Clinical Trial Design and Scoring of Radionuclide Therapy Endpoints: Normal Organ Toxicity and Tumor Response

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Like other cancer therapy agents under development, radionuclide therapies are usually evaluated in a progressive series of clinical trials after basic science, human cell culture and animal model studies. Toxicities during these trials are graded using common scoring systems that are in widespread use such as the Common Toxicity Criteria from the National Cancer Institute. Information on normal tissue toxicity from radionuclides is more limited than that from external beam radiation and is more variable. Variability is likely due to many biologic factors as well as less precise dose quantitation than those used in external beam radiation practice. As expected based on known radiobiologic effects, tolerance to radionuclide therapy appears to exceed that from high dose rate external beam radiation in most organs. Although the correlation between reported dose estimates and toxicity has progressively and substantially improved over the past two decades, further progress is needed to establish optimal toxicity predictive relationships. Continued refinement of dosimetry techniques and standardization is expected to increase the accuracy and comparability of radiation dose reports between institutions as well as improve dose/response correlation.

INTRODUCTION

Although the major utilization of radionuclides in medicine has been for diagnostic purposes, there has been increasing interest in therapeutic applications for malignancy in the past two decades. The hope that targeted delivery of radionuclides to tumor sites via conjugation of radionuclides to an antibody or other molecules that specifically attach to tumor cells will allow effective, well-tolerated systemic therapy has resulted in the development and testing of multiple agents. Fewer studies have been reported on normal tissue tolerance and anti-tumor efficacy of radionuclide therapy than from external beam radiation. Prior studies have considered a number of radiobiologic factors in the comparison of effects from radionuclides versus external beam radiation.1,2,3,4,5,6 The following review describes: 1. the usual toxicity and efficacy scoring systems used in clinical trials of radionuclide agents, 2. comparison of normal tissue tolerance reported for radionuclides versus that established for external beam radiation, 3. considerations on the accuracy and comparability of radionuclide dose estimates between studies, and 4. examples of anti-tumor efficacy reports.

Toxicity Scoring

The limitation of radionuclide therapy as given for most malignant diseases is the tolerance of non-targeted normal tissues. As experience grows, more information about the tolerance of the various normal tissues for radionuclide therapy is accumulated to direct future administrations and clinical trial design. The toxicities of normal tissue are tracked acutely as well as long

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term after radionuclides in the development of radionuclide therapies. This is similar to that of other therapeutic agents but the spectrum of normal tissues at risk may vary. Standard toxicity scoring systems are used in the design of clinical trials. Frequently used scoring tabulations include the Common Toxicity Criteria serving in National Cancer Institute supported clinical trials and a related system associated with the World Health Organization. Guidelines for Common Toxicity Criteria recommended by the National Cancer Institute can be downloaded from the Internet at http://ctep.info.nih.gov. These criteria use a grading system from 0 to 4.

Grade 0 = no clinically significant toxicity. For toxicities tracked by laboratory values this usually means the result has not fallen out of the normal range even though there may have been some change from baseline that is due to the treatment. For instance, if a patient had a baseline platelet count of 300,000/µl that fell to 150,000/µl after treatment this represents a 50% decline but is still within the normal range and is Grade 0. Grade 1 = mild toxicity, Grade 2 = moderate toxicity, Grade 3 = severe toxicity, Grade four = potentially life threatening toxicity. In some systems, a Grade 5 is used to indicate a fatal complication. This basic grading from 0–4 can be used to score an observed toxicity that is not listed in the Common Toxicity Criteria tables. The criteria for grading toxicity may vary with different clinical circumstances. For example, in a non-stem cell rescue regimen where hematologic toxicity may be the dose-limiting toxicity, a Grade 1 platelet toxicity = 75,000/µl normal, with normal in most laboratories being ≥150,000/µl. In the stem cell rescue criteria, Grade 1 platelet toxicity is defined as 1 platelet transfusion in 24 hours. In this circumstance, the number of platelets is expected to be in the range of Grade 4 for a non-stem cell rescue set of criteria. Some scales such as the Radiation Therapy Oncology Group use different criteria for acute (which may be defined as ≤ 90 days after treatment) versus those for late toxicity. As an example of acute versus late toxicity, hematuria and/or dysuria within days after radionuclide administration would be an acute urinary system toxicity whereas fibrosis leading to bladder contraction 9 months later would be considered a type late toxicity.7 There are a number of other indicators of toxicity that can be monitored but are not reflected in the grading such as the time to the development of moderate to severe toxicity, the duration of severe toxicity and the effect of toxicity on other factors such as performance status. As an example, Figure 1 compares post-treatment depression in platelet counts among three patients receiving increasing administered activity of $^{177}$Lu-CC49. Typical for radionuclide therapy, the highest $^{177}$Lu-CC49 activity resulted in a lower nadir, a greater percent decrease from baseline at nadir and longer recovery than that for the lower doses.

Many studies now incorporate quality of life (QOL) indicators as an integral part of the clinical trial design. A patient’s sense of well-being stems from their satisfaction with aspects that are important to them. Some of these QOL assessment instruments incorporate a pain scale or use a pain scale in addition to other quality of life questions such as fatigue level, mood, and activity level.8 A placebo controlled study of strontium-89 showed improved QOL for several categories among patients who received the active agent compared to those who received the placebo.9 These QOL categories included such items as pain, use of analgesics, constipation, mood, fatigue, and measures of performance status such as physical activity. Some studies now look at quality adjusted time also. For example, if a particular agent when given one day a month prolongs survival by 6 months but with each administration the patient has 3 days of severe pain and vomiting, the days of decreased quality of life are taken into account when assessing the survival benefit. An example of an agent that was approved for the treatment of pancreas cancer due to improved symptom relief, rather than improved tumor regression or longer survival compared to other therapies, is the chemotherapeutic Gemcitabine.10

Clinical Trial Design

New agents being developed for therapy are usually evaluated in a progressive series of study designs. The FDA regulates biomedical research and requires that standards for the design, conduct, monitoring, recording, and reporting are followed. These standards assure that the results reported are accurate, and that the safety and rights of human trial participants is protected.11 Department of Health and Human Services regulations for the protection of human research trial participants is subject to periodic amendment. Vriesendorp et al.12 have suggested that altered
sequential study phases for radioimmunotherapy agents may be preferable to classical phase I and II studies used to evaluate chemotherapeutics. After therapeutic potential of an agent is identified by basic science, as well as often human cell culture and animal model studies, the first clinical trial (Phase I) is designed to determine safety and what toxicities are associated with its use. Phase I studies often establish pharmacologic characteristics in parallel with other biologic studies. A Phase I clinical trial is often designed to determine the maximum tolerated dose, or some other measure of optimum dose if this is less than the maximum dose tolerated. The definition of maximum tolerated dose (MTD) varies but usually is the dose that results in moderate to severe toxicity in the majority of a cohort of at least 5 patients. Grade 4 toxicity may be observed in the cohort but will not be present in the majority of the patients. Although there are commonly used definitions of MTD, the definition in any given study will be defined in that study and may or may not be identical to that in similar studies. There are several options for dose escalation of radionuclide therapies. These include a fixed increase per dose group. In this case a 20–25% increase is usual, at least when the study is in the dose range that results in significant toxicity.

Options for dose escalation based on some patient specific variables are common. This may use administered activity per m² of body surface area, per kilogram of body weight, area under the curve of plasma pharmacokinetics, or to deliver a defined radiation dose to normal organs or the whole body. Some examples are presented in Table 1.

Although therapeutic efficacy is often monitored in a phase I study, a low response rate does not halt further investigation of the agent since most patients may have received a smaller dose than needed for efficacy.

Phase II studies have the goal of determining the response rate at a dose that would be tolerable by most patients. The dose in a phase II trial is often not the full maximum tolerated dose that was established in the phase I trial but reduced by a modest amount such as 80% of the MTD or the next lower dose from the MTD. Phase II oncology trials usually not only look at the objective response rate but also the duration of response, progression free survival and overall survival after therapy. These trials are often set up on a two-stage design such that if no responses are achieved among the initial 14 patients, the trial will be terminated because the probability of a response rate of 20% or greater is less than 0.05. If there are several responses among the initial patients, the number of patients required to determine that the response rate is at least 20% is smaller than initially planned and can be estimated from the fraction of those responding, i.e., the number of patients accrued in the second stage depends on the number of responses observed in the first stage and the desired standard error. If there is at least one response among the first 14 patients, the trial may proceed to accrue 25 patients to provide an estimate of the response rate. Patients entering Phase I and II trials usually have failed standard therapies or have prognosis/circumstances such that standard or alternative therapies are judged not to have substantial impact on their disease outcome. Although pa-

Figure 1. Comparison of depression and recovery of platelet counts as a function of time after escalating doses of 177Lu-CC49.
patients participating in these trials have failed other therapies, the number and type of previous therapies may be restricted by trial design. In addition, patients are usually required to have a high performance status to be eligible for participation.

A Phase III trial is a definitive study. This often adds the new agent to standard care or compares it directly with the current standard in order to determine if the new agent is superior in efficacy or has other advantages such as decreased toxicity for equivalent therapeutic benefit. Some examples of definitive radionuclide studies are presented in Table 2. These include the addition of strontium–89 as an adjunct to external beam radiation for painful bone metastasis compared to similar administration of a placebo. With positive reports of radiolabeled antibodies for B-cell non-Hodgkin’s lymphoma (NHL), definitive studies have been conducted comparing the radiolabeled antibody with unlabeled antibody alone, or comparing the response rate, duration of response and other factors with the history of each patient’s course after their past chemotherapy.  

Although not reported to be a Phase III design, the addition of $^{89}$SrCl was also studied in patients with advanced androgen-independent prostate cancer receiving chemotherapy. Those randomized to receive $^{89}$Sr-Cl in addition to their doxorubicin chemotherapy had improved survival compared to those receiving chemotherapy only.16

Response Evaluation

Many early studies such as Phase I trials often

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monitor for anti-tumor effects even though their main objective is not determination of tumor response rates. For Phase II and III studies objective criteria for response are needed. Although each study defines its criteria for response, there are standardly accepted criteria used in most studies.17 Bidimensional measures of masses with sharply defined borders are desirable for assessing response, but lesions that can only be measured in single dimension can be evaluated also. Measurements of bidimensional lesions are usually recorded as the product of the longest diameter multiplied by the greatest perpendicular diameter as determined by physical examination and/or imaging studies. Non-measurable disease, which includes malignant disease found to be surgically unresectable but not clinically detectable, usually cannot be assessed by objective measurement criteria but response may be assessable by biochemical markers. Patients who have non-measurable disease may be evaluated in Phase I studies for toxicity and can be followed for time to progression and survival as indicators of antitumor effects but they are usually not candidates for Phase II trials where objective measurements are needed. The following represent objective response definitions commonly used.

**Complete response** = disappearance of all clinical evidence of active tumor (objectively measurable and non-measurable tumor sites) for a minimum of 4 weeks. The patient must be free of any symptoms related to cancer.

**Partial response** = fifty percent or greater decrease in the sum of the products of the perpendicular diameters of all objectively measurable lesions, >30% decrease in linear measurement of unidimensional lesions and stable status or improvement in all non-measurable tumor sites. When patients have multiple lesions, 3 or more target lesions may be measured for response. However, there can be no simultaneous increase in the size of any lesion or the appearance of new lesions. The remission must be maintained for at least 4 weeks.

**Stable disease** = steady state or response less than partial remission, or progression of less than 25% for a minimum of 4 weeks. There may be no appearance of new lesions and no worsening of the symptoms.

**Progression** = an increase of at least 25% in the size of any measured lesions or the appearance of new lesion(s).

Duration of response, time to need for more therapy, and QOL improvement are also indicators of therapeutic effects.

**What is the tolerance of normal organs to radiation?**

A number of human cell culture and animal model studies have been designed to determine differences between radiation effects from radionuclide therapy and external beam radiation.1-6,18 Several studies directly comparing the efficacy of radionuclides, or similar exponentially decreasing low dose rate radiation, with high dose rate external beam radiation have shown variable results. As expected based on a low dose rate effect and other radiobiologic factors,1-6,19 many organs appear to have more tolerance for radionuclides than external beam radiation. In the dose rate range between ~0.1 Gy/
hour to several Gy/minute, the lethal effects of radiation on cells diminishes with dose rate and the rate of this decrease is determined by the size of the shoulder on the radiation survival curve. An inverse dose rate effect is also possible when the radiation results in a block at G2, a portion of the cell cycle characterized by increased radiation sensitivity. Other factors to consider in the comparison of radiobiologic effects from external beam radiation include the overall treatment time, reoxygenation during radiation, cell proliferation during the radiation course, and non-uniform distribution of radionuclide that could be more damaging by concentration at vasculature.

Mechanisms explaining some of these differences in radiation sensitivity for radionuclides and external beam radiation among tumor lines (in addition to G2 block effects) include tumor doubling time, the size of the shoulder of the survival curve, and the induction of apoptosis versus classical radiation induced cellular necrosis.

To date, direct comparison of the effects on normal organs between external beam radiation and radionuclide therapy in clinical trials have not been reported. Thus, comparisons are based on toxicities reported separately for each type of radiation and may also be influenced by the fact that the patient groups studied differ. Considerable external beam normal organ tolerance data have been compiled from analysis of literature that deals mainly with irradiation using $\geq 1$ MEV energy treatment of the whole organ, in adults not receiving chemotherapy, and at 2 Gy/fraction, one fraction per day, 5 days/week. The total time of treatment is $\leq 8$ weeks. For this data, the dose rate is considered high, with the usual dose rate $> 100$ cGy/minute. The radiation tolerance doses tabulated are categorized as TD$_{5/5}$ or TD$_{50/5}$. The TD$_{5/5}$ indicates a 5% risk of severe complications by 5 years and a TD$_{50/5}$ indicates a 50% probability of severe complications by 5 years. Since the dose/response curve for normal tissues is steep, the TD$_{50/5}$ is sometimes reached with $< 20%$ dose increment above the TD$_{5/5}$. Additional information has shown that higher doses are tolerated for partial, as opposed to the whole organ, radiation. However, for comparison only whole organ tolerance doses are presented in Table 4. Although partial organ tolerance for radionuclides has not been frequently considered, Bouchet et al. have recently provided dosimetry models for sub-regions of the kidney and MIRD pamphlet #17 addresses dosimetry of non-uniform activity distribution. Yorke et al. analyzed dose volume histograms for human liver after $^{90}$Y-microsphere therapy. Their results were consistent with increased tolerance when much of the organ receives less than the mean calculated dose. In practice, radionuclides administered directly into tumor masses or resection cavities, which provides a high dose to a small rim of surrounding normal tissue, have been well tolerated.

A device for infusional radionuclide, Gliasite from Proxima Therapeutics, Inc., has been developed to facilitate treatment of brain lesions while minimizing radiation dose to normal tissues. There is usually less tolerance for single dose compared to fractionated radiation. 1000 cGy + chemotherapy has been tolerated by normal organs as a preparative regimen for bone marrow transplantation. However, without dose reduction or fractionation the risk of pneumonitis is >25%. Also, most tissues are less tolerant when therapy is combined with other modalities such as nephrotoxicity at 12–14 Gy fractionated external beam radiation to kidneys in bone marrow transplant patients who also received busulphan.

Tissues for which no definite tolerance is listed in Table 4 such as meninges and bowel serosa are felt to have a higher tolerance than the adjacent more radiosensitive tissues such as bowel mucosa and brain. Column 3 of Table 4 lists some doses calculated from radionuclide therapies for which no significant toxicity was reported, while column 4 provides some doses associated with toxicity. The radiation toxicity for radionuclides includes both acute and late toxicity whereas that for external beam data included here applies to late effects. While some tolerance doses for external beam radiation were established from a large patient experience, the data listed for radionuclides is derived from a relatively small number of patients. Also, column 4 lists any toxicity reported even if it affects only a small fraction of the patients in a particular study. For instance, renal toxicity is reported for $^{90}$Y-DOTA-biotin after pretargeted NR-LU-10/SA but this only affected two patients while other patients treated with the same or other radionuclide agents were reported to receive much higher doses without toxicity manifestations. The tolerance for an individual patient to radionuclide therapy may be considerably higher or lower than reported. A number of factors have been identified that may influence tol-
erance. Thus, it should not be surprising that there are some apparent contradictions between the values in column 3 and column 4 in Table 4. These apparent discrepancies may reflect a number of factors including differences in calculated vs. biologic dose, dose rate effects, other modifying factors, different calculation methods or variation due to the characteristics of the radionuclide agent.\textsuperscript{35} Compared to data from external beam, which was primary treatment, or after surgery, radionuclide tolerance data (with the exception of thyroid) has been derived from patients who have failed chemotherapy and/or have widespread disease. Much of the radionuclide data is for a single administration, which would be expected to have a lower tolerance than re-
peated dosing at non-maximum levels for a cumulated higher dose. For instance, a cumulative renal dose of 33 Gy was tolerated for \textsuperscript{90}Y-DOTA-TYR-Octreotide given as repeat therapies every 6 weeks plus intravenously administered amino acids compared to toxicity noted in some patients at lower doses after a single administration of radio-
nucleotide therapy.\textsuperscript{37}

### Table 4. Normal organ tolerance to radiation (cGy)**

<table>
<thead>
<tr>
<th>Organ</th>
<th>External beam (TD5/5, TD 90/5)</th>
<th>Radionuclide-no toxicity</th>
<th>Radionuclide- + toxicity</th>
<th>Comment / (Reference)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marrow</td>
<td>250 450</td>
<td>6, \textsuperscript{177}Lu</td>
<td>≥ 7 \textsuperscript{177}Lu MTD &lt; 185cGy for \textsuperscript{131}I-CC49</td>
<td>\textsuperscript{83} non-marrow targeting therapy \textsuperscript{84}</td>
</tr>
<tr>
<td>Lungs</td>
<td>1500 2500</td>
<td>2500</td>
<td>2725 Grade 3</td>
<td>no chemotherapy \textsuperscript{34}</td>
</tr>
<tr>
<td>Brain</td>
<td>5400 7000</td>
<td>900-8900, mean=4100 to cavity wall \textsuperscript{131}I-81C6, \textsuperscript{45} &gt;30000 intra-tumor \textsuperscript{86}</td>
<td>111MBq \textsuperscript{90}Y to tumor cavity \textsuperscript{87} 44000 cumulative\textsuperscript{\rightarrow} edema; \textsuperscript{88} 3262-9700 \textsuperscript{89}</td>
<td>After pre-targeting \textsuperscript{87} &lt; 30mGy to normal brain; 8/24 headache, 1/24 seizure \textsuperscript{89}</td>
</tr>
<tr>
<td>Meninges</td>
<td>? &gt;7000</td>
<td>Surface=5800 \textsuperscript{131}I-antibody; \textsuperscript{90} Median 3309 from 3700MBq \textsuperscript{131}I-81C6 \textsuperscript{29}</td>
<td>Transient Aseptic meningitis from 740-2294MBq after XRT \textsuperscript{88}; 5920MBq single, 12506 cumulative tolerated \textsuperscript{90}</td>
<td>Intrathecal administration, most after external beam radiation</td>
</tr>
<tr>
<td>Spinal cord</td>
<td>4500 5500</td>
<td>~1700</td>
<td></td>
<td>Synthroid used</td>
</tr>
<tr>
<td>Thyroid</td>
<td>4500 15000</td>
<td>~15000</td>
<td></td>
<td>↑ creatinine \textsuperscript{33} ≤ 5% of patients</td>
</tr>
<tr>
<td>Kidney</td>
<td>2000 2500</td>
<td>&lt; 2170</td>
<td>Delayed &gt;2170 ≤3100 \textsuperscript{35} @</td>
<td>↑ creatinine \textsuperscript{33} ≤ 5% of patients</td>
</tr>
<tr>
<td>Bladder</td>
<td>6000 8000</td>
<td>4000</td>
<td>&gt; 4000 &lt; 15700</td>
<td>hemorrhagic cystitis \textsuperscript{92}</td>
</tr>
<tr>
<td>Stomach, intestine</td>
<td>4500 5500</td>
<td>2700, mild &lt;~6000</td>
<td>N/V/D&lt;6000, 6850-14000\textsuperscript{⇒}Gr4</td>
<td>↑ nausea ≤ 2700 some prior RT \textsuperscript{90, 33}</td>
</tr>
<tr>
<td>Bowel serosa</td>
<td>? &gt;5500</td>
<td>6000++ \textsuperscript{94, 95, 96}</td>
<td>8000 at tumor deposits</td>
<td>Rare adhesions, GI complaints \textsuperscript{97, 98}</td>
</tr>
<tr>
<td>Liver</td>
<td>2500 4000</td>
<td>2400, \textsuperscript{90}Y-CC49 \textsuperscript{99} ≤3100 for \textsuperscript{131}I-anti-B1; \textsuperscript{35} ~150 \textsuperscript{186}Re \textsuperscript{⇒}Mild nausea \textsuperscript{100}</td>
<td>1050 + ≥1200 external beam + chemotherapy \textsuperscript{101, 102} 4166-7394 from \textsuperscript{90}Y microsphere \textsuperscript{103}</td>
<td>\textsuperscript{35, 99, 100, 101, 102} Transient ↑ LFT, mild fibrosis ≥ 7 months \textsuperscript{103}</td>
</tr>
<tr>
<td>pancreas</td>
<td>≥ 4500</td>
<td></td>
<td>Intra-tumor \textsuperscript{32}P-MAA=1.7 x \textsuperscript{10}</td>
<td>30mCi x 2 tolerated; Some liver shunting \textsuperscript{28}</td>
</tr>
</tbody>
</table>

\textsuperscript{++} Risk of complications with \textsuperscript{32}P at ≥ 3000cGy,\textsuperscript{95, 96} but higher doses appear to be tolerated with antibody-targeted radionuclide therapy.

\textsuperscript{@} One of 29 patients had delayed increased creatinine but dose for that individual patient was not described & pancreas tolerance was not listed in tolerance tables. It generally tolerates 5000 to whole organ and ≥ 6000 to a lesser volume. Single dose tolerance is ~2000cGy.

\textsuperscript{**RT= external beam radiation; GI= gastrointestinal; TSH= thyroid stimulating hormone; N/V/D= nausea, vomiting, diarrhea; Gr= Grade; LFT= liver function tests.}

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How accurate are radionuclide dose estimates and comparison between studies?

1.) Radionuclide dosimetry is less accurate than external beam. Compared to methods for measuring radiation delivered to human
tissues by external beam radiation, those from radionuclide therapy are less precise. For example, dosimetry methods for a parenchymal lung tumor treated with a radionuclide conjugate usually will not take into account the difference in attenuation between lung and more dense tissue as is common with external beam radiation dosimetry. The current limitations in obtaining accurate three-dimensional localization of non-uniform radionuclide distribution hamper precise dose computations.

2.) How accurate are tracer studies? On a theoretical basis one would predict that tracer studies using a small amount of the same radionuclide agent would be the most accurate currently available method to estimate organ doses for a larger therapeutic administration. Many studies have been designed such that a tracer dose of the radioactive agent was given initially for biodistribution/dosimetry data collection that would determine administration of the therapeutic level of the radioactive agent. This allowed individualization of administered activity and, in some cases, patient exclusion from therapeutic administration based on results of the tracer study showing an unfavorable biodistribution. Dose estimates predicted from tracer studies have shown considerable variation compared to those obtained after therapeutic dose administration in the same patient. Several reports that allow this comparison are briefly summarized in Table 5. The comparison for the first two reports in Table 5 is given as a ratio of the dose to normal organs predicted from the tracer study to that obtained when imaging and dosimetry were repeated after administration of the therapeutic level of radioimmunoconjugates.

As dosimetry techniques become more accurate, it is anticipated that dose estimate concordance between tracer and therapy administrations will further improve.38

3.) Calculated dose is not equal to biologic dose. There are differences in clinical results of various radionuclides due to non-uniform distribution of the radiation within normal organs and tumors, dose rate effects, the effective range of radiation, relative biologic effectiveness (RBE), and other characteristics.19 For instance, alpha emitters with high linear energy transfer (LET) may provide an advantage when tumor is more radioresistant than normal tissues while beta particles provide an advantage when tumor is less radioresistant than normal tissues.2 However, these advantages vary as the ratio of the dose to tumor relative to dose to normal tissue increases. Biologic factors that affect tolerance of normal tissues may depend on age, prior therapies, the time since prior therapies, disease status—e.g., anemia of chronic disease or marrow replacement by malignancy; genetic factors and/or physiologic conditions such as hypoxia that affect radiosensitivity and re-

<table>
<thead>
<tr>
<th>Agent</th>
<th>Disease</th>
<th>Predicted/received</th>
<th>Comment</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>131I- LYM-1</td>
<td>NHL</td>
<td>0.91 - 1.38</td>
<td>Tracer at day -7</td>
<td>Meredith et al 64</td>
</tr>
<tr>
<td>131I—antibodies</td>
<td>NHL, leukemia</td>
<td>0.67 - 1.15</td>
<td>T1/2 for lung</td>
<td>Eary et al 65</td>
</tr>
<tr>
<td>111In-cT84.66 + 90Y-cT84.66</td>
<td>CEA-positive cancer</td>
<td>Concordance 0.60-0.99</td>
<td>Most normal organs studied</td>
<td>Clark et al 66</td>
</tr>
<tr>
<td>131I-CC49</td>
<td>Breast cancer</td>
<td>*mean 21% increase</td>
<td>Whole blood residence time</td>
<td>Macey et al 67</td>
</tr>
</tbody>
</table>

* Interferon given between the tracer and therapeutic administration significantly increased residence time in blood (42.6 +/- 4.7 vs. 51.5 +/- 4.8 h). However, the range of predictability with an increase of the mean by 21% is not different from other studies where no additional agents that were expected to alter distribution were given.
pair. Biologic effectiveness of radionuclide therapy is also influenced by additional agents/factors that do not contribute to the radiation dose estimates. These factors can include chemotherapy, other biologic response modifiers such as radiosensitizers, cytokines, and growth factor inhibitors (e.g., anti-EGFr antibody). For instance, DeNardo et al. demonstrated that the addition of paclitaxel can improve efficacy of radioimmunotherapy in an animal model without substantially increasing the toxicity. In their study using breast cancer xenografts, 79% of tumor-bearing animals responded to $^{90}$Y-ChL6 alone but none were cured whereas 100% of animals responded when paclitaxel was given 6 or 24 hours after the same dose of $^{90}$Y-ChL6 and 48% were cured.

4.) How accurate are comparisons of radionuclide dose estimates? There are a number of factors that need to be considered in attempts to compare dosimetry among studies. For most studies to date, precise comparisons will not be meaningful, sometimes even between different protocols of the same agent at a single institution. Due to variations in data collection and processing, caution needs to be applied to comparisons. Some aspects for consideration for variance in dosimetry methods include:

a) Measured organ volume such as used in myeloablative studies at the University of Washington versus phantom models
b) Do calculations use computer programs such as MIRDOS 2 or MIRDOS 3

c) Was attenuation correction applied for regions of interest observed on gamma camera imaging or a transmission scan technique used

d) Was background subtraction performed? Was scatter correction performed?
e) What was the frequency and appropriateness of the data collection time points. For instance, with a limited number of sample times for data collection such as gamma camera images, the peak concentration may be missed. This would result in a lower dose estimate than actually delivered.

Variability for marrow dose computation has improved greatly over the past two decades but still could be further reduced. In the 1980s variability for marrow dose computation was 700%. This improved to ~200% in the 1990s and recent analysis shows a yet smaller range. For this analysis, Wessels et al. collected data from non-myeloablative radioimmunotherapy trials in 7 institutions, using radionuclide conjugates of $^{131}$I or $^{186}$Re that did not target the marrow. The blood method for marrow dosimetry was used and the results of bone marrow radiation doses compared with marrow suppression toxicity. Data were reanalyzed at a central facility using methods similar, but not identical, to those at each participating institution. The absolute value of the marrow dose computed by the central facility had an average variation of $-15\%$ from that of the contributing institutions (range $-35$ to $+6\%$). The implementation of biologic markers to dosimetry methods such as quantitation of chromosomal translocations in blood cells after radionuclide therapy may provide insight to improved accuracy and standardization for some dosimetry methods.

What radiation doses have been delivered to tumors and how effective have they been?

Table 6 shows a large range of administered activity of radionuclides in a variety of tumors varying in radiosensitivity. In general, there have been responses to solid glandular or other common adult tumors and pediatric malignancies that are considered more radioresistant than hematologic malignancies. Responses have been more readily achieved in pediatric malignancies than some adult tumors. This should not be surprising since in general doses that control pediatric non-CNS solid tumors are less than required for comparable results in adults. Of adult tumors, although some studies do not show responses even with high doses of administered activity, responses have been noted in other studies. Such responses have been more frequent when radionuclide therapy was used in conjunction with other modalities for hepatoma but the combination therapy makes it difficult to determine how much of the effect was due to the radionuclide conjugate portion of the therapy. In the relatively radioresistant adenocarcinoma of the prostate, radionuclides have been successful in palliation of bone pain but objective responses are not usually reported for bone seeking radionuclides $^{89}$Sr and $^{153}$Sm, or with antibody-targeted radionuclides $^{131}$I-CC49, $^{90}$Y-Cyt356, or $^{90}$Y-K4C alone. However, when $^{131}$I-CC49 was given with interferon enhancement and/or as part of a combined modality regimen, objective responses were observed. When radionuclide
therapy can be given in a non-systemic manner such as local/regional administration into the CSF, cranial tumor cavity, or peritoneal cavity higher activities can be tolerated than when given systemically. The higher administered activity of radionuclides may account for the improved response rates observed with non-systemic administrations. In some instances, response rates may also be influenced by more radiosensitive types of disease and smaller tumor deposits. As expected, smaller tumor masses have a higher probability of response for both solid non-hematologic malignancies and NHL. Press et al. showed that response rates were less for NHL patients receiving $^{131}$I-antiB1 therapy who had splenomegaly and/or tumor burden > 500 ml. Similarly, using an alternate anti-CD20 antibody carrying $^{90}$Y, more than double the response rate

<table>
<thead>
<tr>
<th>ANTIBODY CONJUGATE</th>
<th>TUMOR route*</th>
<th>DOSE GIVEN MBq/infusion</th>
<th>DOSE (Gy)</th>
<th>TUMOR RESPONSE</th>
</tr>
</thead>
<tbody>
<tr>
<td>$^{131}$I-U13A</td>
<td>Neuroblastoma IV</td>
<td>295-2035</td>
<td>mean 13-21</td>
<td>1/5 CR</td>
</tr>
<tr>
<td>$^{131}$I-anti Ferritin</td>
<td>hepatoma IV</td>
<td>1110 day 1 740 day 5</td>
<td>10-12 per cycle</td>
<td>7% CR 41% PR</td>
</tr>
<tr>
<td>$^{131}$I-CC49</td>
<td>colon IV</td>
<td>3700-11100/m²</td>
<td>6.3-33</td>
<td>0/12</td>
</tr>
<tr>
<td>$^{186}$Re-NR-CO F (ab²)</td>
<td>gastrointestineal IV/IA</td>
<td>925-12913</td>
<td>6-20 for PR patient</td>
<td>1/31 PR 1/10 PR</td>
</tr>
<tr>
<td>CNS non-systemic administration</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$^{131}$I-anti EGFr</td>
<td>Glioma IA</td>
<td>1665</td>
<td>55</td>
<td>radiographic PR</td>
</tr>
<tr>
<td>$^{125}$I-anti EGFr</td>
<td>gliomas IA</td>
<td>962-4810</td>
<td>divided doses</td>
<td>1/15 CR; median surv. 14 mo.</td>
</tr>
<tr>
<td>$^{131}$I-Various Antibodies</td>
<td>leptomeningeal CSF</td>
<td>629-2294</td>
<td>6/17 CR</td>
<td>3/17 PR</td>
</tr>
<tr>
<td>$^{131}$I-BC-2</td>
<td>gliomas IT</td>
<td>403</td>
<td>37-763</td>
<td>2/7 stable 3/7 PR</td>
</tr>
<tr>
<td>$^{131}$I-8IC6</td>
<td>gliomas IT</td>
<td>4440</td>
<td>25-146</td>
<td>↑ survival</td>
</tr>
<tr>
<td>IP salvage or adjuvant</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$^{131}$I-HMFG1</td>
<td>Ovary IP</td>
<td>740-7585</td>
<td>80</td>
<td>9/16 CLR &lt;2cm 3/6 CR for microscopic</td>
</tr>
<tr>
<td>$^{131}$I-AUA1</td>
<td>Ovary IP</td>
<td>2220-3700/m² ≤ 36 most</td>
<td>5/12 PR for &lt;1cm lesions</td>
<td></td>
</tr>
<tr>
<td>$^{186}$Re-NR-LU-10</td>
<td>Ovary IP</td>
<td>≤ 1665mCi/m² 21-46</td>
<td>PR for ~3cm + survival</td>
<td></td>
</tr>
<tr>
<td>$^{90}$Y-HMFG1</td>
<td>Ovary</td>
<td>685/m²</td>
<td></td>
<td>↑ survival</td>
</tr>
<tr>
<td>$^{32}$P</td>
<td>Ovary</td>
<td>555-740</td>
<td>20-40</td>
<td>↑ survival</td>
</tr>
</tbody>
</table>

* IV=intravenous, IA=intra-arterial, IT=into tumor cavity, IP= intraperitoneal
was observed among patients with tumor masses < 7 cm. (86%) compared to the 41% response rate for those with larger tumor masses.\textsuperscript{81} For solid non-hematologic malignancies, Behr et al. have shown excellent response rates among patients with limited tumor burden.\textsuperscript{96} More details of radionuclide clinical studies are presented in recent reviews.\textsuperscript{67,68,69,70}

\begin{table}
\centering
\caption{Tumor Dose Vs Response Rates in Selected NHL RIT Trials*}
\begin{tabular}{|l|c|c|c|}
\hline
Antibody Conjugate & Tumor Dose (cGy) & Response Rate & Reference \\
\hline
\textsuperscript{131}I-Lym-1 & 16-1485; median = 241 & 54\% & Lamborn\textsuperscript{106} \\
\textsuperscript{67}Cu-Lym-1 & 5429-7000 for CR, \geq 613 for others & 67\% & DeNardo\textsuperscript{109} \\
\textsuperscript{131}I-anti-B1 myeloablative & 2200-9200 median = 3800 +/- 1200 & 86\% & Press\textsuperscript{39} \\
\textsuperscript{131}I-anti-B1 & mean: 734 for men, 1197 for women & 79\% & Kaminski\textsuperscript{13} \\
\textsuperscript{131}I-anti-B1 & 369+/-54 for PR, 720+/-80 for CR & 100\% & Koral\textsuperscript{102} \\
Y2B8 & 580-6710; median = 1700 & 26\%CR, 41\%PR & Wiseman\textsuperscript{110} \\
Y2B8 & 53-4291; mean = 740 & 72\% & Knox\textsuperscript{111} \\
\textsuperscript{90}Y-biotin + C2B8/SA & 260-14,000 & 86\% & Weiden\textsuperscript{112} \\
\hline
\end{tabular}
\footnote{*In was used as a surrogate for \textsuperscript{90}Y in following biodistribution for dosimetry measurements. The number of patients may reflect the total number in the study or those for whom the dosimetry information was reported. Some numbers may appear slightly different than in referenced publications due to rounding off; also, information is taken from various publications from the same group with some assumptions that results apply to the same patients.}
\end{table}

Figure 2. Longer response duration for patients achieving a CR compared to all patients receiving treatment.
Some of the best response rates have been achieved in NHL, which is considered a relatively radiosensitive malignancy, and may be effectively treated with low dose rate radiation as provided by radionuclide therapy. Table 7 lists several selected studies from a few of the promising radioimmunoconjugates currently under investigation. Although there is a range of response from 54% to 100%, the patient eligibility criteria and other prognostic factors varied such that these studies should not be directly compared for efficacy. However, compared to many new single agents that are developed for cancer therapy, a response rate of > 50%, as seen in all of these selected studies, is very favorable. The dose to tumor masses varies widely from 16 – 14,000 cGy. Although there is a trend for a dose response relationship, this has usually not reached statistical significance with relatively small numbers of patients in each study. Some of the potential difficulties in the relationship may be the heterogeneous nature of the radiation deposition. Whereas the radiation dose is reported as the mean to a tumor mass, the region that receives the lowest dose may be the area determining efficacy. As indicated in Table 7 and other reports, there is a tendency for more complete responses with increasing dose and these responses achieved with higher doses tend to be more durable. This is illustrated in Figure 2 which shows a much longer duration of remission among patients receiving high dose radioimmunoconjugate therapy followed by stem cell rescue than in non-myeloablative studies with $^{131}$I-antiB1 whether conducted at the University of Michigan or as part of a multi-institutional effort. A trend of dose response is also noted with analysis of non-myeloablative studies with $^{131}$I where 30 tumors in PR patients had a mean = 369 +/- 54 cGy compared to 56 tumors in CR patients having a mean = 720 +/- 80 cGy.

Improved dose/response relationships between the bone marrow toxicity and dosimetry estimates of radiation to the bone marrow have improved when biologic factors have been taken into account or individualized marrow measurements were performed. Considerations for biologic factors that have improved correlation includes prior chemotherapy and/or radiation, time since prior chemotherapy, age, and gender. For instance, Wessels et al. found that the correlation coefficient between marrow toxicity and marrow dose improved from $r = 0.57$ to $r = 0.80$ by adjusting for age, gender and prior therapy. Further improvement in correlation may result from additional analysis of biologically relevant factors in addition to more precise physical methods of dosimetry calculations.

**SUMMARY/CONCLUSION**

Information on normal tissue toxicity from radionuclide therapy is more limited than for external beam irradiation and appears more variable, as expected, due to a number of biologic and physical factors. However, with the increasing expansion of agents being developed for targeted radionuclide therapy more accurate radiation dose estimates and improved dose-response correlations are expected. More refinement in dosimetry techniques as well as standardization for data collection and processing should increase the accuracy and comparability of radiation dose estimates. Additional knowledge about biologic modifiers of radionuclide effects such as chemotherapy or other radiosensitizing agents that increase response without changing dose calculations can be applied to improve dose-response correlation for normal organs and targeted masses.

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