Monoclonal Antibodies in Lymphomas

Richard R. Furman, MD,
John P. Leonard, MD,
Julian Decter, MD,
and Morton Coleman, MD

Summary

Immunotherapy has markedly altered the treatment options available for patients with non-Hodgkin’s lymphoma (NHL). Monoclonal antibodies have revolutionized the treatment of cancers in two respects. First, they represent a therapy with a different mechanism of action than chemotherapy. By providing an alternative type of attack, they may improve outcomes through better efficacy. Second, they represent a major step forward in improving the tolerability of cancer therapies. As a more targeted therapy, monoclonal antibodies enable patients to receive treatment that might not have otherwise been tolerated, potentially extending their lives and decreasing symptomatology. Although each monoclonal antibody was initially developed for one indication, their approvals have enabled exploration of other possible indications. We are only beginning to understand the breadth of diseases, malignant and non-malignant, that might benefit from treatment with these monoclonal antibodies, and how best to use them. Attempts to further improve outcomes in NHL are being explored, including the role of modifications of dose and schedule, chemotherapy combinations, and through the use of other biologics. Monoclonal antibodies represent the epitome of targeted therapy and have the potential to move forward the treatment of lymphoma more than any other development since the first use of multiagent chemotherapy.

Key Words: Monoclonal antibodies; immunotherapy; targeted therapy.

1. INTRODUCTION

The goal of cancer therapy is to eliminate the malignant cells without harming the patient. Current cancer treatment is dependent primarily upon three different modalities: surgery, chemotherapy, and radiation. Surgery and radiation therapy are effective at removing local disease while only damaging non-malignant tissue in the immediate
vicinity. Thus, although surgery and radiation have no damaging effects on distant cells, they also do not treat malignant cells that have spread outside of the immediate area. Chemotherapy, on the contrary, penetrates throughout the body and is able to eliminate malignant cells that have spread beyond the local area. Unfortunately, chemotherapy will also damage normal tissues.

Although chemotherapy might demonstrate specificity by inhibiting a particular enzyme or damaging a particular protein, the targets of chemotherapeutic drugs are also typically found in normal tissue. This results in chemotherapy harming normal cells, with the primary impact generally expressed in rapidly dividing tissues, such as the bone marrow and gastrointestinal epithelium. The “selectivity” of chemotherapy is generally ascribed to the increased sensitivity of cancer cells to these agents. This increased sensitivity results, in part, from the malignant cells being under greater biologic stress because of their greater cell proliferation rate and energy demands, and because of less time and opportunity for repair prior to the next cell division. Although this strategy is somewhat effective, there is a great deal of damage to normal cells. This damage is seen as toxicities of therapy. These toxicities often result in painful and undesirable outcomes and limit the use of these conventional treatments.

If cancer treatments could be delivered specifically to the cancer cells, there would be the expectation of less associated toxicity. The therapy could also be delivered more safely and possibly in higher doses, potentially with greater effectiveness. Antibodies offer a means to target specific cells in the body, thereby limiting the toxicity to non-targeted tissues.

Antibodies are composed of two identical heavy chains and two identical light chains held together by disulfide bonds. Each antibody can bind two copies of its target antigen. The antigen binding domain is composed of the variable region of one light chain and one heavy chain. Each light chain possess one variable and one constant region. Each heavy chain possess one variable region and either 3 or 4 constant regions depending upon the immunoglobulin class. The effector functions of an antibody are mediated by the constant domains of the two heavy chains. (See Figure 1).

The specificity of antibody therapy results from features of both the antibody and the antigen. Through the processes of VDJ recombination, somatic hypermutation, and nucleotide base addition, the immune system is able to generate antibodies that possess extraordinary specificity. The second level of specificity is derived from the selection of an appropriate antigen whose expression is restricted to the targeted cells. The ideal target for a therapeutic antibody would be an antigen expressed only on malignant cells. Unfortunately, the identification of such malignancy-associated antigens, or tumor markers, has been difficult. The epitome of such selective expression would be the idiotype demonstrated by a particular lymphocyte clone. This target, created by the hypervariable region of the surface immunoglobulin of the lymphocyte, is unique to that one clone of lymphocytes. Currently, many investigators are working on developing anti-idiotype vaccines as treatments for lymphomas. This approach is difficult as it requires that a novel treatment be developed for each individual.

Lymphocyte differentiation is well characterized by the expression of a series of surface proteins termed “cluster of differentiation” (CD) antigens. Given the ontogenic relationship between lymphomas and normal lymphocytes, the antigens expressed on lymphomas are almost always expressed by their non-malignant counterparts. The damage that might result from targeting of an antigen on both normal and malignant