EDITORIAL

Radioimmunotherapy of Cancer: Arming the Missiles

The advances made in the development of anticancer monoclonal antibodies (Mabs), and their successful use in diverse laboratory and clinical procedures, have spurred considerable interest in their potential role in the treatment of cancer. Mab immunotherapy can involve the administration of unconjugated, or "naked," antibodies for direct killing and as active immunogens (vaccines), or as carriers of drugs, toxins or isotopes. Toxin and drug immunoconjugates need to be accreted by each cell and then transferred into the cytosol to be effective. In contrast, radiolabeled Mabs can kill cells at a distance from the targeting, without the Mab conjugate being internalized. Therefore, radiolabeled Mabs can distribute their cytotoxic energy to antigen-negative cells in the vicinity of antigen-positive cells, thus alleviating some of the problems of cell- and antigen-heterogeneity within a malignant mass.

The attractive feature of radioimmunotherapy (RAIT) is the prospect that most normal tissues are spared intensive radiation. Unfortunately, RAIT has thus far failed to fulfill this promise. Nevertheless, considerable progress in RAIT in recent years suggests that many of the major problems can be overcome. Based upon clinical experience of over a decade, mostly with ^{131}I-labeled polyclonal and Mabs, it has been found that: (a) partial and transient responses can be achieved in certain solid tumors, (b) lymphoproliferative malignancies are generally more responsive to RAIT, (c) there is usually, but not always, a dose-dependent effect, (d) bone marrow has been the dose-limiting organ and the sole site of known toxicity, (e) the amount of radionuclide targeted to tumor is very small, since from 0.0007%–0.01% of the injected Mab dose per gram of tissue is targeted, (f) the total dose of radiation delivered to tumor is generally low, usually less than 2,000 cGy and often less than 1,200 cGy, especially with ^{131}I-labeled Mabs, and (g) murine Mab immunogenicity has limited the use of multiple courses of therapy (*1–6*). Toxicity is principally thrombocytopenia, with nadirs appearing 4–6 wk post-therapy; leukopenia also results, but is usually less severe. Among the leukocytes, the B-lymphocytes appear to be the most radiosensitive population (*7*). The extent of hematological toxicity is dose-dependent and is also related to the patient's bone marrow status as a result of prior therapy. The radiosensitivity and good vascularization of lymphomas and leukemias probably contribute to their showing a relatively good responsiveness to RAIT. For example, ^{90}Y-labeled anti-ferritin polyclonal antibodies given to patients with end-stage Hodgkin's disease has resulted in a 62% response rate (50% complete remission); these patients also received autologous bone marrow (*8*). Very high ^{131}I-Mab radiation doses (over 600 mCi) administered with bone marrow transplantation to patients with B-cell lymphoma resulted in all four patients showing a complete remission (*9*). Overall, usually at least half of patients with lymphatic tumors have responded to RAIT (*6*). However, it is also interesting that low doses of ^{131}I, below 50 mCi, can result in therapeutic responses in patients with B-cell lymphoma (*10*).

In contrast to lymphoreticular neoplasms, patients with solid tumors have responded relatively poorly to RAIT. In the majority of studies, this has been in the range of 20%, with rare reports of complete remission (*4,5,6,11*). The tumor doses achieved, usually with ^{131}I, have been mostly less than 2,000 cGy, whereas higher doses are probably required. Thus, the majority of studies have involved ^{131}I and intact murine Mabs. This radionuclide has a long history in thyroid cancer therapy and is suitable for RAIT, having an average beta energy of 0.183 MeV and a physical half-life of 8 days, while emitting gamma rays for imaging and quantitation. It is also very easy to bind to antibodies, and the minimal toxicity to normal tissues (hypothyroidism) and the extensive clinical experience with this isotope favor its use. However, it has shown relatively low tumor dose rates of 5 cGy/hr in clinical studies (*4*), and rapid excretion after antibody degradation and/or dehalogenation has been observed. Also, with ^{131}I there is an excessive radiation exposure to the patient and attending staff due to a high level of high-energy gamma radiation from an 81% abundant emission at 364 keV. Finally, its average beta-energy penetration of less than 1 mm restricts its efficacy in larger tumors.

Other radionuclides of interest for RAIT have included ^{90}Y, ^{67}Cu, ^{212}Bi, ^{211}At, ^{125}I, ^{188}Re and ^{186}Re (*12*). The rhenium isotopes, ^{186}Re and ^{188}Re, do not have the high-energy gamma radiation of ^{131}I nor the high bone uptake of ^{90}Y. The major drawback of ^{188}Re is its short half-life (17 hr), and that of ^{186}Re is its availability in a carrier-added form. All potential isotopes for RAIT have their perceived advantages and limitations. In this issue of *JNM*, Breitz and coworkers have developed ^{186}Re-based immunoconjugates and have demonstrated the feasibility of their use in RAIT, even achieving some evidence of therapeutic response in a patient with metastatic colonic carcinoma (*13*). This represents a potential advance in the use of a deeper penetrating beta-emitter for RAIT, possibly as an alternative to ^{90}Y and other metallic beta-

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emitting radionuclides. On the other hand, this study affirms a number of problems that continue to frustrate RAIT and suggests a modicum of caution with regard to the interpretation of the authors' findings.

Breitz and coworkers report that ^{186}Re can be stably linked to intact and F(ab')$_2$ Mabs and administered to cancer patients for RAIT and show that higher doses can be tolerated with the fragment than with whole IgG, an observation that is in agreement with numerous animal studies. Also, it is interesting that the blood pharmacokinetics of intravenous and intraarterial administration of the radiolabeled Mabs was similar. Despite apparent accumulation of the radionuclide in the kidney, liver and large intestine, dose-limiting toxicity appears to be for the bone marrow, which is again similar to that of other therapeutic radionuclides. However, abnormal changes in liver function tests indicate that additional RAIT doses may induce more severe hepatoxicity. The study estimates organ and tumor dosimetry based upon conjugate view counting and the MIRD schema without the authors elucidating how tumor quantitation and dosimetry were performed. Were absorbed fractions set to unity for the beta particles or were they determined for a particular tumor size? Also, what were the tumor sizes for the dose estimates given? The SPECT studies that were performed could have been utilized to determine tumor volumetrics and uptake, and SPECT volumes could then have been compared to the CT volumes in the same patients. This would have resulted in improved dose estimates as compared to the use of quantitative planar imaging. Further, there is no mention of how the marrow dose was calculated, although this is the critical tissue affected by the internal radiation administered. The authors also fail to explain some basic aspects of their protocol, such as the rationale and advantage for the predosing with unlabeled F(ab')$_2$ in the patients given the radioactive NR-CO-02 fragment, but not in the other group of patients. Also disturbing is a lack of information regarding the characteristics of the Mabs and the epitopes that they recognize, particularly if the antigens are shed into the blood and result in complexation with the injected Mabs. This could affect targeting and pharmacokinetics and result in increased uptake of the radioactive complexes in the liver and spleen. Referring to NR-CO-02 as an IgG_1 that "recognizes an antigen expressed on an uncharacterized subspecies of carcinoembryonic antigen" portends that a new CEA determinant has been identified. At the very least, the authors could have indicated whether or not the Mab falls into any of the published classifications of CEA Mabs. This is not trivial for an agent used in vivo, since some CEA-reactive Mabs have shown critical cross-reactivities with different normal tissues and cells. Finally, it is unfortunate that the authors used CT scans of different levels to depict tumor regression.

Despite these shortcomings, the study showed that even with an uptake of 0.004% of the injected dose per gram of tumor and tumor doses of up to 2,100 cGy, objective evidence of a tumor response was claimed in one of the 46 patients studied. Although this response rate would be a disappointment in a Phase II trial, any efficacy in a dose-finding study in advanced cancer patients can be encouraging. Nevertheless, the apparent preclusion of repeated therapy because of the induction of HAMA is a major problem. With low Mab accretion and tumor radiation doses, repeated doses with less immunogenic antibodies are probably essential. Therefore, human and humanized Mabs and/or methods to enhance targeting of radiation to tumor need to be developed.

This does not discount the importance of advances in the radiochemistry of antibodies, such as with rhenium isotopes, which will be needed as advances in antibody engineering and targeting are achieved. However, even with the progress reported by Breitz et al. for ^{186}Re chemistry, this agent is far from a clinical therapeutic. The 100–600 mCi of ^{186}Re used in this work are equivalent to 40–240 μg (2–13 $\times$ 10^{-7} mol) of ^{185}Re/^{186}Re, given the capability of the University of Missouri Research Reactor to produce ^{186}Re at a specific activity of 2–3 Ci/mg rhenium. It seems that there may be a significant logistical problem to supplying clinical grade ^{186}Re in sufficient quantity and at high specific activity. Currently, the highest specific activity material available commercially is supplied as 900 mCi/mg rhenium by NEN Dupont (i.e., at one-half to one-third the specific activity of rhenium used in these trials). The chemistry used for conjugating rhenium by Breitz et al. is necessarily somewhat wasteful of the isotope, since 20%–50% of the isotope may not be bound to antibody, mostly because hydrolysis of the rhenium-MAG_2-GABA-activated ester is competing with the coupling reaction. In this study, approximate doses of 40–300 mCi ^{186}Re are administered from 100 to 600 mCi of initially reduced perrhenate. At the 2.5 Ci/mg specific activity level of ^{186}Re, the 40–300-mCi doses would require 12–100 mg of antibody per label when loaded in a 1:1 ratio to antibody. Since 36 to 47 mg of Mab were in fact used in each label, it appears that two to three rhenium-MAG_2-GABA chelates were loaded onto each antibody molecule. We believe that the availability of a higher specific activity ^{186}Re may be required before this method can be adopted more generally. A different approach for rhenium therapy involves the use of carrier-free, generator-produced, ^{188}Re (β; E_{max}, 2.12 MeV; γ photon, 155 keV; 15%). Despite its 17-hr half-life, ^{188}Re labeled by a direct method of Mabs, in high specific activity, has shown adequate in-vivo stability for encouraging tumor targeting in human tumor xenograft models (*14*). Since the clinical studies by Breitz et al. did not indicate any renal toxicity despite increased radiation doses to the kidneys, it is possible that either rhenium isotope conjugated to antibody fragments may prove effective against tumor

without inducing irreversible renal toxicity, especially with fractionated doses.

The report by Breitz and coworkers raises a number of questions and problems. Nevertheless, it is a stimulating contribution to the advance of cancer RAIT and encourages the improvement of isotope selection and conjugation to antibody, human antibody development and murine antibody humanization and the design and prosecution of well-controlled clinical trials. These are not insignificant tasks, given the multidisciplinary requirements of antibody-based radiation therapy.

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AWARD OF MERIT WINNERS

The editorial board of the *Journal* is pleased to announce the recipients of the second annual JNM Award of Merit. Manuscripts published in the *Journal* in 1991 were rated in four basic categories: presentation, evidence, innovation, and contribution to the literature. The winners (listed by first author and article title) are:

Harry R. Maxon, III, for "Rhenium-186(Sn)HEDP for Treatment of Painful Osseous Metastases," which appeared in the October 1991 issue of the *Journal*, pages 1877–1881.

B. Leonard Holman, for "Brain Perfusion Is Abnormal in Cocaine-Dependent Polydrug Users," which appeared in the June 1991 issue of the *Journal*, pages 1206–1210.

David Piwnica-Worms, for "Enhancement of Tetraphenylboate of Technetium-99m-MIBI Uptake Kinetics and Accumulation in Cultured Chick Myocardial Cells," which appeared in the October 1991 issue of the *Journal*, pages 1992–1999.

Presentation of the awards to the respective authors will be made during the Editorial Board Breakfast at this year's Annual Meeting in Los Angeles, CA.