Targeted Therapy of Cancer with Radiolabeled Antibodies

David M. Goldenberg, ScD, MD

Garden State Cancer Center, Center for Molecular Medicine and Immunology, Belleville, New Jersey

This review focuses on the use of radiolabeled antibodies in the therapy of cancer, termed radioimmunotherapy (RAIT). Basic problems concerning the choice of antibody and radionuclide and the physiology of tumor and host are discussed. Then follows a review of pertinent clinical publications on various radioantibody constructs in the treatment of hematopoietic and solid tumors of diverse histopathologies, grades, and stages, and in different clinical settings. Factors such as dose rate delivered, tumor size, and radiosensitivity play a major role in determining therapeutic response, while target-to-nontarget ratios and, particularly, circulating radioactivity to the bone marrow determine the major dose-limiting toxicities. RAIT appears to be gaining a place in the therapy of hematopoietic neoplasms, such as non-Hodgkin's lymphoma, with several agents advancing in clinical trials toward registration, of which one has just been approved by the FDA. Although RAIT of solid tumors has shown less progress, pretargeting strategies, such as an affinity-enhancement system consisting of bispecific antibodies separating targeting from delivery of the radiotherapeutic, appear to enhance tumor-to-nontumor ratios and may increase rad doses to tumor more selectively than directly labeled antibodies.

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Despite more than 20 years since the introduction of radioimmunodetection (RAID) and radioimmunotherapy (RAIT), representing the use of isotopes conjugated to monoclonal antibodies (mAbs) for imaging and therapy, respectively (*1–3*), only in the last few years has this technology attracted the increasing interest of clinical oncologists. This new interest may be attributed to the encouraging results achieved with RAIT in the management of hematopoietic neoplasms, especially non-Hodgkin's lymphoma (NHL). It should be pointed out, however, that even before the era of mAbs, radiolabeled polyclonal antibodies were shown in animal and clinical studies to be promising ther-

apeutic agents (*3–5*). What has transpired in the ensuing years of development, culminating in the current multitude of agents in clinical trials, represents the focus of this article, which is intended to complement and extend other recent reviews (*6–13*). After efforts during more than 2 decades to implement the use of radiolabeled antibodies for cancer therapy, it is now appreciated (*i*) that many radionuclides and antibodies have potential applicability for this therapy, (*ii*) that antibody accretion remains the major limitation in delivering effective tumor radiation doses, and (*iii*) that multiple administrations and combinations with other treatment modalities will prove necessary, especially in the therapy of solid tumors. Whereas RAIT of hematopoietic neoplasms is gaining attention as a future therapy modality, solid tumors have been less responsive, and targeting minimal or micrometastatic disease appears at present to be the optimal approach in solid tumor therapy. The challenge of treating solid tumors has stimulated several approaches to improve the radiation dose delivered and to achieve a more uniform distribution of ionizing radiation, with the ultimate goal being the delivery of tumoricidal doses while sparing normal tissues.

BASIC CHALLENGES

RAIT is dependent on 3 principal interdependent factors: the antibody, the radionuclide, and the target tumor and host. Several articles have attended to these issues and can be found in a multiauthored book (*7*) or in several journal articles (*6,8–19*). Tumor response depends on numerous variables, including cumulative radiation dose delivered, dose rate, penetration, and tumor radiosensitivity. Two major determinants that have governed the contribution of the antibody in RAIT are tumor uptake and penetration. At an accretion of 0.001%–0.01% of the injected dose of radiolabeled antibody per gram of tumor, a cumulative tumor dose of <1,500 cGy is usually delivered, which falls short of the >5,000 cGy needed to achieve a therapeutic response in most neoplasms, based on external beam irradiation of adenocarcinomas. When tumor accretion is limited, the dose needed to obtain a therapeutic response cannot be achieved because of normal organ dose limitations. For RAIT, this is foremost the bone marrow, for which the dose limitation appears to be about 150–200 cGy. Thus, improvements in

selective antibody accretion in tumors are essential for enhancement of the radiation dose delivered.

Also important in RAIT are tumor physiology and the pharmacokinetics of the targeting antibody constructs. Vascularization and barriers to antibody penetration, as well as intratumoral pressure, influence the amount of targeting antibodies accreted by the tumors, and these are affected also by the nature of the disease (bulky vs. small tumors, location of tumors, etc.) Other factors controlling tumor targeting by antibodies include expression of the target antigens in tumor and other tissues (location on or in the tumor is also important), and bone marrow toxicity resulting from the slow blood clearance of the radiolabeled antibodies (since circulating radioactivity will also accrete in the red marrow). These topics, as mentioned, have been discussed elsewhere (6–19).

Strategies to improve RAIT reduce to 5 basic goals: (*i*) Enhance antibody uptake and distribution in tumor by increasing tumor vascular permeability and flow, using smaller molecules and possibly exploiting pretargeting strategies; (*ii*) decrease nontargeted antibody in the blood by in vivo clearance or ex vivo adsorption mechanisms, as well as the pretargeting approaches; (*iii*) protect normal organs from radiotoxicity, for example, by using hematopoietic growth factors and peripheral blood stem-cell reconstitution, and by blocking readsorption of antibody fragments by the kidneys with cationic amino acids, amino sugars, and their polymers; (*iv*) decrease immunoglobulin immunogenicity by humanization or use of human antibodies, or by immunosuppressing the host; and (*v*) improve the radiation dose and dose rate in tumor without concomitantly increasing cumulative radiation in normal organs, which can be accomplished by many of the other strategies and perhaps also by adjusting the antibody dose and the dose schedule (e.g., dose fractionation) of the radiopharmaceutical. Since these topics have been covered in other publications (6–19), they will be addressed here only briefly, and mostly in reference to clinical studies.

Targeting Antibodies

One major problem that appears to be basically overcome is the immunogenicity in humans of the foreign immunoglobulin used for targeting the radioactivity. The first studies of RAID and RAIT were performed with polyclonal antibodies derived from animals such as rabbits, goats, and sheep (1,4,5,20–22) and in some cases made monospecific against a target antigen by affinity purification methods (22). In the 25 years since the development of hybridomas to produce mAbs, many advances have been made in the development of antibody-based targeting agents using mAbs derived from mice. The change to murine mAbs did not result in improved tumor uptake, since in fact the number of binding sites on tumor cells was reduced in comparison with polyclonal antibodies. However, antibody uniformity, production, and expansion were improved with hybridoma-derived clones producing the mAbs, thus resulting in a rapid adoption of this technology. The immunogenicity of the antibody, as with antibodies from other species, limited administrations to one or two times, after which antispecies antibodies would develop. With relatively low accretion of the antibody and modest radiation doses, repeated administrations would appear to be desired, making the immunogenicity of the mAb an important concern.

The antibody should not only have minimal immunogenicity to permit repeated administration, but also optimal antigen binding, penetration, and rate of clearance from normal tissues for efficient and specific tumor targeting. One strategy to overcome these problems has been the development of small molecular constructs, such as radiolabeled antibody fragments and subfragments, which are capable of binding to the tumor while clearing from normal tissues rapidly (Fig. 1). Bivalent $F(ab')_2$ and monovalent Fab' fragments have shown excellent tumor penetration and good therapeutic results in animal and clinical studies (23–32), although tumor residence time is less than with intact IgG. Smaller single-chain constructs (i.e., scFv-based fragments) with molecular weights above the range for rapid renal clearance, such as diabodies (M_r 50,000), $(scFv')_2$ (M_r 55,000), and various minibodies (30), have been constructed to bind to 2 antigen molecules while allowing rapid clearance from the body. The various immunoglobulin-derived molecules that may have potential in RAIT have been reviewed recently (30) and are depicted in Figure 1. Unfortunately, tumor residence time, which is important for delivering therapeutic radiation doses, decreases as the immunoglobulin fragment becomes smaller (Table 1). Therefore, some of these constructs are being considered in pretargeting strategies that separate tumor targeting from delivery of the therapeutic radionuclide. Although the ideal targeting and binding immunoglobulin construct has not been finally defined, considerable attention is being given to developing more optimal antibody reagents.

The properties of different constructs are summarized in Table 1. For a considerable time, the use of antibody fragments and subfragments has been discouraged because of their lower affinity and lower absolute uptake in tumors compared with intact immunoglobulin, despite the fact that antibody fragments achieve higher tumor-to-nontumor ratios due to their rapid background clearance. More recent studies, however, appear to challenge this view (28), as will be discussed later. Animal studies of RAIT published some years ago indicated the advantage of $F(ab')_2$ constructs compared with intact IgG (23,24,27). As discussed below, this may be due to the higher initial dose rates observed with antibody fragments, particularly the efficacy of Fab' (28). Indeed, by 1983 it had already been suggested that Fab' fragments could have therapeutic advantages over bivalent conjugates in clinical RAIT trials with ^{131}I-labeled Fab' in patients with metastatic malignant melanoma (31–32). Unfortunately, this was not pursued further clinically.

Antibody fragments and subfragments and reengineered (chimerized and humanized) forms of mAbs (Fig. 1) have
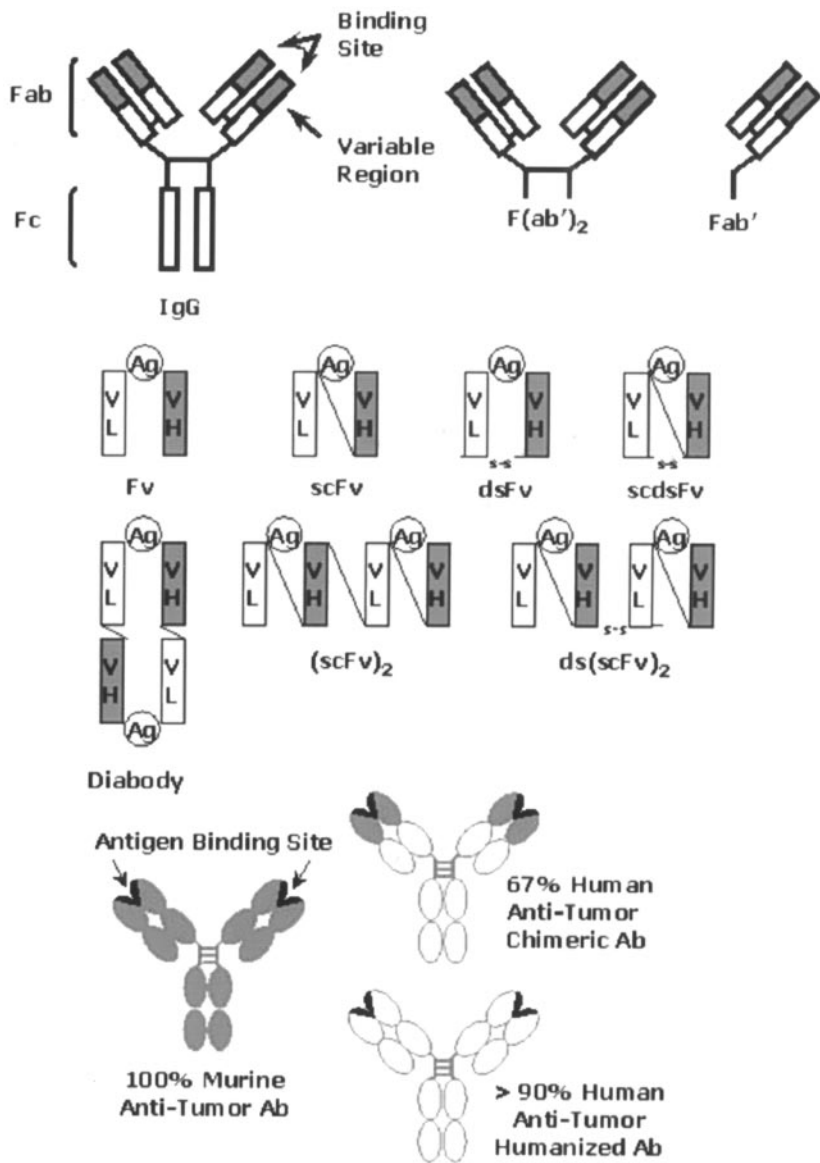
FIGURE 1. Schematic representation of diverse antibody-derived targeting molecules being investigated in RAIT, including intact IgG, F(ab')₂, Fab', single-chain Fv, diabody, chimeric, and CDR-grafted (humanized) antibody constructs.

been used to mitigate the immune response by the patient, especially after repeated administrations. Murine mAbs were made first into murine/human chimeras, then murine CDR-grafted human antibodies, and finally fully human antibodies. However, clinical experience has been almost exclusively with chimeric and CDR-grafted antibodies, and the results support the view of reduced immunogenicity. Whether the chimeric or CDR-grafted form (where the latter has less murine protein than the former) is preferable has not been determined, since this would require a controlled trial of both forms made from the same antibody. Initial clinical studies suggest, however, that chimeric antibodies do evoke antibody responses (*33*). Similar comparative studies of CDR-grafted (humanized) versus fully human antibodies are needed to determine if fully human antibodies are truly an improvement, since CDR-grafted, humanized mAbs contain 5%–10% murine constructs, with the

rest being human (*30,34*). Indeed, even fully human antibodies may evoke T-cell or antiidiotype responses.

Radionuclides

A second major factor is the radionuclide, where the nonpenetrating emissions are relevant for therapy. The suitability of a radionuclide for RAIT depends on its physical and chemical properties, its fate after antibody metabolism in vivo, and the nature of the radiation, such as low or high linear energy transfer (LET) emission. The efficacy of the radiation is in turn influenced by target tumor location, size, morphology, physiology, and radiosensitivity, and by the kinetics of the antibody. Finally, the availability of simple, efficient, and reproducible clinical-scale radiolabeling procedures is also essential for creating commercial products. Although many potential radionuclides have been studied clinically (Table 2), only a limited number are commer-

TABLE 1
Targeting Properties of Different Forms of Antibodies

	IgG	F(ab')$_2$	Fab'	Diabody	scFv
Physical					
Molecular wt	150 K	100 K	50 K	40 K	20 K
Biological					
Immune effector function	Yes	No	No	No	No
t$_{1/2}$, blood	2–3 d	1–2 d	4 h	<4 h	1 h
Target organ	Liver	Liver	Kidney	Kidney	Kidney
Tumor binding					
Uptake					
1 = highest, 4 = lowest	1	2	3	3	4
Duration					
1 = longest, 4 = shortest	1	2	3	3	4
Optimal accretion time	Days	Day	Hours	Hours	Hour

cially practical at this time. However, as with any emerging technology, validated clinical utility will eventually lead to solutions for any problems of availability and cost. Whether the best choice is a low-energy, high LET, Auger-emitter or a traditional β-emitter is a basic question that is still open and needs to be considered in the context of the tumor type and size, and the disease state.

The two most widely used radionuclides are the β-emitters ^{131}I and [90]Y. The former is readily available, inexpensive, provides γ-imaging emissions (at high energy), an 8-day physical half-life, and simple protein labeling chemistry. In the United States, the Nuclear Regulatory Commission's new guideline on the release criteria for patients undergoing ^{131}I radionuclide therapy permits many RAIT regimens involving this isotope to be performed on an outpatient basis (35). However, ^{131}I does have some drawbacks. The conventional conjugation of this radionuclide to antibodies results in rapid degradation and a reduced residence time in the tumor, thus diminishing the tumor dose. Also, the γ-emission component presents patient and environmental safety concerns.

In contrast, ^{90}Y is a pure β-emitter, and thus has fewer environmental radiation restrictions. Further, in contrast to ^{131}I, which has a maximum particle range of 2 mm, ^{90}Y has higher energy and a particle range of up to 12 mm, making

TABLE 2
Radionuclides of Current Interest in RAIT

Isotope	t$_{1/2}$ (h)	Emission (for therapy)	Maximum energy (keV)	Maximum particle range (mm)
Iodine-131 (^{131}I)	193	β	610	2.0
Yttrium-90 (^{90}Y)	64	β	2,280	12.0
Lutetium-177 ([77]Lu)	161	β	496	1.5
Copper-67 ([67]Cu)	62	β	577	1.8
Rhenium-186 ([186]Re)	91	β	1,080	5.0
Rhenium-188 ([188]Re)	17	β	2,120	11.0
Bismuth-212 ([212]Bi)	1	α	8,780	0.09
Bismuth-213 ([213]Bi)	0.77	α	>6,000	<0.1
Astatine-211 ([211]At)	7.2	α	7,450	0.08

it more suitable for irradiation of larger tumors. Since it is a residualizing label (i.e., has a long residence time in the tumor), it delivers a large radiation dose. It is important to have a stable attachment of the radiometal to the antibody, because unbound radioyttrium accretes in bone. In past years, chelating agents that form stable complexes of ^{90}Y with antibodies have involved bifunctional reagents. The macrocyclic chelator 1,4,7,10-tetraazacyclododecane-N,N',N'',N'''-tetraacetic acid (DOTA) is known to form very stable chelates with metals, and is being used to prepare protein/antibody-DOTA conjugates by activation with N-hydroxysulfosuccinimide. In a simplified scheme of labeling antibodies with ^{90}Y, the antibody–DOTA conjugate is aliquoted into a ^{90}Y shipment vial, and heated for 5 min at 45°C. High-yield radiolabeling (>92%) is achieved without the need for postlabeling purification (36).

Other potential metallic β-particle-emitting radiolabels for therapy include ^{177}Lu and [67]Cu, which have been studied clinically (37–40). Consistent production of [67]Cu at high specific activity has been a problem. [177]Lu is similar to ^{90}Y in chemistry, but is more like ^{131}I in half-life. Rhenium isotopes ([186]Re and [188]Re) have also been used for RAIT, and have sufficient γ-energies for external scintigraphy, similar to [131]I. Encouraging tumor responses have been achieved with antibodies labeled with either of these radionuclides (41,42).

α-Particle therapy has received renewed interest recently, especially with bismuth nuclides (43,44), such as [212]Bi and [213]Bi as eluates from [234]Ra and [225]Ac generators, respectively. The cyclotron-produced radiohalogen [211]At has also been developed for RAIT (45,46). These radionuclides have energies in the several MeV range, resulting in high LET emissions (~100 keV $\cdot$ μm)$^{-1}$ compared with the β-emission of ^{90}Y, with a 0.2 keV $\cdot$ μm^{-1} LET$_{mean}$. Such high LET radiation has profound effects on DNA, causing strand breaks, which can be targeted selectively to the tumor because of the α-particles' short range. Hence, α-particle RAIT is best used when there are micrometastases or circulating tumor cells, not bulky disease.

Since these α-emitters have short half-lives, their conjugation to antibodies must be rapid, and many of the methods used have been less than 2 hours long. Still, even more facile methods need to be developed because most α-particles have even shorter half-lives.

It has even been suggested that combinations of radionuclides with different energies may prove more beneficial than using a single radionuclide (*47*). For example, a radionuclide with a higher energy and longer tissue range could be combined with a radionuclide of medium energy and shorter range, thus destroying both bulky disease and micrometastases.

Combination Therapy and Optimization of RAIT

Most efforts to improve RAIT have focused on increasing the uptake of the radioimmunoconjugate, improving its penetration and distribution within the tumor, and enhancing tumor-to-nontumor localization ratios, so as to afford more selective tumor targeting. Since these elements have been reviewed elsewhere (*13–19*), they will not be discussed again here. Even more than external-beam irradiation, RAIT is potentially used optimally in combined therapy modalities, since the carrier antibody can also deliver other therapeutic agents, radiosensitizers, or vascularization and biological response modifiers (*7–19*). Since the dose-limiting toxicity of RAIT is primarily bone marrow suppression, hematopoietic cytokines and autologous blood stem-cell grafting can be combined with RAIT in order to overcome myelosuppression.

Several experimental and a few clinical studies have been reported on the combination of RAIT with chemotherapy. Most preclinical experiments involving xenografted human tumors in nude mice have shown evidence of improved therapeutic efficacy for the combination, but there is a paucity of data supporting any particular schedule for the two modalities. The few clinical studies reporting on the combination of chemotherapy and RAIT indicate an acceptable toxicity and some antitumor activity, but as yet no additive or synergistic effects have been shown in a randomized trial. Another problem in such trials is the generally poor condition of the study subjects, most of whom have large, progressing tumors that have relapsed after prior chemotherapy. This is why patient selection, emphasizing more limited disease, is essential for the true assessment of RAIT alone or RAIT in combination with other modalities. RAIT in combination with external-beam radiation is also being studied clinically in colorectal cancer, and will be discussed later.

Pretargeting Strategies

In order to increase tumor-to-background ratios in antibody targeting, several promising pretargeting strategies separating antibody targeting from radionuclide delivery are being developed. These methods are intended to minimize the systemic radiation resulting from prolonged circulation of antibodies directly conjugated with isotopes, so that delivery of the radionuclide is accomplished only after most of the antibody has cleared from normal tissues. In general, a nonradioactive antibody containing a second recognition site, such as to a radiolabeled small molecule (or a hapten) is injected. At a time of maximal tumor accretion and circulatory clearance of the antibody, the relevant hapten bearing the radionuclide is injected as a second step. The radiolabeled hapten binds to the second recognition site of the tumor-localizing antibody, whereas unbound hapten is rapidly cleared from the body. Compared with directly labeled antibodies, these methods achieve higher tumor-to-blood and tumor-to-nontumor ratios, but timing and doses given are critical (*15,48,49*).

One approach has been the noncovalent interaction between avidin or streptavidin and biotin, which have a high binding affinity, in the order of $Ka = 10^{15}$ M^{-1} (*50*). Avidin or streptavidin conjugated to antibody is targeted first, followed by the administration of radiolabeled biotin. Conversely, the targeting antibody can be biotinylated and, after being injected, avidin or streptavidin is administered in order to bind to the antibody at the tumor. The final step involves injection of radiolabeled biotin, which attaches to avidin at the tumor. Modifications of both approaches are being made, including also using clearing agents that reduce the amounts of the targeting antibody at nontumor sites (*51*). Thus, these can involve 2-step or multistep procedures, all intended to increase tumor-to-nontumor ratios. However, endogenous biotin, and the immunogenicity of avidin and streptavidin, can be problematic (*48–50*).

Despite impressive results in animal studies of biotin/avidin methods (*51*), clinical trials have been less encouraging. A phase I clinical dose-escalation study found that nonmyeloablative doses exceeding 7,400 MBq (200 mCi) ^{90}Y could be tolerated, with radioactivity in the tumor equaling that achieved with conventional RAIT (*52–54*). However, untoward side effects, particularly intestinal toxicity, limited further escalation and resulted in these particular studies being abandoned. Using another system involving CD20 antibody for the treatment of NHL, doses of up to 1,850 MBq/m² (50 mCi/m²) ^{90}Y-DOTA biotin resulted in tumor regression (*55*). Since this hematopoietic neoplasm is very radiosensitive and has responded well to virtually all forms of RAIT, it is not clear whether this demonstrates the advantages of this pretargeting method or the optimal results obtained with radiosensitive lymphomas.

Paganelli et al. have pioneered a 3-step pretargeting method that involves the administration of (*i*) biotinylated antibody, (*ii*) streptavidin or avidin to clear circulating antibody and to couple to biotinylated antibody localized at the tumor, and finally (*iii*) radiolabeled biotin (*56*). In a phase I/II clinical trial of high-grade glioma, 48 patients with residual disease or recurrence were treated with ^{90}Y-DOTA biotin at 2,220–2,960 MBq/m² (60–80 mCi/m²). The primary biotinylated antibody was an antitenascin mAb. An objective response in 25% of the patients and stable disease in 52% were reported. The mean absorbed dose to tumor, at the maximal tolerated dose (MTD), was

1,200 cGy per cycle. In some cases, the duration of response was more than 1 y, which is an encouraging finding in this tumor type (*57*).

A different pretargeting approach to increase the radiation dose delivered to tumor compared with blood and other normal tissues has involved reengineering of the targeting antibody molecule as a bispecific antibody (bsAb). This is made chemically or recombinantly from monovalent antibody fragments that target 2 different antigens, one at the tumor and the other a hapten chelate. After the bsAb localizes in the tumor and clears from normal tissues, the second agent, which binds selectively to the second arm of the antibody and delivers the radioactivity to the tumor, is administered (*58*). A diagram of this method, termed "affinity enhancement system" (AES), is presented in Figure 2. In the most extensive study of this approach, the targeting antibody is against carcinoembryonic antigen (CEA) and the second arm recognizes a DTPA-indium chelate (*58*). After the localization step, a bivalent hapten, which is a peptide incorporating 2 DTPA-indium moieties as well as tyrosine carrying a diagnostic or therapeutic radionuclide, is given. The novelty appears to include the use of a bivalent hapten, which forms a stable complex with 2 molecules of pretargeted bsAb at the tumor. Timing of the second injection of the radiolabeled hapten is important in order to achieve high tumor-to-background ratios when there is little or no bsAb circulating in the blood. Excellent tumor imaging has been obtained with this AES method in several clinical trials (*58–61*). Figure 3 is an image of a metastatic CEA-expressing carcinoma targeted by the radiolabeled hapten given as a second step in this AES system, showing excellent targeting with virtually no background radioactivity. This involved a half-humanized (anti-CEA), half-murine (antihapten) bsAb (Pentacea; IBC Pharmaceuticals, LLC, Morris Plains, NJ) (*61*).

Using a different bsAb, excellent targeting results have been reported in a preclinical model of human renal carcinoma. With the G250 bsAb and pretargeting, Boerman et al. (*62*) showed that tumor-to-blood ratios increased to values as high as 3,500 at 72 h after radiochelate injection. At 20 h after injection, about 50% of the whole-body activity was localized in the tumor. Therapy experiments in animal models have also confirmed the efficacy of AES, including substantial cures of xenografted human colon carcinoma (*63*). This AES approach appears to hold much promise for RAIT, but may also be applicable to more selective and enhanced delivery of drugs to tumors.

CLINICAL RESULTS

Hematopoietic Tumors

Various antibodies, labels, and treatment strategies have been studied in hematopoietic tumors, and most have shown evidence of efficacy, particularly in NHL. For example, antibodies against CD20, CD22, CD37, and HLA-DR antigens have been used with ^{131}I, ^{90}Y, or, rarely, other radionuclides such as [186]Re or [67]Cu. Most initial studies showed favorable results with indolent forms of NHL, but more recent trials have also shown efficacy in aggressive NHL. Four agents have been studied most often in NHL: ^{131}I-B1, [90]Y-2B8, [131]I-^{90}Y-LL2, and [131]I -Lym-1. Table 3 lists the characteristics of these agents and the principal references for efficacy. Several excellent reviews of the progress of
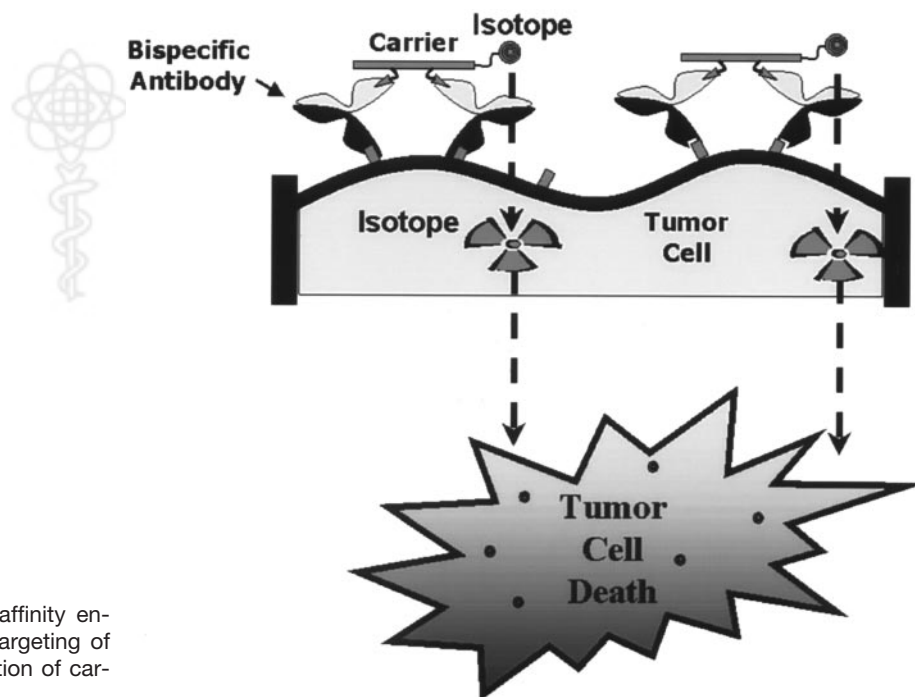

FIGURE 2. Diagram depicting the affinity enhancement system (AES) 2-step pretargeting of bispecific antibody, followed by injection of carrier hapten bearing the radionuclide.

¹³¹I-AES 100 (3.7 GBq)
Pentacea™: 100 mg / m²
ANT view

Tum: 0.0145% ID/g
T/ WB: 63.2
T/ KID: 13

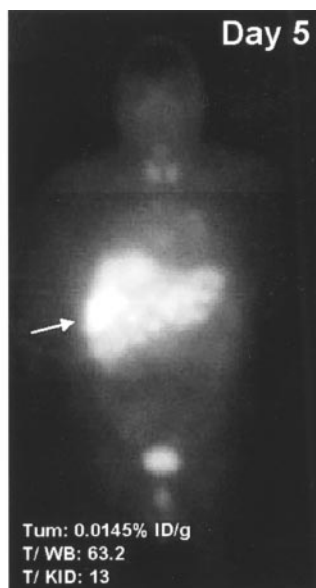**FIGURE 3.** Total-body scan done 5 d after injection of ¹³¹I-hapten given 7 d after infusion of 100 mg bispecific anti-CEA (hMN-14)/antihapten antibody in patient with metastatic CEA-producing tumor. Large metastasis (arrow) and numerous small foci are seen in liver. Small foci could not be observed when only the bispecific antibody was radiolabeled and imaging performed serially thereafter.

RAIT in lymphomas have appeared in the past (6–13, 17,64,65).

The antitumor activity of RAIT is primarily due to the radioactivity of the radiolabel attached to the antibody, which emits continuous, exponentially decreasing low-dose-rate irradiation with a heterogeneous dose deposition. In some cases, as is evidenced in lymphoma, the antibody itself may contribute to tumor destruction. There may also be an immune response of the host to tumor antigens released after antibody- or isotope-mediated cell destruction, as has been suggested in NHL treatment (66). In summary, important considerations in the efficacy of RAIT include the nature of the antibody (specificity, affinity, avidity, dose, immunoreactivity, mechanism of action of naked antibody), the radiolabel (emission properties, half-life, stability of radioconjugate), the antigen targeted (location, modulation, stability, density, expression), and the nature of the target neoplasm (radiosensitivity, location, size, vascularization, immunogenicity, proliferative rate). Other factors include heterogeneity of dose deposition, dose-rate effects, and the status of the host bone marrow and normal organ functions after other forms of cytotoxic therapy. These considerations are important in RAIT of NHL, but are also relevant to other neoplasms.

Non-Hodgkin's Lymphoma

The two most advanced RAIT products under regulatory review for NHL therapy are Bexxar (¹³¹I-tositumomab; Corixa Corp., Seattle, WA) and Zevalin (⁹⁰Y-ibritumomab tiuxetan, IDEC-Y2B8; IDEC Pharmaceuticals, San Diego, CA). Both are murine antibodies directed against the CD20 antigen expressed on the surface of normal and malignant B-lymphocytes. Bexxar is conjugated with ¹³¹I, whereas Zevalin is labeled with ⁹⁰Y. Bexxar is used as an IgG2a murine mAb with cold murine antibody added, whereas Zevalin has the murine antibody labeled and cold human/mouse chimeric rituximab (Rituxan; IDEC/Genentech) added to the product. Bexxar is given according to a patient-specific dosimetric pretherapy study, whereas Zevalin has been developed so that this pretherapy dosimetry is not needed and is administered on a body-weight basis. Both products, however, require a pretherapy cold antibody dosing in order to improve tumor targeting: with Bexxar this involves a 1-h infusion of 450 mg of unlabeled antibody, while Zevalin requires a much longer infusion (4–6 h) of 450 mg rituximab. Hence, Bexxar involves 3 injections and 3 imaging sessions, while Zevalin requires only 2 injections, unless the early imaging with ¹¹¹In becomes required as a pretherapy step. Nevertheless, the time involved in treating

TABLE 3
Recent Clinical Studies of RAIT in Hematological Tumors

Tumor type	Target antigen	Antibody	Radiolabels	Representative references
Non-Hodgkin's lymphoma	CD20	B1	¹³¹I	69,70,76
	CD20	Y2B8	⁹⁰Y	77, 78
	CD22	hLL2	¹³¹I, ⁹⁰Y	89–93
	HLA-DR	Lym-1	¹³¹I, ⁶⁷Cu	37, 100
Hodgkin's disease	Ferritin	Rabbit	¹³¹I, ⁹⁰Y	105
Myelocytic leukemia	CD33	HuM195	¹³¹I, ²¹³Bi	110
	NCA95	BW250/183	¹⁸⁸Re	42

a patient with these radiolabeled antibodies is even shorter than with nonradioactive rituximab, which is administered weekly over 4 to 8 wk. Both products have shown higher and more durable responses than naked antibodies, but they also have dose-limiting toxicity, predominantly myelotoxicity. Infusional adverse reactions are minimal for Bexxar compared with Zevalin, and both show minimal nonhematological toxicities, with no hair loss or mucositis and generally minimal nausea. Because of the usually high release of ^{131}I from Bexxar, thyroid blockage is required; yet Bexxar can pose a complication of hypothyroidism even with such blockage. Some patients have shown myelodysplasia on long-term follow-up after Bexxar, but they were heavily pretreated with chemotherapy, which could have contributed to this complication.

Antibody responses to the injected antibody can have adverse consequences, including anaphylaxis. When murine antibodies are administered, a human antimouse antibody (HAMA) response is usual, but this is diminished in patients with NHL who have had prior chemotherapy. In chemotherapy-naive patients, the HAMA response can be considerable, such as ~60% for Bexxar (67). Also of concern is that HAMA can alter murine-based immunoassays for analyses that may be important for patient management, as discussed elsewhere (68). But most critical may be the altered biodistribution and targeting that would preclude readministration of the foreign protein. In fact, if HAMA is present, administration of a chimeric antibody or even a humanized antibody may enhance the HAMA response (personal observations).

As already mentioned above, with the new Nuclear Regulatory Commission's regulations for ^{131}I providing that if the total effective dose equivalent to another individual from exposure to a treated patient is <500 mrem (35), Bexxar can be given throughout most (but not all) of the United States on an outpatient basis. Zevalin and other products using pure β-emitters, such as ^{90}Y, can be used throughout the United States on an outpatient basis. Both products were studied predominately as a 1-cycle therapy.

A phase III clinical trial of Bexxar in patients with follicular low-grade and transformed low-grade NHL who were heavily pretreated and chemotherapy-resistant (69) showed a response rate of 65%, compared with 28% for the prior chemotherapy. A complete response (CR) rate of 30% was reported, with a median remission duration of almost 5 y (69).

Bexxar was also studied in a phase II trial in previously untreated patients with low-grade or transformed NHL (67). Of the 76 patients, 74 (97%) had an objective response, with 63% achieving CR. None of the patients required hematological supportive therapy, but HAMA was observed in 64% of the patients. It was found that less heavily pretreated patients responded more favorably to RAIT, at least with Bexxar and probably also with other such agents.

Kaminski and associates recently summarized their experience with Bexxar in 59 chemotherapy-relapsed/refractory NHL patients (70). They determined that the maximal total-body dose was 75 cGy for patients not requiring autologous stem-cell transplantation (ASCT), and 45 cGy for patients after ASCT. Of the 59 patients, 42 (71%) responded and 20 (34%) had a CR. Of 42 patients with low-grade or transformed NHL, 35 (83%) responded versus 7 (41%) of 17 de novo intermediate-grade NHL patients ($P = 0.005$). For all 42 responders, the median progression-free survival was 12 mo; for those with CRs it was 20.3 mo. Seven patients were still in CR 3 to 5.7 y later. Sixteen patients were retreated after progression; 9 responded and 5 had a CR. Ten patients (17%) had HAMA elevations. Long-term, 5 patients developed elevated TSH levels, and 5 were diagnosed with myelodysplasia and 3 with solid tumors.

Bexxar has also been studied in combination with fludarabine as a front-line therapy for follicular and transformed NHL, where 3 sequential cycles of fludarabine followed 6–8 wk later by Bexxar in 38 previously untreated patients did not cause excessive hematological or nonhematological toxicities (71). Of the 14 patients assessable for response at the time of analysis, 4 of 11 partial responders after fludarabine became complete responders with the addition of Bexxar, while one patient with stable disease converted to a partial response (PR) after Bexxar. None of the patients developed HAMA, indicating that the administration of fludarabine prevented this immune response.

Press and associates (72,73), using myeloablative doses of the B1 antibody of Bexxar labeled with ^{131}I and combined with peripheral blood stem-cell transplantation, showed that objective response rates as high as 86%, with 79% CR, could be achieved; 39% of the patients survived free of any recurrence for 5–10 y without any further therapy. This was extended in a study of 29 patients receiving therapeutic infusions of 10.4 to 29.0 GBq ^{131}I-murine B1 (74); 14 patients achieved unmaintained remissions ranging from 27+ to 87+ mo after RAIT. The estimated overall and progression-free survival rates were 68% and 42%, respectively, with a median follow-up time of 42 mo (74). Nonhematological dose-limiting toxicity was reversible cardiopulmonary insufficiency, which occurred in 2 patients at RAIT doses that delivered >27 Gy to the lungs. Late toxicity has been uncommon, except for elevated TSH levels found in about 60% of the patients. Two patients developed second malignancies, but none developed myelodysplasia (74). The Seattle experience with myeloablative RAIT of B-cell lymphomas has been summarized recently (75).

When the Seattle group extended RAIT at myeloablative doses to include chemotherapy with etoposide and cyclophosphamide (followed by ASCT), an overall survival rate of 83% and a progression-free survival rate of 68% were observed after a median follow-up of 2 y (76). These results compared favorably with those of a nonrandomized control group of patients treated at the same institution with the same doses of the drugs, but who received total-body irradiation instead of the radiolabeled antibody (overall sur-

vival, 53%; progression-free survival, 36%). Of the 52 patients treated, 4 died of opportunistic infections.

^{90}Y-labeled Zevalin (^{90}yttrium ibritumomab tiuxetan, IDEC-Y2B8) was studied by Wiseman et al. in a phase I/II dosimetry trial in relapsed/refractory NHL patients (77). Patients received ^{111}In-Zevalin on day 0 followed by a therapeutic dose of ^{90}Y-Zevalin on day 7, in a dose-escalation mode (7.4 to 15 MBq/kg). Both doses were preceded by an infusion of the chimeric unlabeled rituximab antibody. Median estimated radiation absorbed dose was 3.4 Gy to liver, 2.6 Gy to lungs, and 0.38 Gy to kidneys, with the median estimated tumor radiation absorbed dose being 17 Gy. Thus, Zevalin administered at nonmyeloablative MTDs resulted in acceptable absorbed doses to normal organs.

Results of a prospective, randomized trial of Zevalin in 143 patients with relapsed/refractory low-grade follicular or transformed NHL showed an overall objective response rate of 80% for the Zevalin group versus 56% in the group that received a standard course of unlabeled rituximab ($P = 0.002$), with a 30% CR rate for Zevalin versus 16% for rituximab ($P = 0.04$) (78). These investigators also determined that Zevalin given at nonmyeloablative doses of 15 MBq/kg delivered acceptable radiation absorbed doses to normal organs without the need for pretherapy-based dosimetry with ^{111}In-labeled Zevalin.

Another study was conducted to evaluate the response rate to Zevalin in follicular NHL patients who were refractory to rituximab (defined as those who failed to achieve an objective response or had time-to-progression of disease within 6 mo of the most recent course of rituximab given 4 times weekly at 375 mg/m²). In the analysis of the 54 patients, an overall objective response rate of 74% and a CR rate of 15% were achieved according to the Cheson criteria (79), or an objective response rate of 59% and CR rate of 4% by the prior IDEC criteria (80). Duration of response was significantly longer (7.7+ mo vs. 4 mo) for Zevalin compared with prior rituximab ($P < 0.01$). In an analysis of 211 patients receiving Zevalin, it was reported that 1.4% developed HAMA and 1 patient (0.5%) developed human antichimeric antibody (HACA) (81). Zevalin is the first RAIT product to be approved by the FDA.

Another antibody for NHL that targets a different antigen, CD22, is also emerging as potentially a third radiotherapeutic (82) or a second unlabeled product (83). This CD22 antibody (first named EPB-2 and subsequently LL2) was first developed as a murine form (84) and then shown by labeling the Fab′ fragment with ^{99m}Tc (LymphoScan; Immunomedics, Inc., Morris Plains, NJ) to target all forms, stages, and sites of NHL, with only normal spleen showing accretion of this antibody (85,86). Subsequently, the murine antibody was humanized, or CDR-grafted onto human framework regions of IgG (hLL2 or epratuzumab; Immunomedics, Inc.) to reduce the murine component to less than 10%, resulting in an antibody with more human components than the chimeric rituximab anti-CD20 antibody. The LL2 mAb has been determined to target the surface CD22 anti-

gen and then internalize rapidly into the cell (87). Later resumption of synthesis and expression of CD22 permits binding of the antibody and further internal processing. This internalization has enabled the attachment of radiometals for a higher residence time, and thus dose delivered, in the tumor (88). One of the interesting observations of the first RAIT trial in NHL with the murine LL2 labeled with ^{131}I was the apparent efficacy of very low doses of radiation (82), confirmed also in further studies (89–91). Subsequent studies with a ^{90}Y form of hLL2 indicated antitumor activity at the first dose levels of a dose-escalation study, even in patients who had failed prior high-dose chemotherapy (92). A clinical trial comparing the dosimetry and pharmacokinetics of hLL2 labeled with ^{131}I or ^{90}Y in patients with NHL showed the advantage of the ^{90}Y label with this antibody (93). At present, a phase I/II study with myeloablative doses of ^{90}Y-hLL2 in patients with predominantly aggressive NHL, including those who had prior high-dose chemotherapy, is being conducted (92). It is noteworthy that the ^{90}Y-labeled hLL2 is given as a single injection with a protein dose of about 100 mg in these studies, without the need for predosing to improve its biodistribution. ^{111}In-hLL2 is given in advance for targeting and dosimetry purposes, but it is not anticipated that ^{90}Y-hLL2 will need individualized patient dosimetry (93), as it is not required for Zevalin (77,78,94). Another difference between hLL2 and the other radiolabeled antibodies used for NHL therapy is that this antibody has the humanized form labeled, whereas Zevalin and Bexxar have murine antibodies radiolabeled, thus involving the administration of a murine antibody with its potential immunogenicity and the prospect of precluding repeated administrations.

The hLL2 antibody labeled with ^{90}Y is also being studied in a dose-fractionation schedule, beginning with 2 doses given once weekly and expanded up to 4 weekly doses. Initial results show responses at the schedule of 2–3 weekly doses (95). Another phase I trial is in progress with hLL2 labeled with ^{186}Re, which also allows simultaneous imaging and therapy (like ^{131}I), and is showing antitumor activity at the initial doses (96). Finally, comparing myeloablative and conventional doses of ^{131}I-labeled CD20 (chimeric rituximab) and hLL2 antibodies in a small series of NHL patients, Behr et al. reported superior results with the high myeloablative doses (97). These various reports indicate that chimeric CD20 and humanized CD22 mAbs can be effective in NHL with diverse radiolabels, such as ^{131}I, ^{90}Y, and ^{186}Re, but it is premature to determine which label and dose schedule will prove best for the treatment of NHL, or how it will be incorporated in a management paradigm. A preclinical study of rituximab labeled with the α-emitter ^{211}At also supports its potential use with this radiolabel (46). In addition to antibodies against CD20 and CD22, a recent experimental study suggested that radiolabeled CD19 antibodies could also be of value in the RAIT of NHL (98).

A fourth radiolabeled antibody product under development for RAIT in NHL is Lym-1 (Oncolym; Peregrine

Pharmaceuticals, Inc., Fullerton, CA), which targets the HLA-DR10 β-subunit expressed on most malignant B-cells (99). DeNardo et al., whose work forms the basis of virtually all current information about the role of this antibody, have shown that it is useful for treatment of NHL when labeled with ^{131}I or [67]Cu (37,99–102). In a low-dose trial of ^{131}I-Lym-1, 17 of 30 patients (57%) had durable responses, including 3 CRs. An MTD trial of this agent yielded responses in 11 of 21 patients (52%), including 7 CRs (100). Thrombocytopenia was the only dose-limiting toxicity. [67]Cu used as the radiolabel provides both imaging and a β-emitting therapeutic, and has shown responses in 7 of 12 NHL patients (58%) (102). Since Lym-1 is a murine antibody, these investigators studied the HAMA response in their patients, and found a 28% response rate among 43 patients treated with multiple doses of the antibody, with no evidence of anaphylactoid or related complications (103). However, HAMA activity interrupted therapy in 6 of the 43 patients (14%). It is interesting that the median survival was longer for HAMA-positive patients (18 mo) than for those who did not develop HAMA (9 mo). The authors speculated that HAMA might contribute to the antitumor response (66).

The various trials of RAIT in NHL lead to the following tentative general conclusions (104): (a) Durable and major responses can be achieved, even following relapse to chemotherapy and with bulky tumors; (b) low radiation doses can achieve objective tumor responses; (c) administration of unlabeled antibody may improve biodistribution of the labeled antibodies, either as a predose or concomitantly; (d) high-dose therapy combined with autologous bone-marrow or peripheral stem-cell transplantation can result in higher overall response rates of longer duration than the application of nonmyeloablative doses; (e) patients with low involvement of disease in the bone marrow, with low tumor burden, and without an enlarged spleen respond more favorably; (f) mAbs with radiometals, such as ^{90}Y, show better tumor dosimetry than ^{131}I-labeled antibodies, and the former do not appear to require the pretherapy dosimetry essential for ^{131}I-labeled antibodies; (g) when combined with certain chemotherapeutic agents and autologous stem-cell transplants, RAIT may be more effective than any single modality; (h) RAIT appears to be more effective than use of the same antibody unlabeled; and (i) long-term side effects may include hypothyroidism (with ^{131}I products), myelodysplasia, and, possibly, secondary neoplasms.

Despite these encouraging advances in NHL, several questions remain unresolved: (a) How does RAIT fit into a management paradigm of patients with indolent or aggressive NHL in relationship to naked antibody therapy? (b) How effective is RAIT without predosing with naked antibody, which can be active by itself? (c) Since the antibodies that are radiolabeled in RAIT can also be active without the radionuclide and since total body irradiation due to the radiopharmaceutical may also contribute to therapeutic responses in radiosensitive neoplasms, is pretherapy targeting to verify antibody uptake truly predictive of tumor response? (d) Are fractionated doses preferred over single doses of RAIT? (e) To what extent and in which setting can retreatment be safe and advantageous? (f) Does therapy with murine antibodies affect a subsequent therapy with chimeric or humanized antibodies by provoking an immune response?

These questions also may be of importance in RAIT of other neoplasms. Indeed, one of these considerations, related to the potential advantage of fractioned RAIT over single high-dose therapy, is gaining support from experimental and clinical studies of both NLH and solid tumors (13,95,101). However, the studies by Vriesendorp et al. (105) using ^{90}Y-conjugated rabbit IgG produced against human ferritin demonstrated that response rates were poorer in patients receiving fractionated therapy of 2 × 9.25 MBq/kg (2 × 0.25 mCi/kg) than those who received a single dose of 14.8 or 18.5 MBq/kg (0.4 or 0.5 mCi/kg). Interestingly, an antirabbit antibody response rate of only 5% was noted in this study of 90 patients. This low immunogenicity is more likely due to the prior chemotherapy given these patients than the immunosuppressive state induced by Hodgkin's disease.

In general, fewer studies have been pursued with RAIT in malignancies other than NLH, but efficacy in Hodgkin's disease, T-cell leukemia, and acute myelocytic leukemia (AML) has been reported.

T-Cell Lymphoma

Over a decade ago, an ^{131}I-labeled murine antibody (T101) was used for imaging and therapy of a small number of patients with cutaneous T-cell lymphoma (CTCL), with doses up to 555.37 MBq (150.1 mCi) being administered, including subsequent retreatment following plasmapheresis in 3 patients at the time of disease progression (106). Regression of skin lesions and peripheral adenopathy and resolution of the chronic pruritis were observed. The same antibody has been labeled with ^{90}Y and studied in 10 patients with CD5-expressing leukemia and lymphoma (chronic lymphocytic leukemia [CLL] and CTCL), using the ^{111}In-conjugate for pretherapy targeting and dosimetry (107). No retreatment was attempted in the CTLC patients, since they all developed HAMA, but 1 patient with CLL received a second therapy cycle. The authors reported 5 PRs, 2 with CLL and 3 with CTCL.

Myelocytic Leukemia

The CD33 antigen expressed on early myeloid precursor cells and myelocytic leukemia cells has been a target for RAIT. Both the murine and, more recently, the humanized forms of the M195 antibody labeled with ^{131}I have demonstrated improved efficacy in combination with busulfan and cyclophosphamide before first or second bone marrow transplantation in patients with AML (108). A humanized IgG1 antibody has been developed and used in patients with relapsed or refractory AML at doses of 0.5 to 10.0 mg/m^2 given 6 times over 18 d, without evidence of immunoge-

nicity (*109*). A recently published article showed impressive induction of molecular remissions in patients with acute promyelocytic leukemia (*110*).

^{213}Bi, which has a half-life of 45.6 min and emits high LET α-particles (8 MeV) with a pathlength of 50–80 μm, has also been conjugated to this humanized antibody (*44*). Results in 9 patients showed that the dose ratio between marrow, liver, and spleen volumes and the whole body for the radioconjugate is 1,000-fold greater than that usually observed with β-emitting radionuclides used in RAIT (*44*). These findings support the feasibility and potential of using this α-emitting radionuclide in the treatment of leukemia.

Further support for the use of RAIT in leukemia is derived from studies with the CD45 antibody. When the ^{131}I-labeled anti-CD45 murine antibody BC8 was combined with cyclophosphamide and 12 Gy total-body irradiation as a bone marrow conditioning regimen in patients with acute leukemia (^{131}I dosage, 2,812–22,644 MBq [76–612 mCi]), it was estimated that the marrow dose was 6.5 cGy/mCi and the spleen dose was 13.5 cGy/mCi; 7 of 25 patients with AML/myelodysplastic syndrome survived disease-free for a median of 56 mo (range, 15–89 mo) (*111*). Patients with acute lymphoblastic leukemia also showed good survival results for up to 6 mo after transplant (*111*). These results, as well as the findings in yet another study by this group (*112*), support the view that RAIT can improve the outcome of bone marrow grafting in patients with acute leukemia by decreasing the relapse rate.

A study has appeared recently on the use of an antibody against the granulocyte antigen NCA95 labeled with ^{188}Re for the treatment of AML and as a marrow ablation agent (*42*). Also, there is also a growing interest in the prospect of treating multiple myeloma with certain radiolabeled antibodies (*113,114*). These diverse studies involving different antibodies and radiolabels all suggest that RAIT is advancing in the therapy of several hematopoietic tumors.

Solid Tumors

The more radioresistant solid tumors have not been as responsive to RAIT as hematopoietic neoplasms, and for this reason several strategies to improve results are being pursued. Clinically, the major interests have been colorectal, ovarian, breast, medullary thyroid, and brain cancers, with some early studies being reported also in urinary bladder cancer, prostate carcinoma, and other tumors, as summarized in Table 4. Many different radionuclides, antibody forms, and methods to increase antibody accretion and penetration are under investigation, and in fact several approaches appear to be promising. On the other hand, methods to prevent or alleviate dose-limiting side effects, such as myelosuppression, are also of interest as they could potentially enable the administration of higher radiation doses. However, at this moment no radiolabeled antibody has yet shown sufficient antitumor activity in advanced metastatic disease of any solid tumor type to suggest that it represents a new therapy modality. Nevertheless, recent

TABLE 4
Recent Clinical Studies of RAIT in Solid Tumors

Tumor type	Target antigen	Antibody	Radiolabels	Representative references
Glial tumors	Tenascin	BC4	^{131}I, ^{90}Y	57
	Tenascin	816C	^{131}I, ^{213}Bi	118
	EGFR	425	^{125}I	120
Leptomeningeal cancer	ED2	3F8	^{131}I	124
Ovarian carcinoma	MUC1	HMFG1	^{90}Y	128
	Glycoprotein	MOv18	^{131}I	131
	TAG-72	B72.3, CC49	^{131}I, ^{90}Y, ^{177}Lu	40
	CEA	MN-14	^{131}I	133
Colorectal cancer	TAG-72	B72.3, CC49	^{131}I, ^{90}Y	148, 149
	CEA	hMN-14	^{131}I, ^{90}Y	141
	A33	Anti-A33	^{131}I	150
	Pancarcinoma	NR-LU-10	^{90}Y/biotin	54
Breast cancer	MUC1	HuBrE3	^{90}Y	157
	L6	chL6	^{131}I	159
	TF-antigen	170H.82	^{90}Y	161
	TAG-72	CC49	^{131}I, ^{177}Lu	162, 163
Prostate cancer	TAG-72	CC49	^{131}I	167
	PSMA	J591	^{131}I, ^{213}Bi	171, 174
Bladder cancer	MUC1	HMFG1	^{125}I	177
	MUC1	C595	^{67}Cu	38
Renal cell carcinoma	Glycoprotein	chG250	^{131}I	181
Medullary thyroid cancer	CEA	hMN-14	^{131}I, ^{90}Y	183
	CEA	F6	^{131}I/hapten (AES)	182
Hepatocellular carcinoma	Ferritin	Rabbit	^{131}I, ^{90}Y	20
Small cell lung cancer	CEA	F6	^{131}I/hapten (AES)	190

results in the therapy of small-volume or micrometastatic disease, such as in colorectal and ovarian cancers, suggest that these neoplasms, in the minimal disease setting, may be the best first opportunity for systemic RAIT under current limitations of the technology.

The principal antibodies being studied are against CEA, TAG-72, MUC1, and other glycoproteins (e.g., Le-Y); tenascin; and prostate-specific membrane antigen (PSMA) (Table 3). The majority are being used as directly labeled intact IgG immunoglobulins, labeled with either ^{131}I or ^{90}Y, in either chimeric or humanized forms. Most have been studied as single-dose therapy, but evidence is mounting that a fractionated dose schedule is more efficacious (115,116). As mentioned earlier and as shown by several reviews of the progress of RAIT in solid tumors (6–13), advances have not been as impressive as have those for hematopoietic malignancies, and at this time the role of RAIT in any single neoplasm is still not established. The recent excellent review of clinical RAIT by Knox and Meredith (11) has catalogued several studies in solid tumors, so this discussion will only select representative reports of interest. It should be noted that almost all of the trials reported are phase I-II dose-escalation studies, so that suboptimal doses were used in many cases. Indeed, the antibodies and their forms, the doses of antibodies, the radionuclides administered, the stage of disease studied, and the radiation-absorbed doses accreted in tumors have varied considerably among the clinical trials. Most investigations have involved a single dose of [131]I- or ^{90}Y-labeled antibody, mainly at low but occasionally at myeloablative doses requiring hematopoietic support. The majority of trials have involved patients with advanced disease who had failed other forms of therapy, which are difficult patient populations in terms of therapeutic response. Although CRs are rare, PRs and minor responses and durable disease stabilization have been observed, suggesting that optimization of RAIT in future clinical trials could improve the prospects of RAIT in solid tumors.

Brain and Other CNS Cancers

Results from numerous studies have shown that the best efficacy is achieved by locoregional administration or systemic administration for treatment of small tumors or minimal disease. Brain and central nervous system (CNS) tumors are particularly good candidates for locoregional therapy. Using antitenascin antibodies labeled initially with ^{131}I and more recently with ^{90}Y, Riva et al. (117) injected these into the tumor bed after surgery of malignant gliomas, and have reported impressive growth control. The median survival for patients with glioblastoma was prolonged to 25 mo with the ^{131}I-labeled antibody and 31 mo with the ^{90}Y group. In many cases, significant tumor shrinkage was observed. Compared with the ^{131}I-labeled antibody, the ^{90}Y radioimmunoconjugate showed more favorable results in bulky lesions and has fewer radioprotection problems. When another antitenascin antibody labeled with ^{131}I was injected directly into surgically created resection cavities of patients with malignant gliomas, average absorbed doses in the tumor cavities were 41 Gy (118). In yet another study with a different ^{131}I-antitenescin antibody (81C6) given intrathecally to 31 patients (119), only 1 patient had a PR and 13 (42%) had disease stabilization; tumor-absorbed doses were estimated to range from 14.4 to 34 Gy. In this patient group, 17 of the 23 adults had recurrent glioblastoma multiforme and some of the others had cerebrospinal fluid carcinomatosis from metastatic breast cancer, thus representing a diverse patient group with poor prognoses. The MTD of a single intrathecal administration in adults was 2,960 MBq (80 mCi). Encouragingly, 12 patients were reported to be alive at a median follow-up of >320 d, and 3 were progression-free at a median of >409 d after treatment.

Systemic or intraarterial RAIT with [131]I- and ^{125}I-labeled antibodies has also been explored for brain tumors, and these studies have provided evidence of objective responses without significant toxicities (120,121). In established disease and as adjuvant therapy, ^{125}I-antiepidermal growth factor receptor antibody 425 has been shown to be active in the treatment of patients with primary glioblastoma multiforme, with a 20% objective response rate (121–123). The intraarterial route of administration did not appear to offer any advantage over intravenous infusions, and this has also been confirmed by others (123).

In addition to using radiolabeled 3F8 antibody in neuroblastoma therapy, Cheung et al. have studied this RAIT for leptomeningeal cancer by intraventricular administration, with estimated radiation doses to the cerebrospinal fluid of 14.9 to 56 cGy/mCi and less than 2 cGy/mCi to blood and other organs outside the CNS (124). Intrathecal RAIT has also been applied to patients with medulloblastoma and neuroblastoma, resulting in objective and durable responses in some patients, for example, in 5 of 11 patients with recurrent neuroblastoma, while a CR was noted in 3 of 15 patients with recurrent primitive neuroectodermal tumors (125,126).

Ovarian Cancer

Intraperitoneal RAIT using a ^{90}Y-labeled MUC1 antibody (Antisoma plc, London, U.K.) in patients with ovarian cancer stage IC-IV and no evidence of disease after debulking and platinum-based chemotherapy, produced significantly prolonged durations of disease-free survival: an 80% survival rate at 5 y, compared with 55% for nonrandomized chemotherapy controls without RAIT ($P = 0.0,035$), and a projected 10 y survival rate of 70% versus 32% for the same controls ($P = 0.003$) (127). It was reported later that in the 21 patients who achieved complete remission following surgery, chemotherapy, and intraperitoneal RAIT, the median survival was not yet reached at a maximum follow-up of 12 y, with 78% surviving >10 y (128). Earlier work by this group demonstrated that the therapy was more effective

in patients with tumor nodules less than 2 cm, with no responses when the tumors were larger (129).

[186]Re-NR-LU-10 (NeoRx Corp., Seattle, WA) and ^{177}Lu-CC49 have also been administered intraperitoneally and have shown evidence of activity when small tumor nodules (<5 mm) or micrometastatic disease were present (39,41).

A study of ^{131}I-labeled OC-125 murine antibody F(ab′)$_2$ given intraperitoneally at a dose of 4.44 GBq was reported in 6 patients with minimal residual ovarian adenocarcinoma after primary treatment with surgery and chemotherapy (130). This therapy was administered 5–10 d after surgery, but the patients were given laparoscopic examination or laparotomy 3 mo later and little therapeutic benefit was observed for the intraperitoneal route. Also, all of the patients showed HAMA production.

The ^{131}I-labeled MOv18 chimeric antibody is being evaluated in patients with ovarian cancer at 3-GBq intravenous doses, with no HACA responses observed in the 3 patients studied (131). Tumor-absorbed doses ranged from 600 to 3,800 cGy, and all patients achieved stable disease lasting from 2 to >6 mo without major toxicities.

A phase I dose-escalation trial of ^{90}Y-labeled B72.3 murine mAb given intraperitoneally to patients with ovarian cancer showed the MTD to be 370 MBq (10 mCi) (132). In order to suppress bone uptake of the radiometal, patients were given a continuous intravenous infusion of EDTA immediately before intraperitoneal RAIT, which resulted in significant myeloprotection that allowed dose escalation.

Fourteen patients with advanced refractory ovarian cancer were given escalating intravenous doses of ^{131}I-labeled MN-14 anti-CEA IgG (Immunomedics, Inc.) and studied for tumor targeting, toxicity, and response (133). Tumor targeting was observed in all patients. The MTD was determined to be 1,480 MBq/m^2 (40 mCi/m^2). Of the 14 treated, 1 patient with diffuse peritoneal implants of <2 cm had a CR for 8 mo, followed by a PR for 10 mo after retreatment at the MTD, and became apparently free of ovarian cancer while also having a HAMA response (134). Another patient had a mixed response, while the remainder progressed.

Colorectal Cancer

The findings in ovarian cancer patients with minimal disease are consistent with those in metastatic colonic cancer xenografts, where it has been observed that radiolabeled CEA antibodies can be curative of minimal metastatic disease (28,135–138), and that the highest rad doses delivered to tumor are inversely proportional to tumor size (139). Similar calculations and predictions were made by Sgouros (140). Clinical studies with humanized CEA antibodies labeled with ^{131}I confirmed these animal studies, since patients with colorectal cancer metastases of small volume after unsuccessful chemotherapy showed encouraging responses (141). In an ongoing trial of RAIT with humanized anti-CEA MN-14 IgG (Immunomedics, Inc.) in an adjuvant setting following resection of metastatic colorectal cancer, 8 of 9 patients showed no relapse at up to 15 mo, compared with 47% in a control group at the same institution (142).

Early studies with ^{131}I-labeled CEA and B72.3 murine antibodies in colorectal cancer showed modest antitumor effects at nonmyeloablative doses. Four of 15 patients showed an objective response with B72.3 and other antibodies (143), while CEA antibodies showed antitumor effects in 12 of 35 patients with colorectal and other CEA-expressing cancers (144). Studies with diverse CEA antibodies have also shown modest therapeutic responses with nonmyeloablative doses of ^{131}I-labeled antibodies (26,145).

Buchegger et al. have suggested in early clinical studies (29,146) that RAIT in close association with external-beam irradiation is more efficient in an adjuvant setting after surgery. Clinically, 6 patients with limited liver metastases from colorectal cancer were treated with RAIT using 740 MBq (20 mCi) ^{131}I-labeled anti-CEA antibody F(ab′)$_2$ fragments combined with fractionated external beam radiation of 20 Gy to the entire liver. Spontaneously reversible bone marrow toxicity of grades 3 and 4 and reversible liver toxicity of grades 1 to 3 were observed. Three of the patients showed stable disease and 1 had a PR, while 2 progressed.

A phase II RAIT trial with ^{131}I-CC49, which is the second-generation murine B72.3 pancarcinoma antibody, reported no objective tumor responses at the MTD dose of 2,775 MBq/m^2 (75 mCi/m^2) (147). Twelve of 13 patients developed HAMA at 6–8 wk after infusion. High-dose RAIT with autologous stem-cell replacement was then undertaken with ^{131}I-labeled murine mAb CC49 in 15 patients with gastrointestinal cancer in a dose-escalation study from 1,850 to 11,100 MBq/m^2 (50–300 mCi/m^2) (148). Tumor localization was excellent, the %ID per kilogram of tumor ranged from 0.2 to 2.1, and the absorbed dose in metastatic tumor sites ranged from 630 to 3,300 cGy. These authors then tested the same antibody labeled with [90]Y (149) and found heterogeneous liver and splenic uptake, photopenic lesions in the liver for metastases, and generally poor uptake of the antibody in metastases. Absorbed tumor doses ranged from 180 to 3,000 cGy, but tumor-to-normal-liver dose ratios were less than 1. No objective responses were observed. Doses up to 18.5 MBq/kg (0.5 mCi/kg) could be administered with reversible grade IV myelotoxicity.

Another target for colorectal cancer RAIT is the A33 antigen, which is a transmembrane glycoprotein of the immunoglobulin superfamily (150). In one study, 23 patients who had failed prior chemotherapy were treated with escalating doses of ^{131}I-A33 murine mAb, and the MTD was found to be 2,775 MBq/m^2 (75 mCi/m^2) in these heavily pretreated patients (151). The antibody showed variable uptake in the normal bowel, and no objective responses.

The NR-LU-10 pancarcinoma antibody (NeoRx Corp.) was also studied in colorectal cancer patients by the pretargeting scheme using a streptavidin conjugate of the antibody (54). Twenty-five patients were treated with a single dose (4,070 MBq/m^2 [110 mCi/m^2]) of ^{90}Y-DOTA-biotin,

24 h after a clearing agent was given to remove the NR-LU-10/streptavidin. Diarrhea was the most frequent grade 4 nonhematological toxicity. A modest overall response rate of 8% was reported, with 4 patients having stable disease and freedom from progression for 10–20 wk. These results do not confirm the promising preclinical studies with the same reagents and technology (*51*).

Breast Cancer

Several studies have explored the use of RAIT in breast cancer, but it is still too early to advocate one antibody or therapy system over another. Antigen targets have included primarily CEA, MUC1, and L6. These and other antibodies used in breast cancer detection have been summarized in a recent review (*152*). CEA has been of interest for breast cancer targeting and imaging for many years, but the variety of methods used to demonstrate the expression of this antigen in breast cancer specimens has led to conflicting views, as discussed elsewhere (*153*). When highly sensitive immunohistochemical and RT-PCR methods are used, up to 90% of breast cancer specimens can be shown to express CEA, and this is in fact consistent with radioimmunodetection studies of breast cancer with ^{99m}Tc-labeled anti-CEA Fab' fragments (CEA-Scan; Immunomedics, Inc.), where a 94% sensitivity in confirmed tumors was observed (*153*). In very early studies conducted with a murine CEA-specific antibody (NP-4) labeled with ^{131}I, some responses were noted (*144*). Preliminary results of a trial involving a chimeric anti-CEA antibody (cT84.66) labeled with escalating doses of ^{90}Y under stem-cell reinfusion showed promising indirect evidence of antitumor activity (*154*).

MUC1 mucins are expressed in elevated quantities in the tumors and blood of patients with diverse carcinomas, but especially breast and ovarian cancers. The BrE3 antibody is a murine IgG$_1$ that reacts with an epitope on the tandem repeat of the peptide core of MUC1 (*155*) and has been shown by immunohistology to be expressed in over 75% of the cells of more than 95% of breast cancers (*155,156*). A clinical trial is ongoing with ^{90}Y-labeled humanized BrE3 antibody given in dose escalations with autologous peripheral stem-cell reinfusion. Doses as high as 2,923 MBq/m^2 (79 mCi/m^2) followed 14 d later by stem-cell grafting have been achieved without any severe nonhematological toxicity. In an interim analysis, the authors reported 2 PRs, 2 mixed responses, 5 no response/progressive disease, 3 not evaluable, 2 clinical improvement (no measurable disease), 1 normalization of tumor marker (no measurable disease), and 2 too early to assess (*157*).

L6 is a 24-kDa cell-surface glycoprotein expressed on 50% of breast cancers (*158*), but antibody targeting studies have also shown its presence in human vascular endothelium (*159,160*). The chimeric antibody (chL6) labeled with ^{131}I achieved tumor radiation doses as high as 3,700 cGy per therapy dose of 740–2,590 MBq/m^2 (20–70 mCi/m^2) and resulted in some evidence of tumor response in 6 of 10 patients (*159,160*).

Relatively high tumor doses were achieved with the administration of a ^{90}Y-labeled murine antibody, 170H.82 (Biomira Corp., Edmonton, Alberta, Canada), against the Thomsen-Friedenreich disaccharide antigen (*161*). In this study of 10 patients, who were also given autologous peripheral stem cell reinfusions, encouraging evidence of tumor activity was seen at doses of 1,369–2,109 MBq (37–57 mCi) ^{90}Y, at a mean dose to tumor of 81.1 cGy/mCi (range, 14.1–141.5). Unfortunately, the murine nature of this antibody limits repeated administration.

The CC49 mAb binding to TAG-72 is also reactive with breast cancer and has been studied with ^{131}I and ^{177}Lu radionuclides (*162,163*). Tumor localization was excellent, and in the patients receiving the ^{131}I-CC49, interferon was also administered to upregulate the expression of the TAG-72 antigen, but unfortunately this was not sufficient to significantly increase the accretion of radioactivity in tumors (*164*).

Prostate Cancer

The first demonstration that a prostate-associated marker could be targeted and imaged by antibodies was our use of rabbit antibodies against prostatic acid phosphatase labeled with ^{131}I (*165*). However, imaging of bone metastases was not observed. Thereafter, pancarcinoma antibodies such as those targeting TAG-72, which is expressed by prostate cancer cells, were evaluated. Meredith et al. treated metastatic prostatic cancer with ^{131}I-labeled CC49 antibody and showed that the majority of patients with pain experienced relief, but no objective antitumor responses were observed (*166,167*). In order to increase tumor antigen expression and, in turn, antibody accretion, these authors administered α-interferon in a trial of patients with hormone-resistant metastatic prostate cancer (*167*). The 2,775-MBq/m^2 (75 mCi/m^2) dose of radioiodinated antibody led to transient grade 3 or 4 neutropenia or thrombocytopenia. The absorbed dose was >25 Gy in 4 of 8 tumors visualized, representing an increase of >20-fold over the whole-body radiation dose. Only modest antitumor effects were reported (pain relief in 5 of 6 patients, 3 with prostate-specific antigen (PSA) reduction, and 2 minor responses). In comparison with the first study, interferon appeared to enhance tumor uptake by a maximum of 4-fold and showed modest antitumor effects. All patients showed an elevation of HAMA. These findings are consistent with another report of the same reagents given to prostate cancer patients, where efficacy was modest and the treatment did not have a meaningful delay of disease progression (*168*).

The CYT-356 antibody capromab pendetide (ProstaScint; Cytogen Corp., Princeton, NJ) has also been studied as a ^{90}Y-conjugate in a dose-escalation trial, and no therapeutic effects were observed (*169*). When the MTD in this trial was studied in another set of patients, no responses, including reduction of serum PSA, were likewise found, but there was some indication of complexation of the antibody with circulating antigen (*170*).

A mAb targeting the external domain of PSMA has been developed by Bander et al. (171) and is undergoing evaluation (172,173). An α-particle therapeutic with ^{213}Bi conjugated to this antibody has been described (174) and evaluated in vitro and in animals bearing human prostate cancer. RAIT reduced PSA levels in mice treated with this radioconjugate and also showed increased tumor-free survival.

The L6 antibody studied by DeNardo et al. in breast cancer (159–161) has also been shown in xenograft models to have potential for targeting prostate cancer (175).

Urinary Bladder Carcinoma

The urinary bladder is ideally suited for localized intravesical administration of radiolabeled antibodies. Syrigos et al. (176,177) reviewed the use of mAbs in the diagnosis and treatment of bladder cancer and reported that ^{125}I-labeled MUC1 antibody (HMFG1) given intravesically 2 and 24 h before cystoscopy showed localization of the antibody in tumor by biopsy examination, thus indicating the feasibility of this route of administration. Hughes et al. also reported that RAIT could be administered intravesically to treat superficial bladder cancer (38). They administered 20 MBq of ^{67}Cu-labeled C595 murine antimucin antibody intravesically to 16 patients with superficial bladder cancer, and the bladder was drained and irrigated 1 h later. Tumor was correctly identified in the images of 12 of 15 patients. Assay of biopsy samples at 2 h showed a mean tumor uptake of 59.4% of the injected dose per kilogram, with a tumor-to-normal-tissue ratio of 14.6:1. Although the initial tumor uptake was high, it was not sustained at 24 h.

Another trial of intravesical administration of a radiolabeled antibody was reported in China (178), demonstrating that ^{99m}Tc-labeled BD-1 mAb can target superficial bladder cancer.

Renal Cell Carcinoma

Metastatic renal cell carcinoma has been treated with an ^{131}I-labeled chimeric G250 antibody (179). In a phase I/II clinical trial, ^{131}I-labeled G250 was studied in 33 patients with renal cell carcinoma in a dose-escalation scheme from 1,110 to 3,330 MBq/m^2 (30–90 mCi/m^2) (180). All known tumors of 2 cm or more were targeted. The MTD was determined to be 3,330 MBq/m^2 (90 mCi/m^2), and all patients developed HAMA within 4 wk of therapy. Seventeen of 33 patients had stable disease, with no objective responses.

In a study to assess whether multiple injections of radiolabeled antibody can overcome the heterogeneous uptake of antibodies usually experienced in tumors, Steffens et al. (181), administering the chimeric G250 mAb to 10 patients with primary renal cell carcinoma, found that the second injection targeted the same areas within a tumor as the first one. Thus, heterogeneous distribution could not be overcome by another injection of the antibody 4 d later.

Medullary Thyroid Cancer (MTC)

Using the AES pretargeting technology, a phase I/II trial in 26 patients with recurrent MTC was conducted with an ^{131}I-labeled hapten given after a bispecific CEA antibody was administered 4 d earlier (182). Tumor doses were found to range from 2.91 to 184 cGy/mCi. Among the 17 evaluable patients, 5 minor responses, 4 biological responses with decrease of thyrocalcitonin, and 4 with symptomatic (pain) relief were observed. Seven patients showed grade 3 or 4 hematological toxicity (most having bone metastases), and 9 developed a HAMA response.

A phase I dose-escalation study with ^{131}I-labeled anti-CEA F(ab)$_2$ murine antibody in patients with metastatic MTC has been reported, whereby a high dose was administered with autologous stem-cell rescue (183). Of the 12 patients evaluated, 1 had a PR for 1 y, 1 had a minor response for 3 mo, and 10 had disease stabilization ranging from 1 to 16 mo. Experimental studies comparing ^{131}I- to ^{90}Y-labeled CEA antibodies in xenografted human MTC showed much higher accretion in the tumor of the latter radiolabel, as well as better therapeutic results (184). This humanized radioimmunoconjugate is now under study clinically.

Diverse Epithelial Tumors

Lewis-Y monoclonal antibody B3 labeled with ^{111}In or ^{90}Y has been studied in 26 patents with advanced epithelial tumors that express Lewis-Y antigen (185). The ^{90}Y doses were escalated from 185 to 925 MBq (5–25 mCi). Definite tumor imaging with the ^{111}In conjugate was observed in 20 of 26 patients. The MTD of the ^{90}Y conjugate was found to be 740 MBq (20 mCi), with neutropenia and thrombocytopenia being the dose-limiting toxicities. Tumor doses ranged from 7.7 to 65.1 cGy/mCi, but this was not sufficient to show therapeutic effects.

A different antibody type was described by Hornick et al. (186) in which antibodies against intracellular antigens, such as directed against nucleosomal determinants consisting of histone H1 and DNA, were used in RAIT. These authors claim that these antibodies result in high tumor localization and uptake properties.

The majority of human solid tumors express CEA, so that antibodies to this antigen have been studied in colorectal, pancreas, lung, breast, and medullary thyroid cancers (144), as indicated under these tumor sections. In the study by Behr et al. (144), tumor doses were found to be inversely related to tumor mass and ranged between 2 and 218 cGy/mCi; doses of 1,628 to 9,916 MBq (44–268 mCi) ^{131}I-NP-4 murine anti-CEA antibody (Immunomedics, Inc.) were administered. Modest antitumor effects were seen in 12 of 35 assessable patients, comprising 1 PR, 4 minor/mixed responses, and 7 stabilizations of previously rapidly progressing disease. The authors proposed that small tumors are more suitable for RAIT, and that bulky tumors will probably require myeloablative doses.

A mAb called Hepama-I has been studied in China in patients with verified unresectable primary liver cancer (*187*). A mean dose of 18.5 MBq was administered to 12 patients via the hepatic artery. Reduction of tumor volume was reported as a PR in 66.6%, and survival time was claimed to be prolonged in patients given this treatment. In the early years of RAIT, Order et al. used rabbit antiferritin antibodies to treat liver cancer (*188*). Another antibody, in a humanized form, has been developed against α-fetoprotein (AFP) for the treatment of AFP-expressing cancers, such as hepatocellular carcinoma and germ-cell cancers of the testis and ovary, and will soon enter clinical evaluation. Its murine diagnostic imaging counterpart has shown excellent targeting of tumors expressing AFP (*189*).

The AES pretargeting technology (IBC Pharmaceuticals, LLC), using an anti-CEA bispecific antibody and a ^{131}I-labeled hapten given 4 d later, has been studied in the treatment of patients with disseminated small cell lung cancer (*190*). Doses of 1.48–6.66 MBq (40–180 mCi) [131]I were administered, with hematological rescue with autologous stem cells being done at doses above 150 mCi. Tumor targeting was excellent, and the estimated tumor doses in 6 patients were 2.6 to 32.2 cGy/mCi. Among the 12 patients evaluated, 2 PRs, 1 stabilization, and 9 progressions were observed, with efficacy and toxicity being dose-related.

Pretherapy Dosimetry

Dosimetry approaches for estimating tumor and organ doses before RAIT have been derived from external beam radiation calculations but appear to be less accurate for RAIT, thus provoking some controversy on the role of this technology in treatment planning. In contrast to external beam therapy, there are fewer sample points and inhomogeneous dose distributions, and there can be wide dose variability for different lesions in the same patient (*11,191*).

Dose estimations for RAIT are made by calculating the volumes of tumors and normal organs, the estimated cumulative radioactivity accreted in organs and tumors, and the pharmacokinetics of the radioactivity given with the antibody. Various methods have been used to gain these data, including serial gamma-camera imaging, biopsy, and so on (*191–200*), for most organs and tumors, but the bone marrow dose estimates have been based on blood pharmacokinetics or imaging of bone in areas of active marrow, such as the spine or sacrum (*191*). When a therapeutic isotope has a γ-imaging energy, then it can be used in tracer doses for pretherapy dose estimates. In the case of pure β-emitters such as ^{90}Y, a surrogate γ-imaging isotope such as ^{111}In is used to predict the therapeutic dose. Tracer studies often predict the doses obtained from subsequent RAIT well, but variations, even in the same patient, can be experienced (*195–197*).

A major problem with pretherapy dosimetry has been a failure to achieve a consistent dose–response relationship for RAIT. For example, tumor doses in patients with lymphoma show a 10-fold range, from 0.5 to 5.4 mGy/MBq, and have had a variable correlation between estimated dose delivered and response (*191*). But at the extremes, there is evidence for a relationship between estimated tumor doses and response rates (*198,199*). Nevertheless, RAIT appears to achieve responses at dose estimates that are far lower than those calculated for external beam therapy (*21,200*). Normal organ doses from RAIT have ranged from 0.2 to 2.2 mGy/MBq, with considerable variability between patients (*191*). When very high doses of RAIT are given, such as in the myeloablative studies performed by the Seattle group, secondary organ toxicity involved cardiopulmonary complications in patients who received more than 27 Gy to the lungs (*201*). Thus, it appears that the low-dose-rate irradiation given by RAIT is tolerated relatively well by normal organs (*191*). An inverse relationship between tumor size and dose delivered has also been observed (*139*), indicating that small-volume tumors and micrometastases may be the best targets for current RAIT methods. Indeed, this is supported by both experimental (*135–137*) and clinical studies (*141,142*). In a comprehensive evaluation of 119 tumors in 93 patients given the ^{131}I-NP-4 and ^{131}I-MN-14 anti-CEA murine mAbs, an inverse logarithmic relationship between tumor size and antibody uptake was reported (*145*). The most important factor determining the radiation dose to the tumor was found to be the absolute tumor uptake of the radiolabel, and the second most important factor was the biological half-life of the antibody in the tumor. Different antibody affinities did not appear to affect tumor uptake. At comparable masses, colorectal and medullary thyroid cancers had significantly higher uptake of antibody, as well as tumor-to-red-marrow dose ratios, than other cancer types. Thus, it appears that tumor uptake of the antibody is the most important dose-determining factor, so that both colorectal and medullary thyroid cancers seem to be good targets for CEA antibodies used in RAIT.

It is well known from external-beam irradiation that higher dose rates result in higher therapeutic efficacy (*202,203*), but this has not been investigated well with internal emitters (*137*). Recent studies in experimental models (*28,137*), have begun addressing this issue, and it seems that dose rate effects are very important, not only at the comparably high levels experienced with external-beam therapy, but also in the lower ranges associated with internal emitters and RAIT.

In order to put pretreatment dosimetry in perspective, several factors potentially influencing the hematological toxicity of RAIT, which is the major dose-limiting side-effect of RAIT, have been studied (*204*). By means of multivariate analysis, it was determined that red marrow dose, baseline platelet or white blood cell counts, multiple bone or marrow metastases, and chemotherapy 3–6 mo before RAIT were the only 4 significant factors affecting hematological toxicity.

Based on the observation that during the recovery period after anticancer myelosuppressive therapy, hematopoietic

progenitor cells become mitotically active in order to re-plenish the bone marrow compartment, and remain hyper-proliferative even after normalization of blood counts of leukocytes and platelets, Blumenthal et al. (*205*) conducted a retrospective study of the blood levels of several hemato-poietic cytokines following a single dose of RAIT. It was found that the plasma level of flt3-ligand could predict excessive platelet toxicity caused by additional cytotoxic therapy. This encouraging report suggests that the measure-ment of this hematopoietic cytokine may be a reliable surrogate marker of the status of the bone marrow following cytotoxic therapy, thus perhaps predicting how aggressive a therapy, whether RAIT or chemotherapy, may be under-taken in any individual patient. Studies of this kind may be more clinically relevant than current bone marrow dosime-try methods.

CONCLUSION

RAIT of cancer has had a more than 20-year history, and during this time there have been profound advances in the development of tumor-seeking humanized antibodies, in radiochemistry with diverse radionuclides, in the mitigation of dose-limiting myelosuppression, and in the targeting and delivery of radiation doses to tumors in diverse locations. Hematopoietic neoplasms, in contrast to solid tumors, have shown the best responses to RAIT, despite the delivery of relatively low doses. This has resulted in several radiola-beled antibodies advancing toward commercialization for the treatment of NHL, with Zevalin being approved recently by the FDA. These results are due, perhaps, to good vascu-larization, high antigen density on a more homogenous tumor cell population, and possibly the involvement of concomitant apoptotic and immune mechanisms. In con-trast, solid tumors fail to receive the radiation doses required to achieve similar responses. Although RAIT of solid tu-mors represents the principal challenge of the future, it is already apparent that use of this modality in a minimal-disease setting, in locoregional applications, in combination modalities, in fractionated dose schedules, and in pretarget-ing strategies show sufficient promise to justify continued optimism for its future role in the management of cancer.

ACKNOWLEDGMENT

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