Lymphomas – The Diseases That Taught Us Monoclonal Antibodies Can Work

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This issue of *Oncology Spectrums* is devoted to the area of lymphoma. When the technologies for production of monoclonal antibodies were first worked out, there was a tremendous amount of enthusiasm about the clinical application of the technology.[1] However, as is usual with most new discoveries, this initial enthusiasm was followed by disappointment in the clinical arena—mostly because the clinical trials of monoclonal antibodies were conducted against tumor types where the antigen against which the antibody was produced had variable expression on the patients' tumor. Early clinical diagnostic work with radiolabeled monoclonal antibodies was also disappointing, largely because of nonspecific trapping of the material in organs and also because repeated use of these mouse monoclonal antibodies (eg, serial scans) resulted in allergic reactions, some of them severe.

Continued refinement of production of the monoclonal antibodies with development of chimeric (man-mouse) antibodies and indeed fully humanized monoclonal antibodies has nearly eliminated the allergic reaction problem for possible repeated scanning. However, humanizing monoclonal antibodies still didn't solve the problem of what antigens should be targeted.

There had been a tremendous amount of work using antibodies to try to classify lymphomas and leukemias. With that work came the identification of antigens such as CD20, CD52, CD33 and others. Since some of these lymphomas and leukemias were monoclonal in nature, they provided an ideal clinical situation in which to try monoclonal antibodies as therapeutic agents again. The monoclonal antibody against CD20 positive lymphoma cells (generally found in low grade lymphomas) that really broke the field wide open was rituximab.

The initial response rates were modest (40–64%) and complete responses were more unusual.[2,3] However, with a new mechanism of action and real responses, rituximab was rapidly and appropriately approved for treatment of patients with advanced refractory low-grade lymphoma. What is even more encouraging is the activity of rituximab when used in combination with CHOP chemotherapy (cyclophosphamide + hydroxyldaunorubicin + Oncovin (vincristine) + prednisone in patients with high grade lymphoma. Indeed in randomized trials in patients with high grade lymphoma the combination of CHOP + rituximab provided superior survival when compared with CHOP alone.[4] Thus, the field of monoclonal antibodies came into its own—mostly because of the science associated with lymphoma.

Since the success of rituximab, there have been other monoclonal antibodies approved not only for patients with lymphoma but also for patients with acute and chronic leukemia or breast cancer (see Table 1) and there are many more therapeutic monoclonal antibodies on the way, now in late stages of development. In addition, there are monoclonal antibodies used to treat patients with arthritis and other conditions.

There are many who credit lymphoma for teaching us how to use monoclonal antibodies. The research of this disease has been an exemplary combination of the right science and the right clinical trial situation. This experience also reminds us once again that the design of our clinical trials needs to match the science so that we can maximize our chances for a successful outcome for our patients. Hopefully, as you read this issue of *Oncology Spectrums*, you will realize what a terrific therapeutic field lymphoma has helped to establish. OS

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TABLE 1. MONOCLONAL ANTIBODIES APPROVED FOR USE IN TREATMENT FOR CANCER PATIENTS

PRODUCT	TRADENAME	USED FOR	TARGET ANTIGEN
Alemtuzumab	Campath	Treatment of non-Hodgkin's lymphoma, organ transplant rejection, and multiple sclerosis	CD52
Ibritumomab tiuxetan	Zevalin	Prevention of low-grade non-Hodgkin's lymphoma; treatment of relapsed or refractory B-cell non-Hodgkin's lymphoma	CD20
Rituximab	Rituxan	Treatment of intermediate or high-grade non-Hodgkin's lymphoma patients in combination with standard chemotherapy; previously untreated intermediate or high grade non-Hodgkin's lymphoma patients; indolent and aggressive non-Hodgkin's lymphoma in combination with CHOP chemotherapy in previously untreated patients	CD20
Trastuzumab	Herceptin	Used in combination with chemotherapy for the adjuvant treatment of early stage breast cancer in patients who express the human epidermal growth factor receptor-2 protein	HER-2/neu

CHOP=cyclophosphamide, hydroxyldaunorubicin, vincristine, prednisone.

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