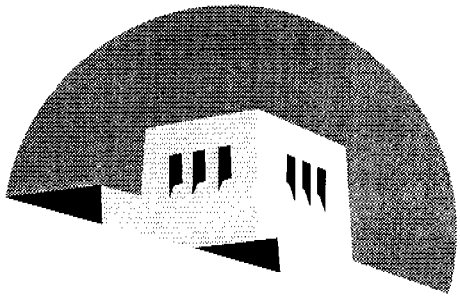

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ALBUQUERQUE, NEW MEXICO

Correspondence Continuing Education Courses for Nuclear Pharmacists and Nuclear Medicine Professionals

VOLUME IV, NUMBER 1

Use of Alpha- and Beta-Emitting Radionuclides for the Treatment of Cancer

by:

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USE OF ALPHA- AND BETA-EMITTING RADIONUCLIDES FOR THE TREATMENT OF CANCER

STATEMENT OF OBJECTIVES

The primary goal of this correspondence lesson is to increase the reader's knowledge and understanding of the use of alpha and beta particle-emitting radionuclides in terms of the historical use, as well as current and potential future applications with regards to radionuclide treatment and radioimmunotherapy of cancer. In order to complete this goal, this lesson considers a wide range of radionuclides that are commercially available as well as those still under investigation. Attention is paid to the important considerations and characteristics of these radionuclides when used in the treatment of cancer, including a summation of the many types of clinical situations in which this form of therapy has been applied and/or considered.

Upon successful completion of this material, the reader should be able to:

1. Discuss the relative value of surgery, external beam radiotherapy, chemotherapy and conventional radionuclide therapy in the treatment of cancer.
2. List four important considerations for selecting a radionuclide to be linked to an immunospecific antibody for use in radioimmunotherapy.
3. Compare the advantages of treating cancer with radionuclides whose emissions exhibit a long particle path vs. those with a short particle path.
4. List five important considerations, stemming from lessons learned in treating thyroid cancer, which can impact on deciding when to use unsealed source material for the treatment of cancer.
5. Describe several disadvantages for using gold Au-198 in the treatment of chronic synovitis.
6. List three radiopharmaceuticals that have been used for radionuclide therapy of central nervous system tumors.
7. List four different types of radiopharmaceuticals that have been used for the treatment of malignant melanoma.
8. List several considerations which help determine which radionuclide(s) can best be used for radiolabeling monoclonal antibodies (MAbs).
9. Describe several important characteristics of alpha particle-emitting radionuclides to be used for radionuclide therapy (RNT) or radioimmunotherapy (RIT).
10. Name four alpha particle-emitting radionuclides that have been discussed as useful for RNT or RIT.
11. Name five radionuclides that have a high neutron capture cross section.
12. Describe several important characteristics of beta particle-emitting radionuclides to be used for RNT or RIT.
13. List three examples each of low-range, intermediate-range, and long-range beta-emitting radionuclides.
14. List four beta-emitting radionuclides that have been used for the treatment of bone cancers.
15. List four examples of beta-emitting radionuclides that can be "activated" *in vivo* and have been used for the treatment of intraarterial or intracavitary radiation synovectomy.
16. Describe the role that Auger electron-emitting radionuclides can play in RNT of cancer.
17. List five examples of Auger electron-emitting radionuclides.
18. List three examples of radionuclides used for RNT that are produced either by an accelerator or a generator system.
19. Describe the types of tumors that have been studied using the MAb NR-LU-10.
20. List four different types of tumors that have a high density of somatostatin receptors.
21. Describe four different characteristics of an antibody that can have an effect on clinical results.
22. Describe five different host factors that can affect the manner of MAb distribution in patients following administration of a MAb.
23. Discuss the importance of dose rate in achieving desired outcomes when using radiolabeled MAbs for RIT.
24. Discuss ways in which hematopoietic suppression (associated with RIT and RNT) can be overcome.
25. Discuss ways in which the problem of human anti-mouse antibody (HAMA) [associated with radiolabeled MAb use] can be overcome.

COURSE OUTLINE

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II. HISTORICAL PERSPECTIVES IN RADIONUCLIDE THERAPY

* Thyroid carcinoma
* Pheochromocytoma
* Somatostatin receptor-containing tumors
* Hepatic tumors
* Chronic synovitis
* Central nervous system tumors
* Chondrosarcoma
* Lymphatic tissue
* Malignant melanoma
* Leukemia and Polycythemia vera
* Malignant lesions of bone
* Radioimmunotherapy (radiolabeled monoclonal antibodies)

III. RADIONUCLIDES FOR USE IN RADIONUCLIDE THERAPY (RNT) AND/OR RADIOIMMUNOTHERAPY (RIT)

A. Alpha particle emitters
B. Beta particle emitters
C. Auger electron emitters
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IV. CLINICAL STUDIES INVOLVING RADIOIMMUNOTHERAPY

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V. PROBLEMS WITH RNT AND RIT (AND POTENTIAL SOLUTIONS)

A. Antibody characteristics
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C. Radionuclide limitations
D. Overcoming barriers to therapy

VI. FUTURE PERSPECTIVES AND CONCLUSION

USE OF ALPHA- AND BETA-EMITTING RADIONUCLIDES FOR THE TREATMENT OF CANCER

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INTRODUCTION

Nuclear medicine has been using radioactive materials in the therapy of benign and malignant conditions for almost 50 years. These techniques are referred to as "radionuclide therapy" (RNT), and more recently as "radioimmunotherapy" (RAIT or RIT). Besides employing the use of RNT or RIT, the conventional treatment of cancer has involved the use of surgery, external beam radiotherapy, and/or chemotherapy (1).

Surgery remains one of the most successful forms of therapy for cancer. However, its effect is highly localized. External beam radiotherapy utilizes anatomical planning employing dose fractionation and dosimetry based on conventional formula in order to minimize irradiation of normal tissues (i.e., toxicity) and to maximize radiation of tumor tissue. Radiotherapy has seen appreciable success in treating cancer but, again, its overall effectiveness is localized. Chemotherapy is also an effective cancer treatment approach, but it lacks selectivity in terms of outcome. In fact, toxicity due to chemotherapy is related to the small drug molecules which can easily penetrate natural barriers so that normal tissues, along with the natural host immune responses, indiscriminately come under attack along with cancer cells. Conventional RNT approaches to date are both systemic and selective, depending on a particular function or tissue characteristic for localization of effect. Success with RNT depends less on the anatomical distribution of the tumor, but more on the physiological and pathological aspects of the tissue and on "continuous fractionation" of the deposited radioactivity. In relation to chemotherapy and radiotherapy, administration of RNT agents is usually straightforward (either oral or intravenous) and is relatively inexpensive.

As early as 1946, Pressman (2) showed that polyclonal antibodies directed against antigens expressed on tumor cells could be used to localize radionuclides in tumor. Iodine I-131 was the first isotope use for RIT. It was a natural choice due to its successful use in the RNT of thyroid cancer, its availability, and the ease with which it could be incorporated into an antibody without affecting immunoreactivity (2,3). It soon became apparent that the physical properties of I-131 (67% of its energy is emitted as gamma radiation) were not ideally suited for RIT.

Advancements in the development and use of RIT today can be traced to the many clinical experiences learned from the use of other cancer treatment approaches in patients. However, in order to develop effective radiopharmaceuticals for therapy, since each is likely to be used for a specific application, careful consideration in the choice of an appropriate radionuclide is essential, especially with regard to *in vivo* localization, as well as pharmacokinetic and decay properties of the radiotracer (4,5). The type of radiation emission, its range in tissue, the tumor dose rate, and the total tumor dose are important considerations when selecting a radionuclide to link to an immunospecific antibody for RIT (6). These features of radiolabeled antibody depend not only on the radionuclide, but also on the ability of the antibody to target the tumor and to deposit there in a significant concentration. Finally, the circulating radioimmunoglobulin must also be evaluated for its potential normal tissue or organ toxicity (6,7). In developing the basic suitability criteria for a radionuclide to be used in RIT, it is clear that no one radionuclide has all the possible advantages to make it the unique RIT candidate. For example, radionuclide emission(s) with long particle path length, which have "crossfire" effects, will be more useful for tumors with heterogeneous antibody distribution, while radionuclides with emission(s) of shorter particle path length may be preferred for linearly-growing homogeneous tumors, so as to decrease the normal tissue radiation dose (8). At the present time, with respect to both RNT and RIT, it appears that our technological inability to make use of a number of radionuclides, restricted availability, and high cost severely limit the number of different radionuclides that can be used for therapy (3). As such, few of the many radionuclides that have been considered as candidates for RNT or RIT have been tested clinically.

This article provides a general overview of the various radionuclides that have been suggested for use in RNT or RIT. In addition, a summary of various conceptual viewpoints with respect to exploring avenues that will enhance the role of RNT, and especially RIT, in patients with cancer is provided.

HISTORICAL PERSPECTIVES IN RADIONUCLIDE THERAPY

Though controversy still exists regarding its efficacy, I-131 sodium iodide in conjunction with surgery has become the oncologic treatment of choice for papillary and follicular ***thyroid carcinoma*** (9,10). In many respects, treatment of thyroid cancer has served as the model by which all subsequent unsealed source therapy has evolved. Several notable facts learned from the use of I-131 include 1) there must be confirmation (quantitated) of *in vivo* tumor uptake with the therapy agent before therapy is prescribed, 2) there must be a rapid excretion pathway of the therapeutic agent that is not taken up by the tumor, 3) interfering medications (prescription and over-the-counter drugs) must be avoided for an appropriate period of time before and around the time of therapy, 4) the cycle of diagnosis and therapy (until a recurrence that is functionally active is demonstrated) can take extended periods of time, where time can vary with the dose retained and other regulatory matters that must be taken into account as well, and 5) the use of unsealed source radiotherapy avoids selective irradiation of the immune system (9,11).

The next therapeutic success was in the application of receptor-binding radiopharmaceuticals, particularly metaiodobenzylguanidine (MIBG) labeled with I-131 for use in patients with malignant ***pheochromocytoma*** (12,13). Receptor-binding diagnostic radiopharmaceuticals, such as octreotide (a somatostatin analogue) radiolabeled with iodine I-123 and indium In-111, have shown uptake in ***somatostatin receptor-containing tissues*** such as carcinoid, gastroendocrine tumors, carcinoma of the pancreas, and pituitary adenomas (14). It is hoped that RNT using substituted somatostatin analogues has a place in the therapy of these lesions (14).

Treatment of ***hepatic tumors*** have utilized intraarterial injection techniques as a means of delivering the therapeutic agent to the intended site(s). Novell et al. have shown encouraging results in the treatment of primary hepatocellular carcinoma via hepatic artery infusions of I-131 labeled lipoidal, with as many as 50% of patients treated surviving more than one year (15). Currently, evaluation is underway to assess this form of therapy for secondary colorectal cancers affecting the liver (15). The use of hepatic arterial embolization with a radiolabeled agent (yttrium Y-90 labeled macroaggregates or glass microspheres) appears to be an appropriate approach given the nature of the arterial bed and the specific arterial supply of liver metastases (16). The addition of angiotensin II as a way of constricting hepatic arterial vasculature in normal liver further enhances the selective localization

of the radiolabeled glass microspheres (17).

Treatment of ***chronic synovitis*** by surgical synovectomy is not always successful as recurrences do occur with regeneration of the synovium; there is also a tendency to experience postoperative stiffness and limitation of motion (18). Intraarticular injection of chemicals such as nitrogen mustard (19) and thiotepa (20), although less invasive, were not significantly successful (21). The potential value of the intraarticular administration of colloidal radiogold (Au-198) was first discussed by Ansell (22), but it was not until the early 1960's that published reports discussing the efficacy of Au-198 in the treatment of recurrent knee effusions began to appear (23,24). Several disadvantages to the use of Au-198 in this manner have been identified: 1) gamma photons are emitted that do not contribute to local synovial irradiation, but do augment total-body absorbed dose unnecessarily (25), 2) there is a substantial leak of activity from the joint cavity (due to the small size of the Au-198 particle) via the lymphatics which is deposited in the regional lymph nodes (26), and 3) with deposition of Au-198 in the inguinal nodes (given that the knee joint is the most frequent site of application), irradiation of the testes can occur with a possible doubling of the natural risk of genetic damage (25). For the knee joint, Y-90 silicate citrate resin (27) and phosphorus P-32 chromic phosphate (28) are presently in use as alternatives to Au-198. Ideally, the penetration of the beta particles should be limited to the thickness of the synovium in order to avoid radionecrosis of cartilage and bone. Thus in smaller joints such as the hips, shoulders, elbows, ankles and wrists, rhenium Re-186 sulfide and erbium Er-169 citrate have been recommended for use in metacarpophalangeal and proximal interphalangeal joints (29).

In order for a radiopharmaceutical to be an effective radioblative agent in the ***central nervous system*** (CNS), it should 1) demonstrate relatively high uptake in target tissue with minimal localization in nontarget tissue, 2) have an effective half-life in target tissue which permits adequate radioblation, 3) provide suitable emission of particulate radiation to achieve ablation of target tissue with minimal gamma radiation to avoid damage to surrounding normal structures, and 4) permit a mode of administration that will avoid or minimize systemic distribution (3). Reports describing radiopharmaceuticals that have been used in CNS RNT include colloidal Au-198, Re-188 as perrhenate, and Y-90 DTPA. The target tissues for ablation include the pituitary gland (30), the choroid plexus (31-33), sites of CNS leukemia (34,35), and metastatic neoplasms of the posterior fossa and spinal cord (34,35).

In 1952, Gottschalk and Smith demonstrated that sulfur S-35 (as a sulfate) when given intravenously is taken up by ***chondrosarcoma*** (36). In most patients, S-35 initially caused minimal adverse effects, but with succeeding radionuclide treatments, there was consistent progression of thrombocytopenia, leukopenia, and lastly, anemia. With repeated treatments and dose accumulation, depression of the hemopoietic system was increasingly more profound, and there was no real recovery of the marrow (37,38). Because of the severity of marrow toxicity, this approach to therapy was abandoned.

Lymphatic tissue plays an important role in mediating the immune process responsible for homograft rejection. Because lymphocytes are highly sensitive to irradiation (39), internally administered radionuclides have been used for the selective destruction of lymphoid tissue (due to their selective localization in reticuloendothelial cells) in an effort to achieve long-term control over homograft rejection. The intralymphatic route has been used for the administration of colloidal P-32 chromic phosphate (40), gold Au-198 (40), and aggregated protein particles labeled with bismuth Bi-206 or silver Ag-111m (41). The intravenous route has been used for the administration of I-131 labeled antigens (42). Although these agents caused severe damage to lymphoid tissue with lymphopenia, homograft survival was not significantly prolonged. Somewhat better results were seen with the use of palladium Pd-106 protoporphyrin complex, whose beta particle (with an average tissue stopping power of 1 mm) was more localized to anatomical sites within lymph nodes that had a high affinity for this agent (i.e., most abundant in the medulla, less so in the paracortex, and least in the cortex) (43,44).

In the treatment of ***malignant melanoma***, several different approaches have been tried involving the use of Au-198 (45,46), Y-90 microspheres (47), P-32 chromic phosphate, and P-32 lipoidal (48). Radioactive chromic phosphates and Y-90 microspheres produced problems with administration, and there was significant liver uptake of Au-198. For a period of time, I-131 labeled ethiodol was used, since its dual beta and gamma emissions allowed for both diagnostic and therapeutic applications, and the tissue penetration from its beta emissions was estimated to be 3 mm (48).

Lawrence started P-32 therapy in ***leukemia*** in 1936, and three years later extended this to include the treatment of ***polycythemia vera*** (49,50). While the discovery of various chemotherapeutic agents has lessened the role that P-32 plays in the treatment of chronic leukemia, it remains a popular and important approach in patients with polycythemia vera. Though there is some concern relative to the leukemogenic effect of this form of radiation therapy in patients with polycythemia vera, the search for a better agent than P-

32 has so far been disappointing (51). Unlike I-131 sodium iodide therapy in hyperthyroidism where outcomes are predicted based on gland size, uptake of I-131 and retention time, it is extremely difficult to assess marrow mass, P-32 uptake, and its residence time within the marrow and bone. Several studies have estimated the radiation dose from P-32 to the marrow to be between 20 and 50 rads per millicurie (52-54). Due to variations in marrow and bone mass, P-32 uptake and effective half-life, and patient sensitivity to radiation, it is impossible to predict an accurate radiation dose for each patient. This has limited the use of P-32 in patients with chronic lymphocytic leukemia (CLL) and with chronic granulocytic leukemia (CGL) (51).

Therapy for ***malignant lesions of bone*** with radionuclides has been a common subject since the 1930's when Chiewitz and Hevesy (55) demonstrated the rapid incorporation of P-32 phosphate into bone salts and established a kinetic concept of regeneration for the mineral content in the skeleton. Others, including Pecher (56), expanded this interest to include other radionuclides, such as calcium Ca-45 and the calcium analogue strontium Sr-89. During the 1940s and 1950s, attention was given to the use of these radionuclides for the treatment of metastatic bone lesions (from primary carcinomas of prostate or breast) and Ewing's sarcoma (57-62). The combination of pretherapy using either testosterone or estrogen (63,64), parathormone (65-67), orchiectomy or adrenalectomy (68) followed by the administration of P-32 orthophosphate, has been reported to relieve bone pain due to prostate or breast skeletal metastasis. This type of therapy has also shown some evidence of bone regeneration and, in a few instances, has enhanced patient survival when compared to therapy involving the use of P-32 alone.

Clinical studies involving RIT have not produced as promising results as demonstrated in imaging trials using ***radiolabeled monoclonal antibodies*** (MAb). A number of reports have addressed issues such as 1) finding a technique to radiolabel the antibody with the radionuclide of interest 2) examining its *in vivo* immunoreactivity with the target tissue and 3) determining its *in vivo* stability (1). While the development of radiolabeling techniques has primarily followed a direction that seeks to minimize changes to the antibody with these various end points in mind, a number of equally important variables may have been overlooked. For example, conditions may vary considerably when labeling a monoclonal antibody with different radionuclides, chelates, or other radiolabeled molecules (1). Many of the properties requiring consideration in the selection of a radionuclide suitable for RIT have been discussed in detail by Wessels and Rogus (6). Some of these areas of concern include the importance of the radionuclides' half-life, radiation emissions, ratio of penetrating to nonpenetrating radiations, decay products (including those agents with multiple decay cascades), and mode of production (i.e., availability).

RADIONUCLIDES SUITABLE FOR RADIONUCLIDE THERAPY (RNT) AND RADIOIMMUNOTHERAPY (RIT)

Several authors, including Wessels and Rogus (6), O'Brien (69), and Jungermann et al. (70) have generated lists of radionuclides that would be suitable for labeling tumor-associated or tumor-specific antibodies. Due to the diversity of the possible requirements that a radionuclide would need to possess if intended for use in RNT, and especially RIT, the following discussion is divided into sections based on the type of radioactive decay encountered (e.g., alpha particle emitters, beta particle emitters, Auger electron emitters, and Coster-Kronig electron emitters following electron capture). It is important to keep in mind that each type of emitted particle has a different range in tissue, effective distance, and relative biologic effectiveness (RBE) (71,72). Gamma-ray emission may or may not accompany these decay processes and, if so, will likely contribute little in terms of overall therapeutic effectiveness due to irradiation of non-target tissues. However, should such gamma-ray emission exist within an energy range that is diagnostically useful, then such a radionuclide may prove useful for routine imaging and determination of in vivo localization (70).

Alpha Particle Emitters

Alpha particle-emitting radionuclides have physical characteristics that make them useful in the treatment of cancer. Alpha particles are high-energy helium nuclei that produce high densities of ionization along the path they travel. Because the path length of an alpha particle with an energy of 5-8 MeV is on the order of 40-80 μm (73), the effective treatment radius is several cell diameters from the atom that emits the particle. This reduces nonspecific irradiation of distant tissues. The high linear energy transfer (LET) of alpha radiation limits the ability of cells to repair damage to DNA and is effective in killing cells in hypoxic conditions (74). Indeed, at doses on the order of 100-200 cGy, alpha radiation may be 5-100 times more toxic than gamma radiation (75). For cells with a mean lethal dose (Do) for alpha particles between 0.7-1.0 Gy (76), only 3-6 alpha hits per cell nucleus are required to reduce the fraction of surviving cells in the population to an average of 37%. The estimated

number of beta particle traversals needed to produce the same energy deposition would be approximately 400 times higher, and one would still need to consider radiation quality or other dose modifying effects (7).

However, relatively few alpha-emitting radionuclides have been considered for RNT or RIT. Bismuth Bi-212 (T1/2 of 60.6 minutes) and astatine At-211 (T1/2 of 7.2 hours) are two radionuclides that have been studied (73,74,77-80). Bismuth-212 is available from a radium Ra-224 generator system (81), whereas At-211 is accelerator produced (82). Bismuth-212 has a branched chain decay scheme yielding both alpha (34%) and beta (66%) emissions, with most of its energy being lost by alpha emission (77%), and lesser amounts via beta, conversion electron, and Auger electron emissions (16%). The Bi-212 alpha particle has an energy of 6.07 MeV, and there is subsequently an 8.78 MeV alpha particle from its daughter radionuclide polonium Po-212 (81). The half-life of Po-212 is 0.3 microseconds; for every three decays of Bi-212 there will be two 8.78 MeV and one 6.07 MeV alpha particles. The higher energy alpha particle from Po-212 has a greater range and therefore will hit more cells along its path than will the alpha particle from Bi-212. Similarly, At-211 decay directly yields a 5.87 MeV alpha particle in its transition to Bi-207, and indirectly a 7.45 MeV alpha particle from its daughter Po-211 (T1/2 0.52 seconds, which subsequently decays to thallium Tl-207) (73). Beta particle-emissions also occur during these decay processes. Despite the high level of *in vitro* and *in vivo* cytotoxicity demonstrated for Bi-212 and At-211 (73,74), the 60.6 minute and 7.2 hour physical half-life of these radionuclides, respectively, limits their overall clinical utility. These radionuclides may be best suited for intraperitoneal administration in the localized treatment of rapidly accessible cancer cells such as peritoneal metastases (83), ascitic cancer (84), or leukemia. Work is currently underway to investigate the potential role of At-211 or Bi-212 as therapeutic approaches in patients with ovarian cancer, colorectal cancer, and melanoma (85).

Some discussion has focused attention on the potential use of lead Pb-212 (T1/2 of 10.6 hours), the parent of Bi-212. Although Pb-212 does not directly emit an alpha particle (only a beta with an energy of 1.1 MeV, with over 90% deposited energy coming from the alpha emission of Bi-212, and a very small contribution from the beta particle), a stable Pb-212 labeled radioimmunoconjugate would retain all the advantages of Bi-212 without the stringent requirement for rapid targeting imposed by the shorter half-life (86). In general, considering that the relative biological effectiveness of alpha particles compared with beta particles can be 10 or higher, the beta energy contribution to the total dose is negligible with respect to that from the alpha particles (86).

Alpha-emitting particles (i.e., Bi-212) possessing a high radiation biologic equivalence (RBE) can be attached to monoclonal antibodies via the use of appropriate bifunctional chelating agents (73,74). On the other hand, At-211 being a radiohalogen should have similar chemical properties to iodine and thus covalent linking to carbon atoms should be possible (87). Bigler (88) suggests that fermium Fm-255 (20.1 hour half-life) may be another alpha emitter that can offer more flexibility in the design of the carrier, assuming that sufficient quantities of the radionuclide can be produced at reasonable costs. Radium Ra-223 (T1/2 of 11.4 days) has been proposed by Fisher et al. (89) as a suitable alpha emitter for RIT. Noting past concerns that there was a lack of any ligand for binding radium, these authors state that Ra-223 can be tightly bound to a suitable ligand without concern for dissolution of free Ra(+2) in body fluids. Some of the short lived decay products of Ra-223 (i.e., lead Pb-211, T1/2 of 36 minutes), have been looked upon as being a dosimetric disadvantage. However, such decay products may actually contribute to the estimated tumor/normal tissue dose ratio, providing a cascade of 3-4 alpha particles per Ra atom which should lead to effective tumor-cell killing while sparing normal tissues (89).

The concept of boron neutron capture therapy (BNCT) focuses attention on the stable nuclide, boron B-10 which is irradiated to an unstable intermediate that promptly decays to yield lithium Li-7 and alpha particles (2.8 Mev) which travel a short path (approximately 10 μm) and has a high LET (90). Other isotopes that have relatively high neutron capture cross sections include cadmium Cd-113, samarium Sm-149, gadolinium Gd-155 and Gd-157, plutonium Pu-241 and americium Am-242 (90). While considered potential candidates for neutron capture therapy, many agents have been excluded for various reasons, such as 1) they are radioactive; 2) they produce gamma photons and other types of radioactive emissions that cannot be confined to individual target cells; and 3) they possess properties that limit their chemical incorporation into tumor localizing agents (90). For these reasons, interest remains focused on boron-10 as the radionuclide of choice in neutron capture therapy.

Actinium Ac-225 (T1/2 of 10 days) decays into a cascade of short-lived alpha- and beta-emitting radionuclides. The last radionuclide in this decay cascade is Bi-213 (T1/2 of 47 minutes), which can be extracted from an Ac-225 source at the bedside of the patient. Thorium Th-229 is but one of the many possible precursors to Ac-225 which, according to Geerlings et al. (91), may be a suitable agent for use

in alpha RIT.

Concerns for the safe handling and administration of alpha emitters may significantly impede their entrance into clinical settings. For example, the allowable level of radioactive contamination on the surface of packages containing alpha-emitting radionuclides is, according to US NRC Rules & Regulations, a factor of 10 lower than that for beta-emitting radionuclides. As such, special facilities and/or equipment will be needed to prevent and monitor laboratory contamination or airborne release of alpha-emitting radionuclides during storage or dispensing.

Beta Particle Emitters

Radionuclides that only emit beta particles are used exclusively for RNT or RIT. Due to their availability, a number of different beta-emitting radionuclides have been evaluated in the treatment of cancer. The primary sources of beta-emitting radionuclides are nuclear reactors that employ a direct (n,γ) reaction yielding agents with relatively low specific activities and may not prove useful in the development of agents for RIT (92,93). Beta-emitting radionuclides can also be prepared via an indirect (n,γ) reaction in many reactors; most of the nuclides obtained in this manner have high specific activity (92).

Besides the manner of production, beta-emitting radionuclides can be categorized on the basis of their mean penetration range in tissue (7). For example, low-range beta-emitting radionuclides with a range of less than 200 μm include phosphorus P-33, tin Sn-121, lutetium Lu-177, osmium Os-191, and gold Au-199. Beta sources with a range between 200 μm and 1 mm include scandium Sc-47, copper Cu-67, arsenic As-77, rhodium Rh-105, palladium Pd-109, silver Ag-111, iodine I-131, and rhenium Re-186. Long-range beta emitters (those with a range of greater than 1 mm) include P-32, Y-90, and Re-188. The emission of internal conversion electrons following beta decay and associated Auger electrons (i.e., Os-191 and Au-199), can contribute significantly to the local energy that is deposited in tissue (7). Finding production methods that will yield carrier-free product have yet to be identified for Os-191, Pd-109, and Re-186 (7); nevertheless, investigations are underway to determine the usefulness of these radionuclides labeled to antibodies in murine tumors.

RNT agents found to be effective in the treatment of bone cancers in patients involve radionuclides that do not require high specific activity, such as P-32 orthophosphate, ionic Sr-89, samarium Sm-153 EDTMP (ethylenediaminetetramethylene phosphonic acid), and Re-186 HEDP (hydroxyethylidene diphosphonate) (93). These examples, along with Sn-117m DTPA exhibit high selective uptake in bone lesions along with associated rapid clearance from nonosseous tissues (93), and demonstrate the potential for using metallic radionuclides complexed to selected ligands for treatment of primary bone cancer (94) and skeletal metastases (95,96). Phosphorus-32 (T1/2 of 14.3 days) decays solely by beta emission (1.7 MeV) which results in an average tissue penetration of 2-3 mm (97). Samarium-153 (T1/2 of 1.95 days) emits both a beta particle (0.810 MeV) and a gamma photon (103 keV, 29% abundance) which makes it suitable for both RNT and conventional scintigraphy. The average penetration range of the Sm-153 beta particle is 0.83 mm in water (97). Strontium-89 (T1/2 of 50.5 days) is another pure beta emitter (1.46 MeV).

In many respects, Re-186 is an attractive radionuclide for RIT. As noted by Griffiths (98) and Wessels and Rogus (6), the 3.7 day half-life of Re-186 is compatible with the pharmacokinetics of tumor localization and clearance of murine monoclonal antibodies. Additionally, the 137 keV gamma photon is ideal for gamma camera imaging, yet its low energy and abundance (9%) and low fraction (0.05%) of higher energy gamma photons (>600 keV) result in minimal radiation exposure to personnel as compared to other radionuclides, especially I-131. The medium energy 1.07 MeV beta particle (91% abundance), with as much as 90% of its energy penetrating tissues to a depth up to 2 mm from the deposited source, makes it suitable for RIT. When used in the form of Re-186 HEDP for treatment of skeletal metastases in patients with advanced cancer, Maxon et al. (99) noted that the beta particle from Re-186 will penetrate dense bone to an average depth of 0.5 mm, and 1.0 mm in soft tissue. Whole blood half-time is 40.1 $\pm$ 5.9 hours, which implies that additional doses may be administered to patients after a theoretical interval of 200 hours (or when upwards of 96% of the drug has been eliminated after five half-lives) (99). However, there can be observed a decrease in bone marrow function; therefore, determining thrombocyte and leukocyte counts are better parameters for establishing a time interval between repeat doses of the Re-186 than using mere whole blood half-time extrapolations alone. In this fashion, it is estimated that a time interval of about 6-8 weeks will be used for patients on a multiple dosing regimen (depending on the overall clinical condition of the patient) (100). Rhenium-186 is primarily excreted into the urine (69% $\pm$ 15%), and is closely correlated with the bone scan index (BSI), which serves as a good predictor for the amount of Re-186 excreted into the urine. Renal excretion depends not only on the physicochemical properties of the drug, or the physiology of the kidney, but also on the extent to which there is binding to plasma proteins. With

respect to Re-186 HEDP, there is a conspicuous increase with time in the plasma-protein binding, which has been speculated to be due to an *in vivo* decomposition of Re-186 HEDP resulting in compounds having two different plasma-protein binding capacities (99). The limiting factor in Re-186 HEDP therapy is mainly confined to the bone marrow toxicity that can occur. The BSI can play an important role in this, because it predicts the percentage of uptake in the skeleton, from which bone marrow absorbed dose can be estimated (101). Similar observations have been noted in the use of Sr-89 (97) and Sm-153 (102) in treating skeletal metastases in patients with advanced cancer.

Radiolabeled particles or microspheres for RNT do not require high-specific activities of the radionuclides. In these preparations, each particle contains large quantities of the stable isotope(s) precursor of the radionuclide (93). For example, Y-90 labeled microspheres have been used for intraarterial RNT of liver tumors (103), and are easily prepared by doping glass microspheres with stable Y-89, then through (n,γ) irradiation in a reactor activate the trapped Y-89 to Y-90 requiring no further processing (93). Preformed microspheres doped with other nuclides that can be "activated" in a similar fashion include P-32 (from P-31), Sm-153 (from Sm-152), holmium Ho-166 (from Ho-165), Re-186 (from Re-185) and dysprosium Dy-165 (from Dy-164), each of which has been evaluated as intraarterial or intracavitary RNT agents for radiation synovectomy (93). Comparison of the gamma emissions from Ho-166 and Re-186 reveal that the 1.38 MeV γ (0.9% abundance) from Ho-166 yields whole body irradiation the same as that realized from the 0.14 MeV γ (9% abundance) of Re-186, and that Re-186 has been determined to be safe for internal radiotherapy (104). Holmium-166 also emits 0.081 MeV gamma photons (5.4% abundance), which can be imaged with a gamma camera, but is a low enough photon yield to result in limited absorbed radiation dose to surrounding tissue (105). In comparing Y-90 to Ho-166, Mumpers et al. (106) noted that Y-90 delivers a higher absorbed radiation dose (28 mGy/MBq) than Ho-166 (8.7 mGy/MBq), but that other factors such as percent natural abundance, neutron capture cross-section, saturation factor, and the isotopic mass of the element must be taken into account when determining the optimal stable isotope for incorporation into biodegradable PLA (poly L-lactic acid) microspheres (106). It has been determined that the irradiation time needed to impart a therapeutically equivalent dose of Ho-166 is 17.6-fold less than the time needed if Y-90 was being used, but approximately three times the total millicuries of Ho-166 would have to be administered in order to deliver an absorbed radiation dose to the tumor equal to that provided by Y-90 (106). However, Spencer (107,108) has described the advantages of having greater dose rates for therapeutic treatments.

Bisunadan et al. (109) described the role of a Re-186(V)dimercaptosuccinic acid (DMSA) as a possible tumor radiotherapy agent, and noted the relative ease in which Re-186(V)DMSA, a β-emitting analogue of the Tc-99m DMSA tumor imaging agent, is prepared by stannous reduction of Re-186 sodium perrhenate in the presence of DMSA (nearly 100%) using a commercially available DMSA reagent kit.

Auger Electron Emitters

Auger electrons (and Coster-Kronig electrons) arise from radionuclides that undergo electron capture (EC) and internal conversion (IC) as part of their decay process, due to an inward filling of electron transition vacancies beginning with the loss of an inner shell electron. Through such a cascade, x-rays and a flux of Auger electrons are released, with energies ranging from a few to several hundred electron volts (110). Most of the Auger electrons that are emitted are of very short range (<1 μm), and produce high radiotoxicity (independent of oxygen effects), but are only of importance if the source is attached or localized very close to the target DNA (93).

The development of RNT agents based on Auger-emitting radionuclides requires methods of selective guidance to target cells with subsequent introduction and good selectivity into the nucleus (93). It is logical to assume that successful targeting of these agents could result in significantly high therapeutic ratio, however, the range of radionuclides that potentially can be used (each with its own unique chemical properties) provides many intriguing challenges in terms of finding those radionuclides with the necessary biological/localization properties (93).

Radionuclides considered for either RNT or RIT, which decay by electron capture and emit low-energy electrons, include germanium Ge-71, palladium Pd-103, antimony Sb-119, cesium Cs-131, platinum Pt-193m, ruthenium Ru-97, gallium Ga-67, thallium Tl-201, iodine I-125, and mercury Hg-197 (7,93). In the case of I-125, for the Auger component to have any significant biological effect, the radionuclide must be deposited intranuclear rather than intracytoplasmic to the target (111,112). There is some consideration for use of Auger emitters in RIT (7), and many of the radionuclides listed above (Ge-71, Pd-103, Sb-119, Pt-193m, and Hg-197) need to be produced in a cyclotron. An exception is Cs-131 which can be obtained from a barium Ba-131 generator (7).

The radionuclide Pt-193m appears to be a natural candidate for use in RNT, being an emitter of low

energy Auger electrons by virtue of its decay mode, and it can be produced with relatively high specific activity and carrier-free (113). Pt-195m could also be a good candidate, but is available with only a low specific activity. Monte Carlo calculations show that about 25 Auger electrons are to be expected per decay of Pt-193m, and that the mircodosimetry for these electrons indicates that the localized absorbed energy around the decay site is more than that observed for I-125 (114).

Gamma-Photon Emitters

Several radionuclides investigated for use in RNT and RIT emit gamma rays in addition to other particulate emissions. As mentioned, there are advantages and disadvantages in using these radionuclides in RNT or RIT. Yields and photon energies are but one consideration that must be taken into account, for it is possible that gamma emissions will increase the absorbed radiation dose not only to the whole body, but also to normal tissues surrounding intended target site(s). Another potential concern is that the presence of gamma radiation can contribute to increased personnel exposure both during the handling of the radionuclide and following patient administration.

However, assuming that one is faced with a situation where the accompanying gamma-ray emissions from a given radionuclide are of low yields and energy range (i.e., 75-250 keV), then use of this type of radionuclide permits scintigraphic imaging of the patient for purposes of ascertaining the pharmacokinetics, biodistribution properties, and dosimetry of the agent (93). Information of this type would be invaluable during safety and efficacy studies as part of the IND drug development process, not to mention determining site-specific dose-response relationships in individual patients, especially if repeat or fractionated dosing schedules are to be used (93).

Generators and Accelerators

Methods that will yield pure "no carrier added" (NCA) radionuclides for use in RNT and RIT have been developed (93). Several radionuclides that could be used in RNT can be produced only in an accelerator (e.g., As-77, Cu-67, Sc-47, Pt-193m, and Sn-117m). Some of these radionuclides, such as Cu-67 have also been discussed for use in RIT, and bifunctional chelating agents have been developed for its conjugation to monoclonal antibodies. The major drawback to radionuclides requiring accelerator means of production is that there is no facility that can assure reliable or regular availability of the agents.

Few beta-emitting radionuclides are obtained from a "generator" system. Yttrium-90 is available from a Sr-90/Y-90 generator system (93). Rhenium-188, In-115m and Bi-212 are examples of other NCA beta-emitters obtainable from generator systems, i.e., tungsten W-188/Re-188, cadmium Cd-115/In-113m, and [Ra-224/Pb-212]/Bi-212.

CLINICAL STUDIES OF RADIOIMMUNOTHERAPY

In 1991, it was estimated that over 100 clinical trials had been conducted or were ongoing in the diagnosis and/or treatment of human malignancies with radiolabeled monoclonal antibodies (115). The goal in RIT is to deliver a sufficiently large dose of the radiolabeled antibody to the tumor in a reasonable period of time without having a significant effect on surrounding normal tissues and bone marrow. Under ideal conditions, this can be accomplished in several different ways: 1) rapid tumor uptake of the radiolabeled monoclonal antibodies; 2) relatively long effective half-life in the tumor; 3) short effective half-lives in normal organs and whole body; and 4) high tumor-to-normal tissue uptake ratio (116). It has been difficult to satisfy these conditions in clinical situations, resulting in limited success of RIT trials.

Although a number of alpha- and beta-emitting radionuclides exist, a review of current medical literature clearly indicates that only a few radionuclides receive the greatest attention for use in RIT. Included are those with relatively short physical half-lives (less than 10 days) such as I-131, Y-90, Re-186 and At-211 (7,70). If the biological half-life of MAbs in the tumors is much longer than the biological half-life in normal tissues, then the use of radionuclides with physical half-lives of several days may provide distinct advantages in RIT, since this could extend the effective half-life of the radiolabeled MAb in tumors (116). Conversely, if the time needed for maximum tumor uptake is similar to or longer than the physical half-life of the radionuclide, then more disintegrations would likely occur in normal tissue, limiting the amount of activity that could be administered (116). Consequently, when tumor uptake time and biological half-life are relatively long, radionuclides with longer physical half-lives may be more effective in achieving maximum tumor dose with minimal damage to critical tissues both of which are essential for success with RIT (116,117).

The first report of imaging and radioimmunotherapy of human tumors appeared in 1967 and described the use of I-131 labeled anti-fibrinogen in 172 patients (118). In 1979, Ettinger et al. (119) administered I-131 labeled polyclonal antibodies against CEA to a patient with advanced ***cholangiocarcinoma*** of the liver, two months after undergoing a course of fractionated

external radiation, and a concurrent course of chemotherapy. A significant reduction in tumor size was seen by computed tomography, the effects of which lasted eight months following RIT. This same group in 1985 (120) published a substantial report involving the use of I-131 anti-ferritin, following external beam therapy (3 Gy fractions, 4 per week) and induction chemotherapy (one time regimen of 15 mg doxorubicin and 500 mg 5-fluorouracil) in 105 patients with unresectable hepatomas, some with metastases. Results showed that external irradiation induced a partial response in 23% of the smaller tumors, whereas combined therapy induced complete response in 7% and a partial response in a further 41%. Four patients showed signs of complete remission, the longest being 42 months, with the longest partial remission being 68 months. In 1986, Order et al. (121) reported on the use of Y-90 anti-ferritin in six patients with hepatoma who were again treated with combination therapy. Partial remission was noted for two primary tumors and one pulmonary metastasis. All the patients in this study experienced acceptable hematological toxicity following the use of the radiopharmaceutical.

Kemshead et al. (122) reported on the use of RIT in children with advanced ***neuroblastoma***. They claim to have evidence of benefit in one child who showed bone marrow clearing lasting eight months along with radiological healing of skull lesions.

MAb NR-LU-10 is a murine IgG2b that recognizes a 40 kilo-Dalton (kD) glycoprotein antigen expressed by epithelial tumors including carcinomas of the lung, colon, ovary and breast. MAb NR-LU-13 is a murine-human chimeric antibody that has been altered by substituting a human IgG1 constant region for the IgG2b constant region of the murine antibody NR-LU-10. These antibodies have been radiolabeled using Re-186, and administered to patients with metastatic ***adenocarcinoma*** with early indications showing promising results (123,124). Langmuir et al. (125) studied the kinetics of I-125 and Bi-212 labeled NR-LU-10 against LS174T human adenocarcinoma spheroids. They noted encouraging results in the cell kill potential of the I-125 labeled agent, although there was slow penetration of the MAb due to the large number of surface binding sites per cell and high MAb affinity. For the Bi-212 labeled RIT agent, there was very effective killing of single cells (over three log reduction in surviving fraction), but less effective results in spheroids (less than one log reduction). This was likely due to inadequate penetration into the spheroids before the Bi-212 decayed. They postulated that the use of higher antibody concentrations, tumors with fewer antigenic sites per cell for the MAb being used, lower affinity MAbs, alpha-emitters with longer half-lives, and pretargeting with bifunctional MAbs are ways of increasing the efficacy of alpha-emitter labeled MAbs for cancer therapy (125).

Visser et al. (126) have labeled the MAb E4IgG (and its Fab' fragment) with Re-186 and have obtained promising results in RIT of squamous cell carcinoma of the head and neck. MAb E4IgG recognizes a 22 kD surface antigen present only in stratified squamous and transitional epithelium or normal tissue, and reacts with as much as 90% of primary ***head and neck tumors***.

Carrasquillo et al. (127) investigated the use of I-131 anti-p97 and I-131 labeled 48.7 (both ***antimelanoma*** Fab fragments) for RIT and have found that large doses of the radiolabeled MAbs (up to 342 mCi) can be repeatedly given to patients without excessive end-organ toxicity. Similar results have been described by other investigators as well (128).

Iodine-131 labeled intact MAbs have been studied, with encouraging preliminary results, in patients with cutaneous ***T-cell lymphoma*** (129), ***non-Hodgkin's lymphoma*** (130), or neuroblastoma (115). Clinical trials with Y-90 labeled polyclonal and monoclonal antibodies have been completed in patients with hepatoma or lymphoma (131), and in patients with ovarian cancer following intraperitoneal administration (132). Myelosuppression with maximum tolerated doses of approximately 150 mCi of I-131 and 15-30 mCi of Y-90 labeled MAbs has been the principal dose-limiting toxicity for both of these radionuclides. Partial response with variable hematopoietic toxicity was observed in non-Hodgkin's lymphoma patients treated with multiple small dosages of I-131 or Y-90 RIT agent (133). In the same study, single very high doses yielded complete responses with hematologic toxicity requiring reinfusion of stored bone marrow (133). In comparing the efficacy of Re-186 and I-131 labeled NR-LU-10 in multicell spheroids, Langmuir et al. (134) concluded that Re-186 may be superior to I-131 in treating tumors as small as 1 mm diameter (or larger), but that in situations of micrometastases (tumors < 1 mm diameter), that I-131 or radionuclides of similar beta particle energies should be more effective.

Foxwell et al. (135) described a procedure for radiolabeling MAbs with carrier-free P-32, yielding products with appreciable specific radioactivities (up to 10 μCi/μg), which would enhance targeting to tumors with the appropriate receptors. This procedure should reduce the incorporation of metabolized P-32 into normal tissues (especially the bone marrow). The first clinical studies of therapeutic efficacy will probably involve intratumor administration, particularly in CNS tumors where escape of P-32 into the bone marrow (and subsequent myelotoxicity) is likely to be minimal (136).

Zeng et al. (137) report good success in treating

patients with ***hepatocellular carcinoma*** (HCC) by intraarterial administration of I-131 labeled Hepama-1 MAb. They noted a decline in alpha fetoprotein levels and a shrinkage of tumor in 75% (12/16) and 78% (18/23) of patients, respectively. Other investigators have reported similar results, but using either I-131 or I-125 labeled ferritin that was also administered to patients intraarterially (138).

Peptide radiopharmaceuticals for use in RIT, similar to In-111 labeled octreotide but employing a number of different radionuclides, offer much potential in the therapy of a wide range of cancers. Tumors reported to have the highest densities of somatostatin receptors are those of the neuroendocrine type (i.e., pituitary adenomas, endocrine tumors of the pancreas, carcinoids, pheochromocytomas, thyroid medullary cancers, small-cell adenocarcinomas, etc.), certain cerebral tumors (astrocytomas, meningiomas), mammary adenocarcinomas and lymphomas (139,140).

Meredith and Buchsbaum (146) offer an excellent summary of the many RIT clinical trials completed, or currently underway, with respect to human malignancies. When considering RIT for cancer, there remains a need for continued improvement of dosimetry of radionuclides localized in tumors. Current methods assume uniform distribution of the radionuclide, despite the fact that experimental evidence suggests nonuniformity. Dose rate profiles have been calculated for the beta-emitters P-32, Cu-67, Y-90, Ag-111, I-131, Re-188 and the alpha-emitter Pt-193m by Howell et al. (147) for nonuniform activity distributions in solid tumors. In general, high-energy beta-emitters, such as Y-90, are most effective in treating large tumors (diameters greater than 1 cm), whereas for small tumors (diameter about 1 mm), medium-energy beta emitters such as Cu-67 are better suited. Very small tumors (diameter < 1 mm) and micrometastases are best handled with low-energy electron emitters such as Pt-193m.

In addition to the clinical studies described, a number of RIT studies in animals bearing transplants of colon cancer, leukemia, lymphoma, hepatoma, renal cell carcinoma, neuroblastoma, glioma, mammary carcinoma, small cell lung carcinoma, cervical carcinoma, ovarian carcinoma and bladder cancer have been performed with I-131, Y-90, Re-186, Sm-153, and Lu-177 beta-emitting and Bi-212 alpha-emitting radionuclides conjugated to various MAbs with a wide range of outcomes (79,91,141-145).

At best, clinical results in RIT appear similar to those seen with conventional therapy. Regional therapy has been studied less than systemic therapy so, again, its use is hard to judge at the present time. There are a number of barriers that need to be considered which seem to prevent greater results from the use of RIT (and RNT too) in patients. Yet, several interesting alternatives have been proposed which may prove useful in overcoming some of these barriers.

PROBLEMS WITH RIT AND RNT (AND POTENTIAL SOLUTIONS)

Antibody Characteristics

MAbs have a number of characteristics which, either singularly or in combination, can impose biological limitations on their use in RIT. Specificity, affinity, titre, fragmentation, species, and labeling ratios all affect clinical results (149). Whether polyclonal or monoclonal in nature, all antibodies bind to Fc receptor sites in the host rendering them nonspecific. Affinity purification is generally used as a means to improve specificity and titre, but can lead to a loss of the highest affinity MAb. It has generally been assumed that only high affinity MAbs should be used, though experimental data supporting this statement seems to be lacking. Advantages with MAb fragments include absence of the Fc portion and more rapid tumor penetration than that observed for intact MAbs. However, the fragments are excreted into the urine faster which reduces tumor dose. Use of monoclonal antibodies rather than polyclonal antibodies seemed to be the ideal answer to many early investigative problems (i.e., in preparing tumor-specific antigens, there would be no cross-reacting antibodies, and no need for affinity purification). However, mouse immunoglobulins (and antibodies) may interact with human Fc receptors and yield false positive localizations. This can be minimized by the use of mouse antibody fragments to some degree. Currently, interest is focused on the use of mouse (or rat) IgM and IgG antibody classes and IgG1, 2a and 2b subclasses, but each type varies in its stability to purification, labeling and storage, and reactions with human Fc receptors (150). Every MAb molecule should be radiolabeled prior to patient administration, but in an effort to increase the number of atoms added, damage can ensue both at the time of labeling and during storage.

Host Factors

Variables such as blood supply and interstitial pressure within the tumor (or surrounding tissues), MAb size, affinity and avidity, the absence of lymphatics, the presence of circulating antigen, clearance rates, expression of the target antigen, relative tissue radiosensitivity, the likelihood of immune reactions taking place in the host following administration of the radiolabeled MAb, and the route of administration of the radiolabeled agent (i.e., intravenous, intracavitary, intraperitoneal, etc) all must

be taken into consideration (149,151-157). Small tumors receive but a fraction of the cardiac output; therefore, that binding of the radiolabeled MAb, if given by the intravenous route of administration, is slow. Other routes of administration such as intraperitoneal, intrapleural, intrathecal, etc., theoretically allow the radiolabeled MAb to bind to antigen in a nonvascular route with high antigenic concentration and slow clearance. From another perspective, immunoglobulin diffusion out of the intravascular compartment can be slow (estimated at 50% in approximately 18 hours), thus a majority of the MAb may never gain access to the tumor and will be catabolized elsewhere within the body. The presence of circulating antigen may limit access of radiolabeled MAbs to receptor sites or may, in fact, only serve as a temporary barrier wherein the MAb will eventually bind to the site of greatest antigen concentration (i.e., the tumor), provided the element of time does not prove to be a negative variable (as would be expected in situation of rapid MAb clearance from the body). Antigen expression by tumors is often heterogeneous; in fact, the pattern of antigen expression of a metastatic lesion may differ from that of the primary tumor. Allergic reactions as a result of complex activation of complement is sometimes reported. Additionally, development of high levels of HAMA or HAHA can prevent continued treatment by radiolabeled MAbs as interaction here leads to accelerated clearance of the agent resulting in reduced efficacy.

Radionuclide Limitations

There are no ideal radionuclides for RNT and RIT. Choice of radionuclide appears to be a compromise between variables such as the physical half-life, biological half-life, radioactive emission(s) in terms of range and quality, dose-rate delivered, ease of production, cost and availability (149,158). Radionuclides with physical half-lives that are relatively short (i.e., hours or less) will decay before an appreciable amount of their energy can be deposited in tumor. On the other hand, radionuclides with physical half-lives of months or longer may deliver dose rates that overall are too low for effective therapy. Many factors can affect the biological half-life of the therapeutic agent, such as the biochemistry of the MAb and the chemistry of the radionuclide. Once the radionuclide is released following catabolism of the MAb, its chemistry will then determine its fate within the body (i.e., rate of excretion dependent on secondary binding to other molecules). Alpha-emitting radionuclides are highly toxic to living cells showing cumulative effects over short ranges, but they are difficult to produce in a desired chemical form and very few seem suitable for use in RNT and RIT. Beta emissions from various radionuclides are essentially the same "biologically" as fast electrons produced from external x-rays or gamma rays. The energy of emission(s) determines penetration into tumors, and depending on the size of the tumor, may be an advantage or a disadvantage (with high energy emissions, insufficient energy would be deposited in micrometastases). Dose rates need to be many times greater than that presently achieved. As the dose rates decrease, so does the extent of cell kill, which means some cells have a better chance to repair sub-lethal damage. The clinical choice of radionuclide not only encompasses the basic concerns of chemistry, production, cost, etc., but also the potential for myelosuppression and other related toxicity associated with their use in patients.

One of the most commonly used radionuclides in RNT and RIT is I-131, which is far from ideal since two-thirds of its absorbed dose equivalent is penetrating gamma radiation, and the mean path of its beta emission is about 800 μm. Therefore, when the RNT or RIT agent successfully targets the tumor cell, a majority of the energy released by radioactive decay is absorbed not by the tumor cell, but by surrounding tissues. For large tumor masses, this may not be a significant problem, but in situations of micrometastases, untargeted cells will be irradiated as a result of cross-fire from adjacent cells that are targeted for therapy.

MAbs labeled with alpha-emitting radionuclides show promise as effective therapeutic agents due to the efficient cell killing ability of high ionizing radiation relative to short-range alpha particle tracks localized at specific antigen sites within the tumor mass. Conventional methods for estimating absorbed doses and specific absorbed fractions for radiopharmaceuticals do not apply to alpha-emitters because of their short range and large variations in the local distribution of energy at the cellular level (148). This creates difficulties in estimating absorbed radiation dose to tumor and normal tissue with alpha-emitting radionuclides.

Overcoming Barriers to Therapy

To improve tumor uptake, small immune molecules (i.e., Fab'2 or Fab fragments) and single chain antigen binding molecules have been used (159). Buchsbaum et al. (160) reported that predosing the patient with unlabeled MAb before the radiolabeled form is given resulted in some improvement in the tumor/whole body ratio. Other types of pretargeting strategies have been proposed (158). A number of radiosensitizer and radioprotective agents have been identified and represent another way to increase efficacy of radiolabeled antibodies (161,162), but there is not

widespread clinical use of these agents in RIT at the present time. The use of external beam radiotherapy prior to the start of RIT appears to enhance tumor uptake due to an increase in vascular permeability (163). Selected vasoactive substances (i.e., interleukin-2) (164), and the use of techniques such as hyperthermia (165) have also been shown to have a positive effect on enhancing RIT outcomes. Schlom et al. (156) discussed the advantages of preparing high-affinity MAbs as a means of improving delivery of the therapy agent to tumor. The use of "cocktails" of MAbs that are reactive with different tumor-associated antigens, appears promising in overcoming the problems associated with tumor heterogeneity and the likelihood that saturation of a particular antigen on a tumor (when others exist) could occur (166,167). Epstein et al. (168) have developed a series of MAbs which target antigens thought to be accessible in dead or dying malignant cells in order to deliver radionuclides to necrotic and ischemic regions of tumors. This approach is based on the fact that degenerating cells found throughout the tumor are abnormally permeable to extracellular molecules (169). Reducing the heterogeneity of uptake within the tumor makes the use of low- and moderate-energy beta-emitters more favorable in large tumors, as well as the small tumors to which they already appear best suited. Increasing the expression of tumor-associated antigen on target cells has been given some attention as a means to improve general issues involving tumor targeting. This may be possible through the use of interferon in selected situations (170,171).

The principal dose-limiting toxicity associated with RIT (and RNT) is hematopoietic suppression. One of the earliest approaches to overcome this limitation was the use of bone marrow transplantation, which has allowed for some escalation in the size of the radionuclide dose administered to patients. Fractionation of the radiation dose by dividing the total amount of radiolabeled MAb into several doses, in order to allow for normal tissue recovery between dosings, follows established radiobiologic principles that have been used for many years in conventional forms of radiotherapy (172). When applied to RIT, this has resulted in a modest reduction of hematologic toxicity, but has not permitted radionuclide dose escalation to any appreciable degree (173-175). The adjuvant use of cytokines (interleukin-1 and colony stimulating factors such as GCSF and GMCSF that stimulate the granulocyte series) appears promising in that some escalation of the radionuclide dose can occur beyond the point of what would be allowable if the cytokine agent was not used (176-178). However, bone marrow suppression remains the principal dose limiting toxicity. The use of a two-step "second antibody" or binding protein (avidin, streptavidin, biotin) approach is simple, and has been shown to reduce radiation dose to critical normal tissues (179). The second MAb can be used to complex and remove the therapeutic agent from the circulation so that subsequent radiation dose to normal tissues is reduced without substantially reducing the radiation dose to the tumor that has specifically bound the therapeutic agent (180-184). Recently, even a three-step approach has been proposed (185).

Several approaches have been attempted in an effort to minimize (or eliminate) the problem of HAMA development (and perhaps HAHA too) against the radiolabeled MAb. In general, approaches under investigation involve genetic engineering ("humanizing" MAbs) and the use of MAb fragments (Fab, Fab'2, single-chain, single-domain or even engineered proteins on a MAb template) to render them less immunogenic (186-192). Removal of the HAMA once it is formed is also under consideration. This may be achieved by procedures known as immunoabsorption and plasmapheresis (158). Various immunosuppressive techniques aimed at preventing HAMA production are also under investigation. The use of immunosuppressive agents such as cyclosporine, cyclophosphamide, or deoxysperqualin has been shown to reduce a HAMA response (193,194), but caution must be emphasized in that these immunomodulatory agents can also lead to renal and gastrointestinal toxicity.

Route of administration has been considered not only in terms of increasing uptake into tumors, but also as a means (in some cases) to reduce potential toxicity associated with RIT. Various approaches to "regional therapy" rather than systemic therapy (as would be achieved from traditional intravenous administration) can be gained by use of intraarterial, intracavitary, intrathecal, etc., administration. Coakham et al. (195) and Epenetos et al. (196) have reported good outcomes when more focused means of delivery of the radiolabeled MAb was given to patients with malignant meningitis and stage IV brain gliomas, respectively.

FUTURE PERSPECTIVES AND CONCLUSION

MAbs linked to radionuclides, drugs, toxins, enzymes, growth factors, and effector MAbs offer a promising approach to the treatment of solid tumors. For any given MAb, the residence time in the blood determines the supply to the tumor and the radiation dose to the critical organ. Since the therapeutic outcome depends on the ratio of tumor-to-normal critical tissue irradiation (therapeutic ratio), and since the tumor uptake is, at best, only 3% of the injected dose (with the remainder irradiating the whole body

while waiting to be cleared rapidly), improvements in RIT (or RNT) will not likely be seen until there is a significant increase in the therapeutic ratio (1). Dose escalation may be achieved by concurrent administration of bone-marrow rescuing cytokines and/or bone marrow transplantation.

It is anticipated that the use of RIT with modifications and in combination with other treatment modalities may be substantially more effective as, for example, is combination vs single agent chemotherapy. Conventional cytoxic drugs such as doxorubicin, bleomycin, methotrexate, chlorambucil, cisplatin, cytosine arabinoside, vinca alkaloids, and mitomycin C, have been conjugated to tumor-seeking MAbs in the hope that selective tumor therapy can be achieved (197). By way of spacer molecules, such as albumin or various dextrans, increases in "cell-kill" potential up to 10-fold have been observed over what could be realized if direct conjugation approaches were employed (198).

Several physical (e.g., radiation, heat) and chemical (e.g, vasoactive drugs) agents may play a useful role in terms of increasing tumor blood flow (152). However, a problem with this approach is that the increase in blood flow is short-lived, and usually confined to areas that are well vascularized.

The use of cocktails of MAbs may not be a viable option, even though it is true that MAb fragments will penetrate tumors better than intact MAbs. The fact remains the MAb fragments are eliminated from the blood/body quite rapidly and their uptake into normal tissue is increased. This elimination problem may be overcome by the use of repeated or continuous injections of high doses of nonimmunogenic fragments of chimeric or human MAbs (198). Some of the toxicity problems associated with therapy may be overcome by employing the use of regional therapy utilizing alternate routes of patient administrations (e.g., intraarterial, interstitial, etc.). Finally, increasing the number of antigenic sites using biologic response modifiers (e.g., interferon) would serve to increase the accumulation of the MAb near the blood vessels, but would not necessarily increase the depth of tumor penetration (198). Hematologic toxicity might be decreased by removal of circulating, non-tumor localized antibody via immunoadsorption, or administration of an "anti-antibody" to increase serum clearance of non-localized MAb (158,180,187). Protecting bone marrow using growth factors (e.g., interleukin 1, interleukin-3, GMCSF, GCSF)) may also alleviate the normal tissue toxicity problem. This and other approaches involving the use of radiosensitizers and radioprotectants may prove beneficial if dosing to the patient can be timed/synchronized with a particular tumor cell cycle (dependent, too, on the type of tumor) (198).

Genetic engineering, as shown by Reichmann et al. (192) and Winter and Milstein (199), will permit the development of designer molecules that would serve as antibody-like constructs enabling the incorporation of sequences to augment binding with the tumor and enhance RIT outcomes. Such approaches may involve sequences that appear as molecular recognition units (MRU's), or single domain or single-chain antibodies, as well as those that permit recognition of the RIT ligand carrier in either a two- or three-stage "anti-antibody" rescue approach.

This review has attempted to provide a window on the history, current clinical status, and future considerations for the use of alpha- and beta-emitting radionuclides in either RNT or RIT of patients with cancer. Even though radiolabeled monoclonal antibodies have been used in RIT for over a decade, they have yet to achieve a standard role in therapy. Investigators may still be looking for that "magic bullet" that will achieve the desired "kill" of cancer in patients. Clearly, some of the avenues being presently investigated hold much promise, and perhaps someday that "magic bullet" will transform itself into a "guided missile."

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QUESTIONS

1. Which of the following statements is <u>not</u> true concerning the utility of various treatment approaches to patients with cancer?

   a. Surgery remains one of the most effective forms of therapy for cancer.

   b. External beam radiotherapy utilizes anatomical planning employing dosimetry based organ-specific formulas.

   c. Chemotherapy lacks selectivity in terms of outcome.

   d. Radionuclide therapy depends more on the anatomical distribution of the tumor, and less on the physiological and pathological aspects of the tissue(s) involved.

2. Which of the following are <u>not</u> important considerations when selecting the type of radionuclide to be linked to an immunospecific antibody for use in radioimmunotherapy?

   a. type of radiation emission(s)

   b. tumor dose rate

   c. range of the radioactive emission(s) in tissue

   d. atomic mass

3. Which of the following statements is true concerning path length of radioactive emissions?

   a. radionuclides with a long particle path length have a more effective cell-kill in homogenous tumors

   b. radionuclides with a long particle path length displays minimal crossfire effects

   c. radionuclides with a short particle path length have a more effective cell-kill in tumors with heterogenous antibody distribution

   d. radionuclides with a short particle path length exhibit a decreased radiation dose effect in normal tissue

4. Which of the following statements is <u>not</u> true with respect to a model for using unsealed radionuclide sources in cancer therapy?

   a. There must be confirmation of in vivo tumor uptake with the intended therapy agent.

   b. Prescription and over-the-counter medications need not be discontinued prior too and during therapy.

   c. The cycle of diagnosis and therapy can take extended periods of time depending on the degree of dose retained

   d. There must be is a rapid excretion pathway for that portion of the therapeutic dose not taken up by the tumor.

5. Which of the following is not a true statement concerning the use of gold Au-198 colloid in the treatment of chronic synovitis?

a. There are gamma photon emissions that contribute only to local synovial irradiation

b. Radiopharmaceutical leakage can occur resulting in deposition in regional lymph nodes via the lymphatics

c. Irradiation of the testes can occur

d. Deposition of the radiopharmaceutical can occur in the inguinal nodes

6. Which of the following radiopharmaceuticals has not been used for treatment of central nervous system tumors?

a. Y-90 DTPA

b. Au-198 colloid

c. Er-169 citrate

d. Re-188 perrhenate

7. Which of the following radiopharmaceuticals has not been used for the treatment of malignant melanoma?

a. Y-90 microspheres

b. S-35 sulfate

c. P-32 chromic phosphate

d. I-131 Ethiodol

8. Which of the following is not an important consideration when determining which radionuclide to use in conjunction with the radiolabeling of monoclonal antibodies?

a. ratio of penetrating to non-penetrating radiations

b. mode of production and availability

c. neutron cross section

d. type of decay products

9. Which of the following statements about alpha-particle radionuclides is true?

a. Alpha emitters are high-energy helium nuclei that produce low densities of ionization along the path they travel

b. An alpha particle with an energy of 5 MeV can travel a path length of 200 um

c. The effective treatment radius of an alpha emitter averages several centimeters from the atom that emits the particle

d. The high LET of alpha radiation limits the ability of cells to repair DNA damage

10. Which of the following is a beta emitter that decays to an alpha emitter for use in radionuclide therapy or radioimmunotherapy?

a. Bi-212

b. At-211

c. Pb-212

d. Fm-255

11. Which of the following radionuclides does not have a high neutron capture cross-section?

a. Sm-158

b. Gd-155

c. Am-242

d. Cd-113

12. Which of the following statements about beta particle-emitting radionuclides used in radionuclide therapy is not true?

a. Beta-emitting radionuclides commonly come from nuclear reactors employing a direct (n, γ) reaction

b. Low-range beta-emitting radionuclides have a mean penetration range in tissue of 2 mm

c. Emission of internal conversion electrons after beta-decay contributes to the local energy deposited in tissue

d. Beta-emitting radionuclides produced by an indirect (n,γ) reaction often have high specific activities

13. Which of the following is considered to be an intermediate range beta-emitting radionuclide?

a. P-33

b. Re-188

c. I-131

d. P-32

14. Which of the following has not been used in the treatment of bone cancer in patients?

a. P-32

b. Sr-89

c. Sm-153

d. Sn-121

15. Which of the following radionuclides is not used for radiation synovectomy (employing the use of preformed microspheres doped with a radionuclide that is "activated")?

a. Ho-166 (from Ho-165)

b. Ac-225 (from Th-229)

c. Re-186 (from Re-185)

d. Dy-165 (from Dy-164)

16. Which of the following statements is not true relative to Auger electron-emitting radionuclides?

a. Auger electrons arise from radionuclides that undergo electron capture and internal conversion as part of their decay process.

b. Associated energies with the release of Auger electrons can range from a few to several hundred electron volts.

c. Auger electrons are commonly emitted having a range of over 1 mm in tissue.

d. Auger electrons can produce high radiotoxicity independent of any oxygen effects when localized close to the target DNA.

17. Which of the following is not an Auger electron-emitting radionuclide?

a. Ga-67

b. Cs-131

c. Pd-103

d. Re-186

18. Which of the following radionuclides is not typically produced by an accelerator?

a. Bi-212

b. Cu-67

c. Pt-193m

d. Sn-117m

19. The monoclonal antibody NR-LU-10 has been used to study tumors involving all of the following organs except

a. lung

b. colon

c. breast

d. bone

20. Which of the following have not been reported to possess a high density of somatostatin receptors?

a. astrocytomas

b. prostate tumor

c. lymphomas

d. thyroid medullary carcinomas

21. Which of the following antibody characteristics can affect the clinical outcome when using radiolabeled monoclonal antibodies?

a. titre

b. fragmentation

c. specificity

d. all of the above

22. Which of the following host factors has an affect on the manner of radiolabeled monoclonal antibody distribution in patients?

a. blood supply and interstitial pressure within the tumor and/or surrounding tissues

b. relative tissue radiosenstivity

c. route of administration

d. all of the above

23. Which of the following statements is true concerning dose rates of radiolabeled monoclonal antibodies in achieving desired outcomes in radioimmunotherapy?

a. Dose rates need to be many times greater than those presently achievable in order to reach desired goals in radioimmunotherapy.

b. Energy associated with radionuclide emission(s) has no bearing on the extent of penetration into tumors.

c. Decreases in dose rate can occur yet overall cell-kill potential can be maintained.

d. Beta emissions from various radionuclides are inferior "biologically" when compared to fast electrons produced from external x-rays or gamma rays.

24. Which of the following is <u>not</u> a techniques that has been discussed for overcoming the problem of hematopoietic suppression associated with radionuclide therapy or radioimmunotherapy?

a. The use of "cocktails" of different monoclonal antibodies.

b. bone marrow transplantation

c. fractionation of administered dose(s)

d. adjuvant use of cytokines

25. Which of the following is a technique that has been discussed for overcoming the problem associated with HAMA in the use of radiolabeled monoclonal antibodies?

a. use of monoclonal antibody fragments

b. use of plasmapheresis

c. use of immunosuppressive drugs

d. all of the above