermore, of eight patients who had detectable disease in peripheral blood and bone marrow, based on polymerase chain reaction (PCR) analysis for t(14;18), seven became PCR-negative in the blood and bone marrow after therapy with rituximab plus CHOP—an unusual occurrence among patients treated with chemotherapy alone.[11]

**Ongoing Cooperative Group Trials**

Several large cooperative group trials are exploring the potential synergy between cytotoxic chemotherapy and rituximab and its value as maintenance therapy. For example, the Cancer and Leukemia Group B (CALGB) is studying the efficacy and incremental toxicity of the addition of rituximab to CHOP chemotherapy in elderly patients with aggressive non-Hodgkin’s lymphoma. Already existing data demonstrate that rituximab adds little to the toxicity profile of CHOP chemotherapy alone and may enhance response rates.[7,12] Given the stability of CD20 expression, this trial also is exploring the value of rituximab maintenance by randomizing all patients with responsive disease to observation or four weekly doses of rituximab every 6 months for 2 years. The value of rituximab maintenance therapy in low-grade lymphoma is the subject of two other cooperative group trials. The Eastern Cooperative Oncology Group (ECOG) is conducting a phase III trial of cyclophosphamide and fludarabine (Fludara) vs CVP (cyclophosphamide, vincristine, and prednisone), followed by rituximab or observation. The Southwest Oncology Group (SWOG) is performing a phase II trial of CHOP followed by rituximab, with special attention to measurement of minimal residual disease.

The CALGB also is examining whether the addition of rituximab to fludarabine improves outcome in patients with chronic lymphocytic leukemia (CLL). To date, no studies of rituximab in CLL have been published, but early studies that included patients with small lymphocytic lymphoma had a relatively low response rate, which was attributed to the tumor’s relatively low level of CD20 expression. There is also the potential for synergistic toxicity between fludarabine and rituximab due to combined immunosuppression.

**Conclusions**

Thus, rituximab represents a significant advance in the treatment of lymphoma. It also demonstrates proof of principle that serotherapy is feasible under the right conditions, including the targeting of stable antigens, adequate tissue penetration, and a favorable toxicity profile. Advances also are being made in the development of MoAbs for the treatment of solid tumor malignancies. Recently, Riethmuller et al reported the 7-year follow-up results of a phase III trial of the 17-1A antibody in patients with resected Dukes’ C colon cancer.[13] They demonstrated a 32% decrease in overall mortality and a 23% decrease in recurrence rate, compared with observation. Similarly promising data have emerged from trials of trastuzumab (Herceptin) in metastatic breast cancer and led to the recent FDA approval of this MoAb for the treatment of metastatic breast cancer. These trials demonstrated the efficacy of trastuzumab as a single agent,[14] as well as its synergy with conventional combination chemotherapy.[15] Although not discussed in this article, exciting progress also is being made in the field of iodine and yttrium radioimmunoconjugates. Response rates of 30% have been reported in patients with refractory lymphoma.[16] Further studies with rituximab and other promising MoAbs will help delineate a potentially important role of serotherapy in the treatment of a variety of malignancies.

**References:**


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