Current Status of Radioligand Antibodies in the Treatment of Malignancy

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ABSTRACT

Monoclonal anti-tumor antibodies labeled with a radioactive moiety present an exciting new approach to cancer therapy. With the advent of hybridoma technology, monoclonal antibodies can now be produced in quantity. Indeed, antibodies against tumor-related and tumor-specific antigens have been produced, labeled with a radioactive substance, and used therapeutically. The rationale for this therapeutic approach and the results of human clinical trials will be reported herein.

Introduction

Radiation therapy is a highly effective modality in the treatment of cancer. In the early stages of cervical and laryngeal cancer, radiation treatment alone consistently produces cure rates in excess of 85 percent. Even in patients with advanced local malignancies, radiation therapy may offer a chance for cure. There are several factors, however, which currently limit the therapeutic benefits of ionizing radiation. Patients with distant metastases will not be cured by any local control modality, such as radiation therapy. Although radiation therapy offers much in the way of palliation of local symptomatics, once disease has spread beyond the regional lymph nodes, cure with radiation will not be possible. Another limitation of treatment with ionizing radiation is normal tissue tolerance. Precise beam shaping and the use of multiple treatment ports allow high tumor to normal tissue doses; at times, sufficient radiation to eradicate the malignant disease can not be given without causing unacceptable complications.

The ability to label a tumor-specific or tumor-related antibody with a radioactive substance such as I would, ideally, overcome these limitations by allowing ionizing particles to locate preferentially in sites of malignant growth. Until relatively recently, however, it was not possible to produce antibodies in sufficient quantity for therapeutic purposes. Now, with the advent of hybridoma technology, it is possible to produce large quantities of monoclonal antibodies. These monoclonal antibodies can be raised against oncofetal antigens, such as carcinoembryonic antigen (CEA) or alpha-
fetoprotein (AFP), or against tumor-specific antigens, such as the p97 antigen associated with melanoma.13

Hybridomas

Hybridomas are hybrid cells formed by the fusion of a splenic lymphocyte that produces a desired antibody and a non-secreting myeloma cell.9,18 The resultant clone of cells expresses both the lymphocyte-specific antibody and the immortal character of the myeloma cell. The hybridoma cells can be maintained indefinitely in vitro in mass culture or in mouse ascites. Using hybridoma technology, it is possible to produce large quantities of a specific monoclonal anti-tumor antibody. Simply producing antibodies in quantity, however, is not sufficient. Several conditions must be met if any significant tumor kill is to be accomplished.

First, it is necessary to isolate antigens with the greatest identity to the tumor. The antigens must also be accessible to antibodies, which generally means that they must be surface antigens. The antibodies must also be produced in quantity and have high immuno-reactivity. Cross reacting antibodies must be eliminated. If the antibody is to be linked to a radioactive moiety, then it should be possible to radiolabel the antibody with preservation of immuno-activity. Also, it is often necessary to modify or fragment the antibodies for best results. (Intact antibodies can be immunogenic themselves and are usually picked up avidly by the reticuloendothelial system.)9

Another consideration is the proper ionizing isotope for maximum cytotoxic effect. To date, 131I has been the isotope of choice. Several efficient methods already exist for iodination of antibodies.3 131I also emits primarily high energy beta radiation. These electrons can deposit considerable energy over short ranges and thus produce localized cell kill. The minor gamma emission of 131I can be detected by gamma camera for localizations. With a physical half life of 8.1 days, 131I can deliver a sufficient radiation dose without necessitating long radiological hospital isolation. In addition, there is a considerable body of experience in the therapeutic use of 131I.4 While primary gamma emitters such as 125I, 123I, and 99m-TC have been used successfully in the radioimmunodetection of cancer, these isotopes have not proven as successful in therapy as the primary beta emitter 131I.9

Radiolabelled Anti-tumor Antibodies

Certainly in theory, radioactively tagged anti-tumor antibodies present many therapeutic advantages. The antibody would localize in areas of disease and, therefore, high doses of radiation could be delivered in cancerous tissues with relative sparing of normal tissue. With systemic injection of antibody, metastatic sites as well as the primary site could be treated.

Can malignancies be successfully treated with radiolabeled anti-tumor monoclonal antibodies? Evidence supporting this contention exists from in vitro experiments, animal models, and human clinical trials. Several investigators8,16 have derived radiation cell survival curves using radiolabeled monoclonal anti-tumor antibodies in cell culture systems. They have demonstrated that while the antibodies alone were not cytotoxic, the radioactive complexed antibodies were. Cell killing was also specific only for the malignant cells targeted by the antibody. Multiple studies have also been performed using animal tumor models1,26,27 or xenografted10,12 malignancies. These studies have demonstrated the feasibility of therapeutic radiolabeled anti-tumor antibodies against cancer.
Several clinical trials have been performed on the efficacy of radioactive labeled antibodies in the treatment of human malignancy, including hepatocellular carcinoma, Hodgkin's disease, ovarian cancer, neuroblastoma, and melanoma. The investigators working on these projects have variously attempted to define the characteristics of the antigen, the dosimetry of the radioactive substance in both normal and tumor systems, the response to treatment, and toxicity.2,5,10,13,15,21,22

By far the most common radioligand used therapeutically in humans has been $^{131}$I. Iodination of antibodies is a common procedure and with its energetic beta radiation and biologic half life of 8.1 days, $^{131}$I is superior to the other I isotopes for therapy. Because of uptake of I by the normal human thyroid gland, patients are given Lugol's iodine prior to therapy.13 The radioactive complexed antibody is generally administered intravenously, although other routes have been used.

Larson13 et al., in a phase I clinical trial, treated seven patients with advanced metastatic melanoma with an $^{131}$I labeled monoclonal antibody to the p97 melanoma antigen. Larson had previously studied 33 similar patients with non-therapeutic doses of $^{131}$I anti-p97 and had found antigen-specific localization. Patient doses in this study ranged from 132 to 529 mCi $^{131}$I. Dosimetry estimates were that for every 100 mCi given there were 1,040 rads delivered to the tumor, 325 rads to the liver, and 30 rads to the bone marrow. Several patients treated in this manner have shown tumor regression;14 however, responses have been short lived.

**Therapeutic Considerations**

Toxicity to therapy in this clinical study was acceptable. Acute reactions were uncommon but included chills and fever, transient hypertension, and skin rashes. Radiation side effects were mild with temporary drops in platelet and white counts. Bone marrow depression is a toxic effect of radiation when doses of greater than 500 mCi $^{131}$I anti-p97 are given.

Order et al. at Johns Hopkins University has taken another immunologic tack and has chosen a general tumor-related antigen to target. Ferritin can be selectively synthesized and secreted by hepatocellular carcinoma, Hodgkin's disease, neuroblastoma, and occasionally by other solid tumors such as breast cancer and lung cancer.20,21,26 Anti-ferritin has been labeled with $^{131}$I and has been used to treat patients with Hodgkin's disease15 and hepatocellular carcinoma.19,22 One hundred and five patients with hepatocellular carcinoma were treated with $^{131}$I anti-ferritin injected intravenously and 48 percent of these patients obtained a partial response and four percent a complete response. While most of these responses proved transitory, one patient remained in complete remission for 3.5 years.22 In a series of $^{131}$I anti-ferritin treated patients with Hodgkin's disease who had failed all other therapy, there was a 40 percent partial response rate and a 70 percent remission of B symptoms.15 Unfortunately, no lasting responses or cures were obtained.

No treatment-related deaths in either study using $^{131}$I anti-ferritin occurred. The major toxicity was bone marrow depression particularly manifested as thrombocytopenia. The degree of bone marrow depression was related not only to total dose of the $^{131}$I anti-ferritin but also to prior treatment with external beam radiation and chemotherapy.

Thirty-seven patients with primary non-resectable intrahepatic cholangiocarcinoma have also been treated with $^{131}$I labeled anti-CEA23 in combination with standard external beam radiation and chemotherapy. Twenty-six percent of patients exhibited partial responses
with one patient remaining in remission for four years. Again, toxicity of therapy was acceptable.

Monoclonal antibodies against neuroblastoma cells have also been developed. Investigators have treated four children with disseminated neuroblastoma with $^{131}$I antibodies against neuroblastoma.\textsuperscript{10} Two children with massive bulky disease showed no response. One child, however, had a definite response with clearance of bone marrow and healing of bone lesions for eight months. The authors hypothesized that targeting smaller amounts of tumor is more efficient and that this therapy may be more beneficial for patients with minimal tumor burdens. Bone marrow toxicity was the organ limiting factor, with all patients having some decrease in white counts. Acutely, all patients experienced pyrexia and several patients had mild episodes of nausea and vomiting.

Although the trials previously cited involved radiolabeled antibodies injected intravenously, this is not the only route of administration possible and indeed other routes are sometimes to be preferred.\textsuperscript{5} Using intraperitoneal injections of $^{131}$I anti-tumor antibodies, complete remission was obtained in six of 15 patients with ovarian cancer. Unfortunately, all patients eventually relapsed. Intrapleural injections were successful in palliating malignant pleural effusions in six of seven patients, and intra-pericardial injections for malignant pericardial effusions were successful in three of three patients. A patient with glioblastoma multiforme was treated intra-arterially with some clinical improvement in symptomatology. An $^{131}$I labeled antibody has also been injected intra-the-cally to treat successfully a neoplastic meningitis arising from a pineal tumor.\textsuperscript{2}

Overall, the complications seen with radiolabeled antibodies used therapeutically have been minimal. The most severe acute effects have been seen secondary to allergic reactions to mouse immunoglobulin,—pyrexia, chills, and rash. The most serious side effect of the radiation has been bone marrow suppression, which in all but a few cases has been mild.

What has been learned from the human trials of radiolabeled anti-tumor antibodies? Antibodies can be produced which exhibit a high degree of specificity to tumor cells. High radiation doses can be delivered to tumor with relative sparing of normal tissues; therapeutic responses are possible; and side effects are acceptable. However, to date, although tumor regression has occurred and symptoms have been ameliorated, no cures have resulted from this therapy.

Several problems with therapeutic monoclonal antibodies remain.\textsuperscript{7,25} Complete tumor specificity of antibodies has yet to be obtained. All monoclonals tested exhibit some degree of uptake in normal tissues. Modulation of the antigen expression by the cancer cells can occur with the malignant cells somehow disguising the target antigen. The very basic problem of tumor heterogeneity also works against therapy with a single monoclonal antibody.

Following are some potential approaches to improving therapy:

1. Use of immune fragments rather than intact globulin (decrease immunogenicity and uptake by the reticuloendothelial system).
2. Use of sufficient quantity of antibody.
3. Route of injection—intracavity or intra-arterial may in some cases be preferable to intravenous.
4. Use of multiple monoclonal antibodies to multiple tumor antigens.
5. Complexing of alpha emitting isotopes\textsuperscript{11} to the monoclonal antibodies to obtain a higher degree of radiobiological effectiveness.

In summary, while therapy with radiolabeled antibodies has not yet produced dramatic cures of metastatic disease, the potential for effective therapy is present. As the technology in the field improves and as our understanding of tumor biol-
ogy and behavior expands, continued progress in this area is certain to occur.

References


