Radioimmunotherapy in Experimental Animal Models: Principles Derived from Models

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Abstract

Experimental animal models have made it possible to study some of the biological, biochemical, and pharmacological parameters involved in the use of radiolabeled monoclonal antibody for therapy and detection. Although such models are less appropriate for studies of dosimetry and the host's immune response to the monoclonal antibody, some general principles have been derived from the various model systems that have largely held true in studies in patients. Some of the points learned from experimental animal models will be illustrated in this paper.

Biological and Biochemical Considerations

Biological functions must also be considered in the context of the target antigen, and its molecular form, may have great effects on the ability of the mAb4 to effectively target to tumors in vivo. Once targeted, these features may also affect the residence time at the tumor.

The isotope of the mAb, as well as the animal source from which the hybridoma cell was derived, have a large effect on the serum half-life of the mAb and its ability to reach target sites. Modifications of the mAb, such as fragmentation into Fab or F(ab)2, will also modify function both in vitro and in vivo. The use of chimeric antibodies composed of mouse F(ab) fragments combined genetically with human Fc segments is just beginning, and this approach appears to be very promising clinically, as evidenced by a recent report (1). Initial studies using chimeric antibody are discussed by Buschbaum et al. (2) in this issue.

Antibody purity and immunoreactivity have also been shown to be important issues that must be assessed. MAbs prepared from ascites may be contaminated with nonspecific mouse immunoglobulins. Antibodies produced either in vitro or in vivo may be contaminated with multiple serum components and even other immunoglobulins. Such contamination as well as the method of purification, which often involves multiple steps including large changes in pH and ionic strength, may result in a product that is not 100% immunoreactive when labeled. The methods for labeling with either radiohalides or chelated radioisotopes may further reduce the immunoreactivity of a final product. Significant losses of immunoreactivity have been reported in antibody preparations used in patients for radioimmunotherapy (3). This fact must therefore be taken into consideration in the interpretation of the results.

Biological functions must also be considered in the context of the use of an mAb. For example, many MAbs will adequately fix complement in the presence of rabbit or guinea pig serum but not in human or mouse serum. Certain MAbs bind to biologically active receptor sites, resulting in stimulation or inhibition of cell growth or function (4, 5). These attributes may not be present or may be different in the various model systems. Likewise, the use of mouse MAbs in mouse model systems represents a syngeneic system, which differs substantially from the xenogeneic system in the clinical situation. The immune response of the host to the mouse mAb is one of the most difficult obstacles facing the use of MAbs in humans (6, 7). Most current animal models are not appropriate for addressing this question. However, the use of mouse MAbs in the recently developed primate models may yield new answers to the problem of the host's immune response (8).

Target Considerations

A number of issues related to the biology and biochemistry of the target antigen, target cells, and tissues will also affect on the effectiveness of mAb use in vivo. These tissues have been addressed in models and many of the principles learned have predicted the characteristics of the MAbs when used in patients.

The quantity of target antigen, its expression on the cell surface and among tumor cells (heterogeneity), its modulation from the cell surface after antibody binding, and the presence of circulating antigen will all bear upon the success of antibody targeting and subsequent delivery of a therapeutic dose of radioisotope to a tumor. Circulating target antigen has been studied in mouse models, where increasing antigen load in the plasma has resulted in decreased delivery of isotope to the target (9). Similar blocking effects have now been observed in patients given injections of antidiotypic antibodies who have circulating idiotypes (10). Heterogeneity in the expression of target antigen has been shown in a mouse lymphoma model system, and escape of tumor cells that bear little antigen after treatment has been demonstrated (11). This has directly predicted the same problem in the treatment of human lymphomas, where mAb to tumor-specific idiotypes selected for antigen-negative variants resulted in relapse (12).

Modulation of antigen from the cell surface following antibody binding was demonstrated in mice 20 years ago (13). A variety of mechanisms of internalization or shedding of many glycoproteins have been studied since then. Recently, in the initial studies of MAbs in the treatment of human leukemias, the problem of rapid modulation reappeared as a major obstacle to therapy (14). This problem has continued to plague efforts to deliver an adequate dose of radioisotope to leukemias and lymphomas. The development of MAbs to nonmodulating targets such as glycolipids and mucins may abrogate this problem (15). Alternatively, it may be possible to take advantage of the phenomenon of modulation as a means of internalizing radioisotopes (16).

Modulation of target antigen and bound antibody can also result in catabolism of the radiolabeled antibody with release of radioisotope (17). In the case of radioiodine, this was shown in the murine model to result in the excretion of iodine into the stomach, gastrointestinal tract, and urinary system. In contrast, when the same mAb was labeled with either radioidine or radiotyttrium, the catabolized radiometals were predomi-
nantly accumulated in the liver and bone, respectively (18). Subsequently, these effects have also been observed in patients infused with radiolabeled mAbs prepared in a similar manner (19).

Pharmacology

General pharmacological principles have been derived from initial animal studies. In a murine leukemia model uptake of radiolabeled antibody was extremely rapid, within hours, as might be expected since the target cells are readily accessible (17). In contrast, in models of solid tumor, uptake is often delayed and ratios of antibody bound to specific sites compared to nonspecific sites may actually increase with time over several weeks. In studies by Welt et al. (20), specific imaging improved over 2 weeks and uptake ratios to tumor versus liver reached 100,000 by 8–10 weeks after injection. Studies of mouse mAb in primates have demonstrated the increased difficulty in delivering mAb to more solid tissues (8). These general principles have largely held true in studies in patients, where mAbs directed towards targets on B- and T-cells (lymphomas or leukemias) can be shown to reach tumor cells within hours to 1 day, and mAbs directed against antigens on solid tumors require several days for optimal imaging (19, 21).

Rapid targeting will also result in rapid plasma clearance. This has been shown in murine models and has been confirmed now in patients. mAbs directed against antigens which are less accessible, on the other hand, have longer plasma half-lives.

Combinations of mAbs and Other Agents

As experience with mAbs grows, studies involving mAb used in conjunction with other agents and modalities will become increasingly important. Autologous rescue of bone marrow following radioimmunotherapy of lymphoma has already been used in humans, and models of this modality need to be developed. In this supplement, Morton et al. (22) outline the parameters of bone marrow rescue in mice using syngeneic bone marrow after treatment with 90Y-labeled antibody. Alternative methods to save bone marrow include the use of recombinant growth factors such as tumor necrosis factor, granulocyte-colony-stimulating factor, granulocyte-macrophage-colony-stimulating factor, interleukin 1, interleukin 3, and others. Blumenthal et al. (23) in this issue report encouraging results achieved in radioprotection of bone marrow by pretreatment of mice with recombinant interleukin 1 before infusion of 131I-labeled antibody. Because of the complexity of the interaction of the biological agents and radiosotopes, models in which to study and derive principles of use of these new agents in combination with mAbs will be extremely important.

References

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