
Radioimmunotherapy with Monoclonal Antibodies

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This is the third article in the series on "Nuclear Medicine Updates." Upon completion of this article the technologist will gain an understanding of the: (1) future of radiotherapy, (2) its effectiveness, and (3) its limitations.

The future of nuclear medicine includes imaging and therapy with radiolabeled monoclonal antibodies. The number of clinical trials is expanding due to the encouraging results brought about by better antibodies and radionuclides and more effective labeling techniques. There are currently more than thirty institutions conducting clinical trials of radioimmunotherapy. Results in patients with lymphoma and hepatoma have been particularly encouraging. The use of quantitative imaging to determine the localization and predict the subsequent therapeutic effectiveness of radioimmunotherapy is a critical factor. Complications from radioimmunotherapy are minimal but marrow toxicity has been a limiting factor. Marrow exposure can be predicted by radiation dosimetry derived from quantitative imaging. Numerous methods to enhance radioimmunotherapy have been proposed including the use of drugs and external beam radiotherapy. As our understanding of radioimmunotherapy increases, the formulation of treatment programs becomes more effective.

The use of radiolabeled monoclonal antibodies for cancer therapy has received deserved attention in recent years. Increased understanding of the neoplastic process, tumor-associated antigens, and their potential for targeting tumors with antibodies has led to new treatment for cancers (1). The field of nuclear medicine has historically played a role in the treatment of malignancies such as metastatic thyroid carcinoma and polycythemia vera (2). The groundwork for the effectiveness of radiopharmaceuticals in radiation therapy has been established and the advent of additional targeting modalities, i.e., tumor-seeking antibodies provides limitless potential.

Radioimmunodiagnosis and radioimmunotherapy require selective localization of radioactivity in the cancer. For imaging, this selective localization needs to be maintained for only a brief span of time, if the target-to-nontarget relationship is favorable. For therapy, a less favorable target-to-nontarget relationship may be adequate if the tumor concentration is adequate and maintained for a sufficient length of time.

An inherent advantage of using radiolabeled monoclonal antibodies for treatment is the opportunity that they provide, through imaging, to assess the potential effectiveness of the therapy. An essential concern in radioimmunotherapy is the radiation dose delivered to normal organs. The bone marrow is particularly radiosensitive and must be monitored in order to avoid unacceptable toxicity (3). The radiation dose to the tumor and critical organs can be determined with image quantification.

RADIONUCLIDES FOR THERAPY

The requirements for an ideal therapeutic radionuclide are considerably more demanding than an imaging radionuclide. The choices of radionuclide and labeling technique substantially affect the radiopharmaceutical stability and in vivo kinetics thereby influencing the treatment (4). The optimum radionuclide for radioimmunotherapy should have sufficient gamma emissions in the 100-200 keV range to allow imaging for quantification (5). Physical half-life, types of emissions and particulate energy of the radionuclide are important for therapeutic applications, as are conjugation chemistry, stability and radiolysis. Ideally the half-life of the radionuclide should be comparable to the residence time of the monoclonal antibody on the tumor (6, 7).

The biology of the tumor must be considered when determining the best particle and particulate energy. Long particle range is desirable when the tumor is heterogeneous and consequently the distribution of the monoclonal antibody is not homogeneous. Even though the antibody and the radionuclide will not be localized on every tumor cell, the radionuclide in the vicinity of the tumor cells can deliver a tumoricidal dose (8). The disadvantage of longer particle range is increased exposure to normal cells. Short particle range is preferred when there is more homogeneous distribution of the antibody. The chemical properties of the chosen radionuclide should permit the synthesis of a product that will remain stable after injection. Autoradiolysis, the self destruction of the radioimmunoconjugate due to its own radiation, must be kept at a minimum. Table 1 illustrates characteristics of several radionuclides that have been used or proposed for use in radioimmunotherapy (8, 9).

MONOCLONAL ANTIBODIES

An immunized animal has lymphocyte lines (clones) that produce a variety of antibodies with affinity to antigens. This

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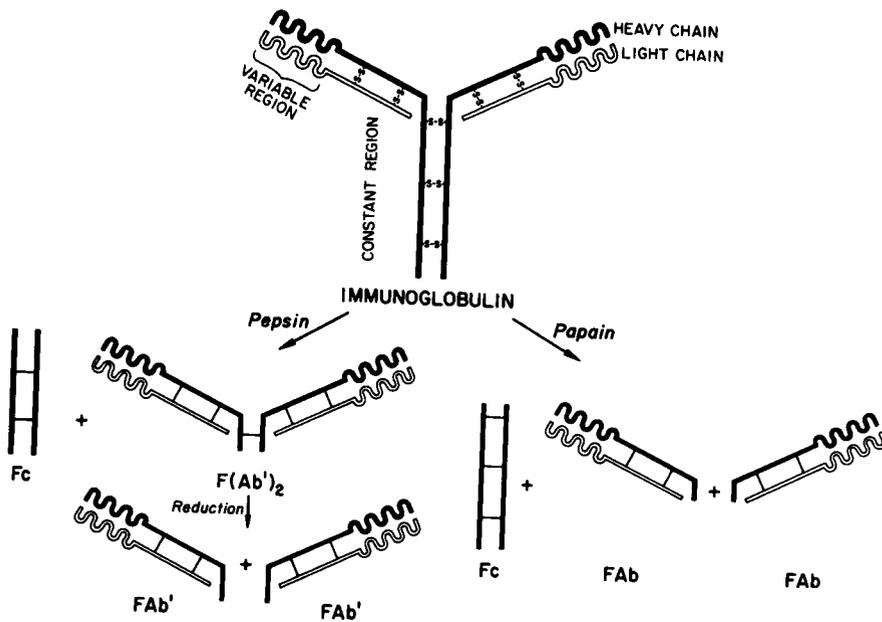


FIG. 1. Diagram of an antibody illustrating the heavy and light molecular chains linked by disulfide bonds. Each chain has a variable and constant region. Amino acid sequences in the variable region differ between antibodies and provide sites that specifically bind to different antigens. Use of antibody fragments for radioimmunotherapy, produced by enzymatic digestion (pepsin or papain) are under investigation as one method to optimize tumor radiation dose. (Reprinted with permission from O'Grady LF, DeNardo GL, DeNardo SJ. Radiolabeled monoclonal antibodies for the detection of cancer. *Am J Physiol Imag* 1986;1:48.)

diverse group of antibodies is referred to as polyclonal. However, if a single cell line is reproduced in cell culture or in the ascitic fluid of a mouse, monoclonal antibodies are produced which are unique for a specific target. Köhler and Milstein (10) were awarded the 1984 Nobel Prize for first describing the process that makes this possible.

An antibody is composed of mirror-image pairs of heavy chains and light chains and can be enzymatically fragmented into smaller pieces (Fig. 1) (4). The larger the portion, the slower the removal from the blood. The time to remove one-half of the amount of an intact antibody from the blood is ~24 hr while removal time is 10 hr for $F(ab')_2$ fragment and only 90 min for Fab or $f(ab')$ fragment. The Fab region contains the part that binds to a specific antigen and the Fc region is the heaviest and most immunogenic (11,12). Thus, the decision to use the whole antibody or merely a fragment of the whole antibody is dependent on the nature of the tumor to be treated.

TUMOR ANTIGENS

Tumor antigens provide targets for MAb. "Tumor-associated" antigens are present in normal tissues but are quantitatively or qualitatively expressed inappropriately in malignancies. Other antigens may be expressed in normal tissues

during fetal life but not later, for example, carcinoembryonic antigen (CEA) or alpha fetoprotein (AFP). Antigens may be "tumor specific" and, as the name implies, these are unique to cancer cells. There is still some controversy relative to the existence of tumor specific antigens. Regardless of the controversy, there are antigenic targets on tumors that are present in quantitative amounts and/or available to the targeting antibody, so as to make them effectively unique compared to normal tissues. A tumor antigen may be present on the surface of the cell in as many as a million sites allowing for attachment of many antibodies (and radionuclides).

The theoretical size limiting factor for the detection of a tumor with radiolabeled antibodies is $\sim 10^4$ cells, which translates to a lesion of 1 mm in diameter (13). Multiple lesions of this size that uniformly express the antigen can be effectively treated with radiolabeled antibodies.

The optimum antigenic target should have the following characteristics (7,14):

1. Unique from non-neoplastic antigens
2. Abundantly expressed on neoplastic cell membranes
3. Homogeneously expressed on all neoplastic cells
4. Not released from the cell in antigen form
5. Remains on the cell membrane for several days.

TABLE 1. Radionuclides for Radioimmunotherapy

Range	Emission	Nuclide	Imaging photon	$T_{1/2}$
Ultra-short	Alpha	^{211}At	no	7 hr
	Internal conversion X-Ray	^{125}I	yes (35 keV)	60 days
Short	Beta	^{199}Au	yes (158 keV)	76 hr
Medium	Beta	^{131}I	yes (364 keV)	193 hr
		^{67}Cu	yes (184 keV)	61 hr
		^{186}Re	yes (137 keV)	90 hr
Long	Beta	^{90}Y	no	64 hr

Unfortunately, the typical tumor antigen seldom manifests all these characteristics.

RADIOIMMUNOCONJUGATES

Radioimmunoconjugate (RIC) refers to a radionuclide attached to an antibody. There are three essential requirements for an effective therapeutic radioimmunoconjugate.

1. The antibody must maintain biological activity after attachment to the radionuclide (14).
2. The radioimmunoconjugate must preferentially bind to the tumor.
3. The radioimmunoconjugate must deliver a lethal dose of radiation to the tumor while maintaining a tolerable radiation dose to non-tumor sites, (15).

There are two significant advantages to using radioimmunoconjugates over antibodies attached to toxins or other drugs. Firstly, the physical range of the emissions of radioimmunoconjugates allows them to irradiate through and beyond a single cell. This extended range makes the internalization of the radioimmunoconjugate into every cell unnecessary, so that not every tumor cell needs to express the tumor antigen. Toxins and drugs, on the other hand, must be incorporated into each tumor cell in order to be effective. Secondly, the ability to image the distribution of the radioimmunoconjugate permits the physician to determine radiation dose rates to both tumor and normal tissues.

HISTORICAL BACKGROUND

As early as the turn of the century, Paul Ehrlich (4) postulated the concept of "magic bullets" to deliver toxins to targeted cells. In 1948, Pressman and Keighley (8) reported the use of radiolabeled antibodies to target a defined cell population in animals. Some of the earliest work in human radioimmunotherapy was begun over a decade ago by Order and colleagues (16) when they demonstrated that iodine-131-antiferritin polyclonal antibody therapy produced tumor regression in hepatomas. The success rate of clinical trials of immunotherapy is increasing as our knowledge of better conditions for applying this treatment expand.

TUMOR RESPONSES

To evaluate a response to radioimmunotherapy, variations of the following systems are used:

- Progression: Increase in tumor size.
- No response: Less than 30% tumor regression.
- Stable: 30-70% tumor regression.
- Partial remission: More than 70% tumor regression.
- Complete remission: Absence of disease.

Tumor regression is usually measured by one or more of the following methods: X-ray, CT or MRI tumor volumes, gamma camera images, caliper measurements of the tumor, blood marker tests (Fig. 2), and biopsies.

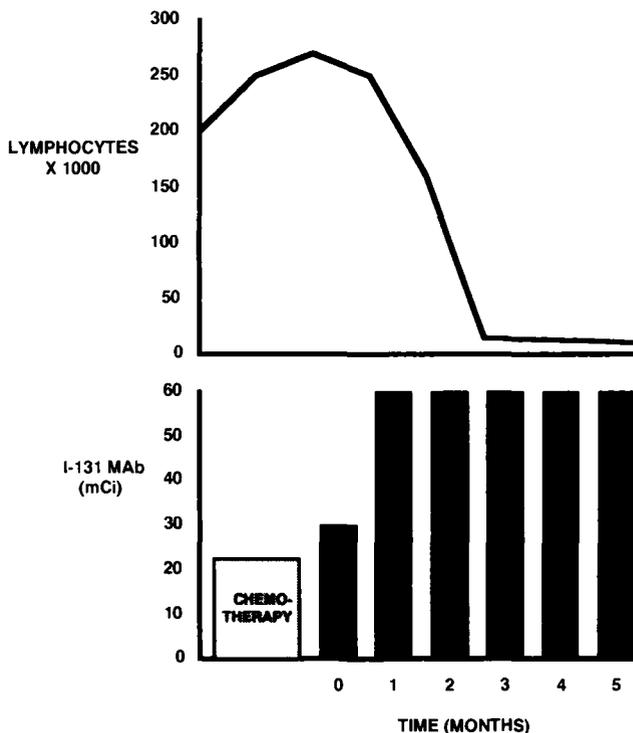


FIG. 2. Response of lymphocytes in patient with chronic lymphocytic leukemia following radioimmunotherapy with ^{131}I -LYM-1. Lymphocyte counts continued to climb during chemotherapy but became normal following treatment with ^{131}I -LYM-1. The ability to fractionate treatment is an advantage with radioimmunotherapy.

When compared to clinical trials of new chemotherapeutic agents, response rates to radioimmunotherapy have been promising because of more frequent regression rates in patients with very advanced disease.

CURRENT TRIALS

There are currently more than 30 institutions conducting clinical trials of radioimmunotherapy. At least four different radionuclides (iodine-131, iodine-125, yttrium-90, rhenium-186) have been conjugated to at least nine different antibodies. Lymphoma, leukemia, Hodgkin's disease, hepatoma, ovarian, breast, neuroblastoma and gastrointestinal cancers have been treated in these trials (17-29). Table 2 summarizes some of these clinical trials.

QUANTITATIVE IMAGING

The distribution and clearance of the radionuclide and, inferentially, the antibody can be quantified using noninvasive imaging techniques. Planar and tomographic imaging can be used to assess tumor volumes and their subsequent regression following therapy (Fig. 3) (9). This information is necessary in order to do treatment planning for each patient.

Some of the indications for performing radioimmunoimaging prior to and after therapy are listed below:

1. Pre-operative staging.
2. Postoperative detection of dissemination.
3. Evaluation of response to therapy.

TABLE 2. Current Clinical Trials

Disease	Radioimmuno-conjugate	Number of patients	Toxicity	Response	Investigators/ Site	References
B-Cell Lymphomas/CLL	¹³¹ I-LYM-1	28	Fever, rash, thrombocytopenia	27/28	DeNardo/UC Davis	17, 19
Hepatoma	¹³¹ I-antiferritin	105		50/105	Order/John Hopkins	28
Ovarian Cancer	¹³¹ I-HMFG/AUA1/H17E2	15	Diarrhea, leucopenia, thrombocytopenia	6 complete remissions	Epenetos/Hammersmith	25
Gastrointestinal	¹³¹ I-anti-CEA	8	None	6/8	Riva/Bufalini Cesena Hospital, Italy	26
Lymphoma	¹³¹ I-MB-1	5	Myelosuppression	5/5	Press/Hutchison Cancer Center	21
Colorectal	¹⁸⁶ Re	15	Myelosuppression	4/15	Weiden/Virginia Mason Med. Ctr.	23
Melanoma	¹³¹ I-anti-97	16	Thrombocytopenia	3/16	Larson/Sloan-Kettering	29
T-Cell Lymphoma	¹³¹ I-T-101	6	Fever	6/6	Zimmer/Northwestern University	24
Lymphoma	⁹⁰ Y-anti-ID	1	None	1/1	Parker/UC San Diego	27

4. Locating the source of occult tumors when blood antigens have increased.
5. Confirming the presence of lesions detected by less specific methods.
6. Serve as a basis for instituting therapy, specifically antibody therapy.

Imaging doses of radionuclides are used to document distribution in the patient, extent of uptake in the tumor and clearance from both. This information can be used to predict therapeutic effectiveness. However, this is only possible when the imaging radionuclide is the same or a close analog of the one used for radioimmunotherapy. The radiochemistry and biodistribution should be identical or, at the least, predictable, so that imaging data can be extrapolated to therapy. For example, ⁹⁰Y does not have a gamma emission for imaging. Indium-111 is from the same periodic group and is a good imaging radionuclide but it does not necessarily predict the behavior of ⁹⁰Y in all circumstances. Greater marrow toxicity from treatment with ⁹⁰Y than was predicted from ¹¹¹In antibody imaging has been reported. This resulted from yttrium being less tightly conjugated to the antibody than indium and consequently accumulated in the skeleton (25).

Antibody accumulation is dependent on blood flow to the tumor as well as extraction of the antibody from the blood. Tumor size also plays a role in the localization of the antibody. As tumor size increases, tumor uptake increases but tumor concentration decreases independent of the monoclonal antibody and the target antigen. This is due to a higher fraction of the necrotic or non-perfused regions in larger tumors (30).

The optimum time for imaging appears to be within a few hours for tumors in the intravascular space, such as hematopoietic cancers. The time frame for the highest level of antibody accumulation in solid tumors is 6–48 hr due to poor accessibility. Clearance of antibody or radionuclide from the tumor (and background tissues), as well as the physical half-life of the radionuclide are also factors in determining optimum time for imaging.

It is critical for quantitative imaging to position the patient consistently. The position that affords the best view of organ and tumor must be determined and that position must be accurately duplicated in all successive imaging sessions (Fig. 4). Reliable comparisons of tumor size can be made only when comparable views are available.

RADIOPHARMACOKINETICS

Radiopharmacokinetics reflect the unique ability to quantify the uptake of the radiolabeled antibody by planar and SPECT imaging, thus allowing for calculation of radioimmunotherapy dosimetry (31). This provides a method to predict the effectiveness of therapy and extent and sites of toxicity.

Absolute values of radiation absorbed dose or the relative fraction of the administered dose in the tissue can be determined as a whole or per unit mass of tissue (concentration). These absolute values define the macroscopic dosimetry but may underestimate the radiation dose and therefore the effectiveness of therapy at the microscopic level (32). This may explain the remarkable tumor regression associated with low macroscopic radiation doses estimated by quantitative imaging (33). The Medical Internal Radiation Dose (MIRD) approach, which takes into consideration organ size and density, is the standard method used to estimate radiation doses for internally administered radiopharmaceuticals. While recognizing the significance of microscopic dosimetry, this method usually addresses the macroscopic dose. A pragmatic index of radiation dose delivered to the tumor is provided by comparing tumor regression induced by radioimmunotherapy to tumor regression from known doses of external beam or sealed source radiation.

Respectable quantification of uptake is possible with the planar method. If a structure can be identified in both the anterior and posterior projection, the more accurate geometric mean method can be used (31). When a structure is visualized

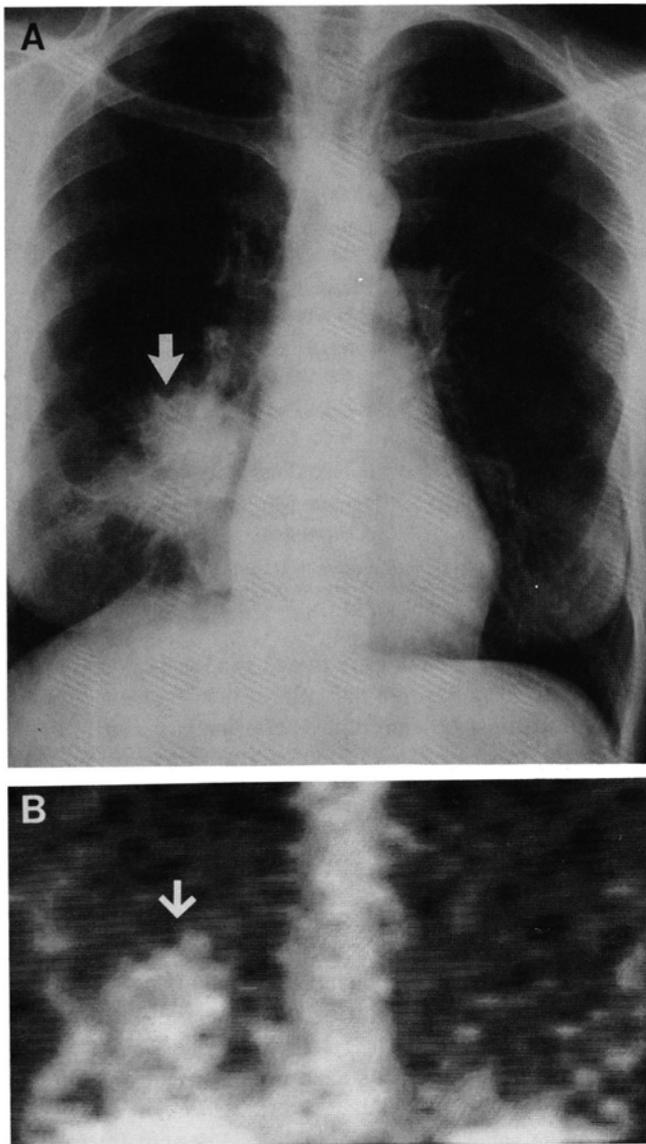


FIG. 3. (A) Radiograph of chest tumor does not differentiate lesion (arrow). (B) Radioimmunoimage of corresponding site demonstrates the specificity of the monoclonal antibody for this tumor. The tumor volume can be calculated prior to therapy and followed through treatment to determine therapeutic effect.

in only one projection, the effective point source method is used. The primary objective of quantitative SPECT is to determine not only the radionuclide uptake but also the volume of distribution. Tomographic imaging reduces the problem of nonspecific uptake in surrounding tissue. SPECT quantification requires scrupulous imaging techniques including:

1. Camera sensitivity determination.
2. Accurate region of interest (ROI) determination.
3. Accurate attenuation correction.
4. Accurate correction for scatter and septal penetration (34).

The method for quantitating uptake in our program has been designed for planar and SPECT imaging (Fig. 5). A

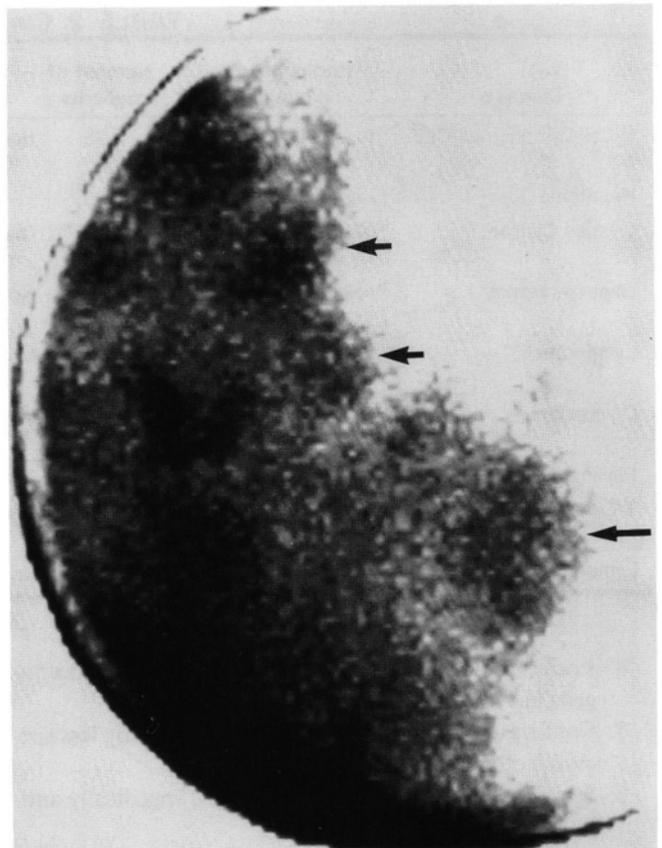


FIG. 4. Radioimmunoimage of lymphoma patient following therapy with ^{131}I -LYM-1. Note uptake in axilla and cervical nodes. Patient's arms were extended to optimize view of tumors and allow comparisons.

transmission scan is performed to determine the attenuation correction factor for the whole body, the tumors and critical organs. Regions of interest are manually drawn around these sites following imaging and therapy to obtain counts and number of pixels. A normalized background is subtracted from the organ count to arrive at a net organ uptake. The choice of background is critical particularly when low organ count rates are present and should be drawn in a contralateral position when possible. The net organ uptake is compared to the known injection activity and the percent of the injected dose is determined (%I.D.). In turn, the %I.D. over time is adjusted using the MIRD tables to obtain the radiation dose to the tumor or organ.

Radiation dose to the bone marrow, the major critical organ in radioimmunotherapy, is of concern particularly when there are tumor cells present in the marrow. Decreased platelet counts, one result of bone marrow toxicity, has been one of the limiting factors in radioimmunotherapy. To control the dose to the marrow, one must quantitate the radiation received during therapy. DeNardo and colleagues (35) have reported a method for measuring marrow uptake of an imaging or therapeutic dose of radiolabeled antibody. Three lumbar vertebrae are defined on sequential planar images of the back and the uptake is determined as described earlier. This value is then multiplied by a correction factor reflecting

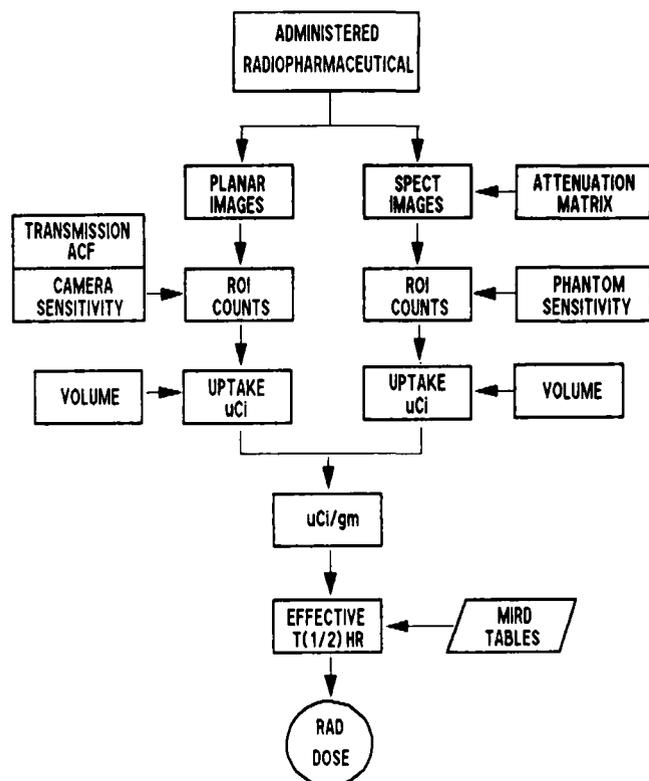


FIG. 5. Outline of quantitative methods to determine the uptake of radiolabeled antibodies with planar and SPECT imaging. The planar method requires the acquisition of a transmission scan to determine the attenuation correction (ACF). SPECT quantitation depends on the use of an attenuation matrix. (Reprinted with permission from DeNardo GL, Macey DJ, DeNardo SJ, et al. Quantitative SPECT of uptake of monoclonal antibodies. *Semin Nucl Med* 1989;19:23.)

the relative portion of whole-body red marrow represented in these three vertebrae.

TREATMENT PLANNING

Radioimmunotherapy treatment planning is still in its infancy. Treatment planning includes questions as basic as:

1. Whether or not the patient should be treated.
2. How to best treat the patient.
3. What radiation dose to the disease should be sought (34,36).

More than eighty years of experience with radiotherapy should be incorporated into this process (12). A critical concern for all therapy planning is to minimize the radiation exposure to normal tissues (37). Clinical experience with radiotherapy has led to a fractionated delivery scheme with 900-1000 cGy (rads) given each week in five doses. This appears to be the best method to achieve tumor cell kill and permit normal tissue repair. When larger daily fractions are given tissue tolerance decreases, normal tissue becomes far too damaged and curative rates are lower. Radioimmunotherapy has proven to be an interesting vehicle for delivery of fractionated therapy because radiation is continuously delivered as the radionuclide decays. The radiobiology of this

circumstance is challenging and important to future therapeutic designs.

In our institution, a number of variations in treatment methodology are under investigation. A flow chart of the typical treatment planning scheme is shown in Figure 6. Prior to treatment with radioimmunoconjugate, patients receive an infusion of unlabeled monoclonal antibody. Small amounts of antibody, such as that present in the radioimmunoconjugate, may be removed rapidly from the blood and are probably localized nonspecifically by organs such as the liver. Larger doses of unlabeled antibody (10 to 100 times the amount present in the radioimmunoconjugate) may need to be infused as a preload to saturate nonspecific sites, allowing the subsequent dose of radiolabeled antibody to circulate sufficiently long so that it can accumulate at the tumor site. After the dose of unlabeled antibody, depending upon the specific therapy protocol, patients receive treatment with 60 mCi, 100 mCi, or 150 mCi of the radioimmunoconjugate. Patients are imaged daily and blood and urine clearances are followed. Uptake and kinetics are determined on all visible tumor and non-tumor sites. Radiation dose distribution is estimated

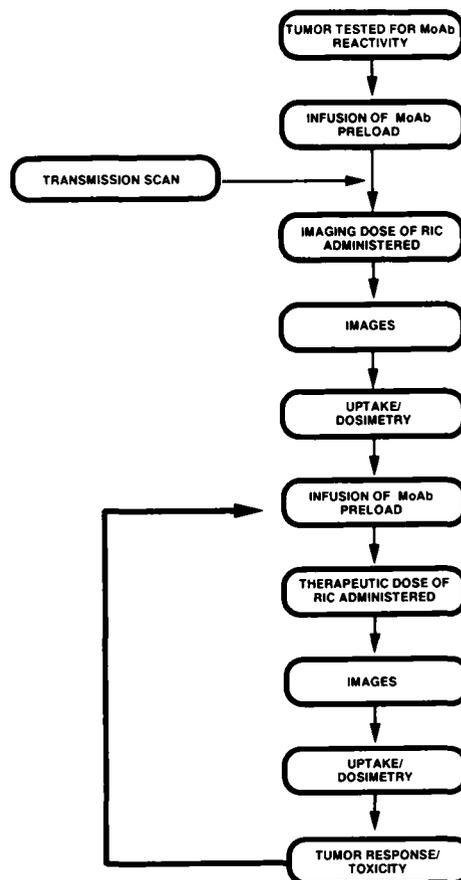


FIG. 6. Flow chart illustrating the general radioimmunotherapy sequence in our facility. Monoclonal antibody (MoAb) preload refers to unlabeled antibody administered to saturate nonspecific binding sites. The preload is followed by infusion of the radioimmunoconjugate (RIC). Planar images are routinely acquired while SPECT images are selectively obtained depending on site of tumor and maximum uptake phase. Tumor response is determined by quantitating tumor regression and toxicity is monitored.

from this data. Laboratory parameters, particularly white blood cell and platelet counts, and clinical findings are monitored in order to develop the treatment plan for each patient (38).

TOXICITY

Toxicity associated with radioimmunotherapy has generally been mild when compared to other forms of cancer therapy. Frequency and severity of reactions vary in part related to the disease state of the patient. For example, patients who are immunosuppressed due to their disease or previous therapies usually tolerate the infusion of the antibody with little or no reactions. In our patients with lymphoma, there has been minimal toxicity.

One of the organs most susceptible to the radiation is the bone marrow with the potential for resulting thrombocytopenia. Transient effects that occur are fever, rash and urticaria. These reactions are generally the direct result of the infusion of the antibody. In some cases the patient develops a human anti-mouse antibody (HAMA) that can preclude further treatment. HAMA forms immune complexes with the antibody used for treatment but an allergic reaction usually does not occur. The presence of a HAMA alters clearance and organ distribution of injected antibodies and can prevent binding to tumor cells. In our program, a HAMA assay is run prior to each therapy and to date about 15% of patients with lymphoma or leukemia develop a HAMA response after multiple treatments. Patients with a more intact immune system generally have a higher incidence of HAMA.

There are methods to potentially decrease these toxic responses to the antibody:

1. Fragments, rather than the whole antibody, may be less immunogenic (38).
2. Pretreatment with more than 400 mg of the unlabeled antibody has been suggested (9).
3. Human chimeric antibodies (antibodies with a human rather than mouse Fc portion) may be substituted decreasing the antigenicity or foreignness of the protein (39).

The future may bring entirely human tumor monoclonal antibodies but to date these have been unstable.

RADIATION SAFETY

Trials are underway to determine the effect of increasing the amount of administered radionuclide. Personnel should be continually aware of methods for decreasing their radiation exposure. The use of lead barriers, distance and decreased contact are essential to reducing radiation exposure. Radiation exposure has not proven to be a major problem and occupational exposures have been uniformly less than one-tenth that which is permitted by regulation.

Currently, patients receiving or containing more than 30 mCi of ^{131}I are hospitalized. The length of hospitalization will

vary with the level of radioactivity as well as the clearance rate of the radionuclide from the patient. The patient and their family should be educated in personal radiation safety techniques to reduce unnecessary exposure. It is also essential to train hospital personnel in the proper methods of caring for patients who receive radionuclidic treatment in order to minimize radiation exposure to personnel while affording dignity to the patients. The patients' needs for physical care are apparent, but appropriate psychological care must be provided as well despite radiation isolation. With the availability of more antibodies for radioimmunotherapy, patients will be treated earlier in the course of their disease. Hospital costs and personnel radiation exposure could be decreased by allowing informed, conscientious patients to isolate themselves in a home environment rather than concentrating them in hospitals (18).

FUTURE DIRECTIONS

Our understanding of this therapy has improved as the number of clinical trials has increased. We understand how to determine the optimum amount of antibody and radionuclide to administer. As research continues, more specific antibodies will be developed to provide even more effective tumor targeting.

There are potential "enhancers" that are under consideration (40, 41). Vasoactive drugs that increase blood flow can increase delivery of the radioimmunoconjugate to the tumor. Interleukin-2 increases capillary permeability and interferon enhances the expression of tumor antigens. External radiation has also been investigated as a method to increase capillary permeability. The ability to image and therefore quantitate the radioimmunoconjugate in the tumor is invaluable in determining the effectiveness of these enhancers.

Investigations are underway to discover more effective labeling techniques. Bifunctional chelating agents have been shown to stably bind to radiometals (^{111}In , ^{67}Cu , and ^{90}Y) under physiological conditions (4). These molecules contain a functional group at one end to immobilize a metal ion and a linker at the other end to covalently attach to an antibody (2, 7).

In spite of the gaps in our knowledge, radiolabeled monoclonal antibodies have shown remarkable promise as therapeutic agents. Patients with generalized, advanced disease, for whom standard methods of cancer therapy are no longer effective, have responded to radioimmunotherapy. Response rates should improve as radioimmunotherapy is more widely utilized as an adjuvant to other established therapies and in patients with less tumor burden (2). It is entirely possible that the future will bring customized antibody/radionuclide pairs that can be selected to fit any disease and be individualized for specific clinical situations (18).

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