Immunotoxins

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28. Clinical studies: Solid tumors

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Introduction

Immunotoxins (ITs) permit delivery of a therapy at the tumor site specifically. The use of ITs as therapy of patients with solid tumors presents problems which require unique solutions. These include stability in vivo, cellular heterogeneity, access to tumor, biodistribution, and the immune response to the immunoconjugate (Table 1). It is necessary to address some of these issues before contemplating entry into clinical trials, whereas others are more appropriately undertaken after clinical trials have been initiated, using the results of the clinical observations as a focus for planning improvements as part of a second generation effort. This involves both optimizing the administration of the currently available products and developing new, improved products.

It is important to know that the conjugates can be expected to have acceptable stability in vivo. Without this, it would not be reasonable to expect the antibody to achieve targeting of the toxin to tumor cells. Such stability can be demonstrated at the preclinical level in vitro by incubation of the IT in serum at 37°C and in vivo by administration to experimental animals. Once a conjugate with reasonable stability has been achieved, one could initiate clinical trials with this agent while proceeding, if appropriate, with second generation efforts to enhance stability through new or improved conjugation techniques.

Similarly, the question of cellular heterogeneity should be considered before initiation of clinical trials. It would only be reasonable to proceed in the trials if it was likely that the antibody used for targeting had reactivity to a high proportion of cells in the patient's tumor. This could be achieved by 1) preselecting an antibody having broad cross-reactivity with tumors of a particular histologic type, 2) selecting the patients to be treated on the basis of demonstrated reactivity of the antibody with biopsies of their tumors, or 3) custom construction of an antibody having reactivity to the patient's tumor. The use of cocktails of ITs to attack a higher proportion of cells in the population could be considered as a second generation effort. Similarly, second generation efforts could involve the use of agents, such as interferon,

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Table 1. Unique problems in consideration of the use of immunotoxins in therapy of solid tumors

1. Stability of conjugates in vivo
2. Cellular heterogeneity
   - — inter tumor
   - — intra tumor
   - — cell cycle/ploidy
   - — antigen expression
3. Access and localization in the tumor.
4. Biodistribution
   - — uptake by the reticuloendothelial system via carbohydrate receptors
   - — internalization into cell
   - — intracellular distribution
5. Immune response to immunoconjugate
   - — murine antibody
   - — ribosomal inhibiting protein

to increase antigenic representation of the tumor cells. Custom construction of an antibody to a patient's tumor is impractical because 1) the time involved generally precludes this approach and 2) for most tumors, antibodies are already available so that all that is necessary is to screen the patient's tumor and select the antibody having appropriate reactivity.

The issue of access of the IT to the tumor and localization can best be addressed after the clinical trials have been initiated. Clinical trials are necessary in order to determine whether or not the IT reaches the tumor and the extent of localization. It is important to determine the optimal dosing regimen for delivery of IT to the tumor. In addition, there are a number of other ways which may improve localization. These include, among other things, increasing vascular permeability, antigen representation, or altering the binding affinity of the antibody.

Some ribosomal inhibiting proteins, such as the A chain of ricin, contain carbohydrates which bind to carbohydrate receptors in the reticuloendothelial system. Immunoglobulins also have carbohydrates which, if exposed, could also bind to such carbohydrate receptors. Clinical trials are necessary to determine the clearance and side effects of the IT to assess the relevance of such carbohydrate binding in therapy. If relevant, efforts could be aimed at deglycosylation/hypoglycosylation and/or use of agents to block the carbohydrate receptors, with the realization that greater toxicity or a different spectrum of toxicity might result because of greater availability of IT.

Finally, entry into clinical trials is necessary to determine if the patients mount an immune response to the components of the IT and, if so, to determine a means to abrogate the immune response. This could be done through second generation efforts using 1) agents to modulate the immune response, 2) induction of tolerance, or 3) modifying the immunoconjugate

to make it less immunogenic. It should be noted that the possibility of the occurrence of an immune response is not unique to IT therapy. It will be a consideration with all products involving monoclonal antibodies since they all represent foreign proteins. The problem may not be circumvented by the use of human monoclonal antibodies since the idiotype is foreign to the patient and an immune response may still occur. Preliminary evidence suggests that this, indeed, is the case.

It is clear from this discussion that there are many considerations in judging the appropriate time for entry into clinical trials. It is important that any agent used in clinical trials be safe and have a reasonable chance for therapeutic efficacy. On the other hand, there is only so much information which can be gained through preclinical evaluation, and then it is necessary to turn to studies in patients in order to gain further information. It is likely that in upcoming years we will see additional clinical testing of ITs and that the information gained from these trials will be used in second generation efforts to improve the efficacy of these products.

FDA review

ITs present special problems in preclinical evaluation that are unlike those presented by other cancer therapeutics [1]. These are shown in Table 2 and are discussed below. These considerations follow concepts proposed by the Food and Drug Administration of the United States in its document entitled *Points to Consider in the Manufacture of Monoclonal Antibody Products for Human Use*.

Binding activity and specificity

For solid tumors, it is important that the antibody to be used in the construct of the IT shows specific reactivity to a high percentage of tumors of the same histological type obtained from various individuals. Techniques often used to evaluate binding include enzyme-linked immunoassay (EIA), radioimmunoassay (RIA), flow cytometry, immunoperoxidase staining, and immunofluorescence.

The antibody must also show reactivity with a high percentage of cells in the population. At the present time, it is thought that ITs kill only the cells to which the antibody component of the IT binds because internalization of the A chain by each cell is necessary for subsequent cell killing. This is unlike the situation with chemotherapeutics and radiotherapeutics conjugated to monoclonal antibodies in which cells surrounding the bound conjugate would also be killed.

Because it has been reported that one ricin A chain entering the cytosol is sufficient to kill the cell [2], it is essential that antibody used in conjugates with each material not have any important cross-reactivity with normal

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