Review of Five Consecutive Studies of Radiolabeled Immunoglobulin Therapy in Hodgkin's Disease

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Abstract

Recurrent Hodgkin's Disease (HD) provides unique opportunities to improve radiolabeled immunoglobulin therapy (RIT). Normal tissue toxicity after RIT is limited to bone marrow damage and is well documented and quantified in HD patients. Anti-antibody formation is rare in patients with HD, allowing for multiple RIT cycles. Overall, 134 patients with recurrent HD were treated on five different studies with i.v. antiferritin, labeled with $^{111}$In or with $^{90}$Y for diagnostic purposes and $^{99m}$Tc for therapeutic purposes.

Patients with recurrent, end-stage HD obtain a 60% response rate following $^{99m}$Tc-labeled antiferritin. One-half of the therapy responses are complete. Responses are more common in patients with longer disease histories (>3 years) and smaller tumor volumes (<30 cm$^3$) and in patients receiving at least 0.4 mCi $^{99m}$Tc-labeled antiferritin/kg body weight. Complete responders survive significantly longer than partial responders (2 years versus 1 year). Partial responders survive longer than patients with progressive disease (1 year versus 4 months). HD in one-third of the patients recurs in new areas. A low protein dose (2–5 mg) and a moderate specific activity (10 mCi/mg) are recommended. Results obtained with $^{90}$Y-labeled antiferritin are significantly better than results with $^{111}$In-labeled antiferritin.

Further translational research in vitro in the radiopharmacy and in vivo with experimental animals is ongoing to improve the therapeutic results of RIT in HD. Obviously, many permutations of RIT cannot be explored in HD patients for ethical, financial, or logistic reasons, and predictive preclinical research is required to achieve further progress. Currently, RIT is a low-toxicity, low-cost outpatient procedure for recurrent HD with a high response rate in a patient population with an unfavorable prognosis.

Introduction

In 1832, Thomas Hodgkin described the malignant disease of lymph tissues that now bears his name. More than a century and a half later, the clonogenic tumor cell in HD$^3$ has not been identified yet. The search continues unabated with the most advanced histological, immunological, and molecular biological techniques. The biology of HD, however, was documented to be a unique, predictable progression of disease from one lymph node region to the next termed "contiguous spread." For prolonged periods of time, HD remains limited to lymphoid tissues. At Stanford University, Kaplan (1) formalized the radiotherapy solution for early stage HD by adjusting to this biological process and treating patients with large radiation fields, including the involved lymph node regions plus the neighboring clinically uninvolved nodes. Kaplan also defined the radiation dose required for control of HD. In advanced stages of HD, the disease is no longer confined to lymph node regions and can no longer be encompassed in acceptable radiation fields. Systemic treatment is required in such patients.

Advanced HD was found to be susceptible to new, multiple agent chemotherapy regimens in pioneering studies at the National Cancer Institute (2). This led to the use of cyclic chemotherapy. In each cycle, multiple chemotherapeutic agents could be combined at a high dose level for each agent, due to their different modes of action and nonoverlapping normal tissue toxicity. The usual cycle length was 4 weeks, and the total number of cycles was six to eight. Later, this concept was extrapolated successfully to the treatment of other malignancies. Survival, free of HD, was found to be over 85% for early disease and over 40% for advanced disease. Dickey and coworkers (3) at M. D. Anderson Cancer Center found recurrent HD to be responsive to conditioning regimens of high-dose chemotherapy followed by autologous bone marrow rescue, demonstrating the benefits of dose escalation in the control of recurrent HD. Most recently, end-stage, treatment-refractory HD appeared responsive to RIT in the work of Lenhard et al. (4) at Johns Hopkins Oncology Center.

In this communication, HD is used once more as a paradigm for the development of a novel cancer treatment concept, RIT. Some aspects of HD continue to resist explanation, notwithstanding intensive research. However, therapy trials of RIT in HD appear extremely helpful in optimizing this new treatment modality for human patients. The application of RIT in patients with other malignancies is expected to benefit from the experience obtained in HD patients.

Materials and Methods

Antigen. Human ferritin, described by Order and coworkers (5) as a tumor-associated antigen in HD was purified using techniques reported previously (6). Ferritin has a high molecular weight ($M_r$ 440,000), is not a membrane antigen, and is present in the interstitium and cell cytoplasm of some normal cells in liver, spleen, and bone marrow and tumor cells of different histologies (6).

Isotopes. $^{131}$I, $^{111}$In, and $^{90}$Y were used for radiolabeling. They were obtained either through the courtesy of Hybritech (San Diego, CA) or more recently bought from New England Nuclear, Boston, MA (indium) and from Westinghouse, Richland, WA (yttrium).

Radiolabeling Methods. Iodine labeling was performed by the lactoperoxidase method that substitutes iodine directly onto tyrosine residues of the immunoglobulin (4). Radiolabeling with indium or yttrium was performed by a proprietary method of Hybritech. Briefly, immunocomjugates were prepared by reacting isothiocyanatobenzyl-DTPA chelators to the lysine residues of the immunoglobulin (4). Radiolabeling with indium or yttrium was performed by a proprietary method of Hybritech. Briefly, immunocomjugates were prepared by reacting isothiocyanatobenzyl-DTPA chelators to the lysine residues of the immunoglobulin for the connection between the protein and the bifunctional chelator. Subsequently, chelate-immunoconjugates were complexed with radiometals. In the second polyclonal antiferritin study, a backbone-substituted isothiocyanatobenzyl-DTPA was conjugated to the immunoglobulin and radiolabeled with indium or yttrium as described by Quadri et al. (7).

Quality Control. Radioimmunoconjugates were tested for radiochemical purity and serum stability in vitro. Prior to in vivo use, they were challenged with a 100-fold excess-free DTPA concentration and purified by column chromatography. Radioimmunoconjugates were filtered through a 0.2 µm sterile filter. A pyrogenicity test was performed prior to injection. One % human serum albumin was added to decrease radiosensitivity of the radiolabeled conjugate.

Patients. End-stage HD patients with measurable disease ($n = 134$) were entered in five different studies. Ages ranged from 10 to 71 years. Male:female ratio was 1.5:1. Most patients were white. Black and Hispanic minorities were proportionally represented. For full protocol description, the reader is advised to consult original publications on these studies (4, 8–11). A summary of the studies is given in Table 1. A complete response was defined as disappearance of disease on physical exam and diagnostic studies. A partial response was...
defined as a decrease in the product of orthogonal tumor diameters by more than 50%. Patients with tumors that did not show a complete or partial response were scored as stable disease or progressive disease.

Administration to Patients. Radioimmunoconjugates were administered i.v. Polyclonal AF was given in a 2- to 5-mg total protein dose by rapid bolus infusion. IgG was purified from sera of immunized rabbits, pigs, or baboons. Cold (unlabeled) polyclonal immunoglobulin was not added to radiolabeled polyclonal AF. Radiolabeled monoclonal AF was given slowly over 15 min, premixed with 20 mg of cold monoclonal immunoglobulin. Blood and urine samples were taken at regular intervals after administration of the radioimmunoconjugate for pharmacokinetic analysis. Gamma camera whole-body and single photon emission computed tomography scans were performed after iodine- or indium-labeled immunonconjugates only.

Animal Models. Nude mice with s.c. xenografted human hepatocellular carcinoma cells (HepG2) were used for tumor targeting studies. HepG2 cells secrete ferritin. Biodistribution, pharmacokinetics, immunoscintigraphy, and tumor therapy studies were performed previously in this same model (12, 13). Beagle dogs, however, were used for biodistribution, pharmacokinetic, and radionuclide studies of radiolabeled AF (6). The dog studies were performed to obtain radiation dose gradients over large normal organs, similar to the ones encountered in human patients. In addition, radiation damage to the hemopoietic system and to the liver of the dog appears to be similar to the radiation response of the corresponding organ systems in human patients (6).

Results

Animal Studies. In the nude mouse model, HepG2 tumors were well targeted by i.v. radiolabeled AF (6, 13). Intact monoclonal antibodies were more effective therapeutic agents than polyclonal antibodies, and 131I was shown to be a less effective therapeutic isotope than 90Y (13). The dose-limiting normal tissue to radiolabeled AF treatment appeared to be the hemopoietic system in mouse, rat, and dog studies (6). The second rank, dose-limiting normal tissue was found to be the liver in an experimental study in dogs using high activity Y-AF i.v., followed by an autologous BMT. Animals died found to be the liver in an experimental study in dogs using high dose-limiting normal tissue was radiation response of the corresponding organ systems in human patients (6).

Antigen. The great majority of patients (>90%) receiving In-AF showed tumor targeting, i.e., increased deposition of the radioimmunoconjugate in areas containing HD in comparison to surrounding normal tissues. In three patients, a 68Ga scan performed 3 weeks prior to their In-AF study indicated smaller tumor areas than the indium scan. The target for the two diagnostic methods is different: a cell membrane receptor for transferrin for gallium (14) and an interstitial antigen for antiferritin. Targeting was not influenced by serum ferritin levels of patients (8).

Antibody. Intact mouse monoclonal AF did not target HD due to high deposition in the normal human liver (~50% of injected activity; Refs. 6 and 8), notwithstanding admixture with 20 mg of unlabeled monoclonal AF. The second trial with a new batch of either indium- or yttrium-labeled polyclonal (rabbit) AF produced higher percentages in tumor targeting and response rates than the batch of polyclonal AF used in the first trial (Table 2). In all studies of polyclonal AF, 2 to 5 mg of protein was administered by rapid i.v. infusion. No acute adverse effects were noted.

Prescription Method. Y-AF levels in blood 1 h after i.v. administration were compared to total administrated activity, the activity administered per body surface area, or the activity administered/kg body weight. At 1 h after administration, only the mCi/kg body weight prescription showed a significant positive correlation with blood radioactivity levels ($r = 0.44; P < 0.05$). For later time points (24 and 48 h after administration), correlations did not reach accepted significance levels for any prescription method due to different pharmacokinetic “complications” that developed over time in some patients (Refs. 10 and 11; Tables 3–5). Patients with and without B symptoms showed different pharmacokinetics for In-AF (Table 3). Results were expressed in primary half-life ($T_1/2$), secondary half-life ($T_1/2$), and the relative importance of the two elimination processes ($a/b$). Patients with B symptoms had shorter secondary blood half-lives. The influence on pharmacokinetics of the amount of 90Y administered/kg body weight is summarized in Table 4. The body weights of patients differed, while the total milligram amount of AF was a standard 2 mg, leading to different specific activities of the radioimmunoconjugate for different patients. Higher specific activities for yttrium caused radiolysis (increased urinary elimination of isotope) and shorter sec-

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Table 1 | Studies of radiolabeled AF in patients with end-stage HD

<table>
<thead>
<tr>
<th>Study first author and Ref. no.</th>
<th>Antibody (species)</th>
<th>Isotope (mCi administered)</th>
<th>Labeling chemistry</th>
<th>Study specifics</th>
<th>No. of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lenhard et al. (4)</td>
<td>Polyclonal* (rabbit, pig)</td>
<td>131I (50 mCi)</td>
<td>Lacto-peroxidase</td>
<td>2 cycles</td>
<td>37</td>
</tr>
<tr>
<td>Vriesendorp et al. (8)</td>
<td>Polyclonal* (rabbit, pig, baboon), monoclonal QC1</td>
<td>111In (3-5 mCi)</td>
<td>ITCB-DTPA (Hybritech)</td>
<td>☞ BMT 1–5 cycles</td>
<td>35</td>
</tr>
<tr>
<td>Bierman et al. (9)</td>
<td>Polyclonal†</td>
<td>90Y (20, 30, 40, and 50 mCi)</td>
<td>ITCB-DTPA (Hybritech)</td>
<td>CBV chemo* + BMT</td>
<td>14</td>
</tr>
<tr>
<td>Herbst et al. (10)</td>
<td>Polyclonal†</td>
<td>111In (3-5 mCi)</td>
<td>ITCB-DTPA (Hybritech)</td>
<td>Long term follow-up</td>
<td>44 (including 35 of Ref. 8)</td>
</tr>
<tr>
<td>Morton et al. (11)</td>
<td>Polyclonal† (rabbit)</td>
<td>90Y (20, 30, 40, and 50 mCi)</td>
<td>ITCB-DTPA (Quadri)</td>
<td>No BMT, pharmaco-kinetics</td>
<td>39</td>
</tr>
</tbody>
</table>

* Different polyclonal antiferritins that were produced by different techniques at different times by different investigators.

† In parentheses, suppliers’ names. ITCB, isothiocyanato benzyl.

Table 2 | Comparison of trials with Indium- or Yttrium-labeled polyclonal AF

<table>
<thead>
<tr>
<th>Polyclonal AF</th>
<th>Tumor targeting</th>
<th>Response rates</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>111In</td>
<td>$90Y^*$</td>
</tr>
<tr>
<td>1</td>
<td>40/45</td>
<td>20/39</td>
</tr>
<tr>
<td>2</td>
<td>39/39</td>
<td>19/22</td>
</tr>
</tbody>
</table>

* $P = 0.04$.

Table 3 | T $B_2$ half-lives of In-AF in HD patients

<table>
<thead>
<tr>
<th></th>
<th>Average $T_{B_2}$ In-AF in hours (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>With B symptoms</td>
<td>39.8 (8–50)</td>
</tr>
<tr>
<td>Without B symptoms</td>
<td>44.3 (27–60)</td>
</tr>
</tbody>
</table>

* $P < 0.01$.

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5889s

5889s
onary blood half-lives. In Table 5, the data were analyzed for specific activities below or above 14 mCi/mg. Higher specific activities led to significantly shorter \( T_\beta \), but urinary elimination remained the same.

**Toxicity.** Hematological toxicity was the dose-limiting side-effect of radionuclide antiferritin treatment. Platelet levels of 20,000 per mm\(^2\) blood occurred more frequently with higher administered activities and delayed the administration of a new RIT cycle. Serious granulopenia was less common and responded to treatment with recombinant human granulocyte-colony-stimulating factor. Average cycle length for the first cycle was 10 weeks. Cumulative hematological toxicity was observed and caused a longer cycle length in subsequent cycles, but some patients did tolerate three or more cycles. One patient was treated six times. Another patient developed a myelodysplastic syndrome after completing multiagent chemotherapy, high-dose chemotherapy, BMT, external beam radiation, and finally, three RIT cycles. Blood count recovery was slowest in patients with prior BMT; patients with bone marrow involvement with HD, and patients with rapidly progressive HD. BMT accelerated hematopoietic recovery after Y-AF RIT (8, 9). A significant amount of toxicity was observed in the RIT-BMT study. BMT is not required for hematopoietic recovery after the Y-AF activity levels currently used. Two patients had preexisting circulating anti-antibodies prior to the initiation of RIT. In one only patient were anti-rabbit antibodies found after a single In-AF/Y-AF cycle. Toxicity was not observed in organ systems other than the hematopoietic system.

**Response of HD.** Response rates for single-agent, radiolabeled antiferritin studies are shown in Fig. 1. The studies were consecutive, not concurrent. As predicted by the RIT therapy trials in nude mice with HepG2 xenografts, response rates were higher after Y-AF than after \(^{131}I\)-labeled AF. The administration of higher \(^{90}Y\) activity levels/kg resulted in significantly higher response rates. Complete response rates showed the same differences among different trials (Fig. 2). The differences between the first and the second \(^{90}Y\) studies were probably due to a better radioimmunoconjugate and a better prescription method in the second study. Response durations lasted from 2 months to years, with an average of 8 months. Survival studies were performed after the first yttrium study (10). Fifty % of complete responders, partial responders, and progressive disease patients were alive at 2 years, 1 year, and 4 months, respectively. Survival data of patients on the second yttrium study are still under analysis. In the Y-AF/cyclophosphamide-carmustine-epotidase/BMT study, four of eight evaluable patients were alive at 2 years, three had no evidence of disease (9). On the different protocols, most HD patients have had disease recurrence after RIT and succumbed to their disease. One patient developed a fatal gliosarcoma of the brain while undergoing RIT. Three patients died without evidence of disease for HD, two died from preexisting lung fibrosis, and one died in a car accident. Small numbers of patients in the different studies are alive 1 to 5 years after RIT. Patients receiving In-AF and Y-AF that were not treated with BMT remained outpatients, unless disease progression made inpatient management necessary. Responses were more common in patients with small volume disease and long disease histories at the time of RIT initiation. One-third of the HD recurrences were in a previously uninvolved area, while the response to RIT was maintained in the initial disease sites (8).

**Tumor Dosimetry.** Tumor doses of up to 30 Gy in 1 week were obtained after polyclonal Y-AF administration. A full dosimetric analysis, including correlation of tumor doses to tumor responses, is being performed. In the first Y-AF study, no correlation was found between tumor dose and subsequent response (8).

**Discussion**

In the United States, approximately 7500 patients are diagnosed with HD each year. For two of three patients, the administered radiotherapy and/or chemotherapy will be curative: one of the success stories in modern oncology. Approximately 2500 patients, however, will not respond to treatment or will have a disease recurrence.

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**Table 4 Pharmacokinetics of In-AF and Y-AF in HD patients**

<table>
<thead>
<tr>
<th>Radioisotope (mCi)</th>
<th>( T_a ) (h)</th>
<th>( T_b ) (h)</th>
<th>( \alpha/\beta )</th>
<th>24-h urine activity % injected</th>
<th>1-h blood activity (µCi/g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(^{111})In (4.5–7)</td>
<td>5.2</td>
<td>42.1</td>
<td>5.0</td>
<td>3.9</td>
<td>6.3</td>
</tr>
<tr>
<td>(^{90}Y) (0.3 mCi/kg)</td>
<td>5.4</td>
<td>47.7</td>
<td>2.3</td>
<td>3.9</td>
<td>4.6</td>
</tr>
<tr>
<td>(^{90}Y) (0.4 mCi/kg)</td>
<td>5.1</td>
<td>34.6</td>
<td>2.6</td>
<td>3.9</td>
<td>5.0</td>
</tr>
<tr>
<td>(^{90}Y) (0.5 mCi/kg)</td>
<td>4.9</td>
<td>30.9</td>
<td>1.9</td>
<td>3.9</td>
<td>5.8</td>
</tr>
</tbody>
</table>

\(^a\) Number of patients: \(^{111}\)In, 38; \(^{90}Y\) (0.3), 10; \(^{90}Y\) (0.4), 21; \(^{90}Y\) (0.5), 7.

\(^b\) See text for explanation.

**Table 5 Pharmacokinetics of Y-AF and specific activity (SA)**

<table>
<thead>
<tr>
<th>SA &lt; 14 mCi/mg</th>
<th>SA &gt; 14 mCi/mg</th>
<th>( P ) ( T ) test</th>
</tr>
</thead>
<tbody>
<tr>
<td>( T_b ) (h)(^a)</td>
<td>37</td>
<td>32</td>
</tr>
<tr>
<td>Urine radioactivity(^b)</td>
<td>7.3</td>
<td>8.0</td>
</tr>
<tr>
<td>No. of patients</td>
<td>40</td>
<td>28</td>
</tr>
</tbody>
</table>

\(^a\) See text for explanation.

\(^b\) Percentage of administered radioactivity recovered in collection of urine for the first 24 h after administration.

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4 P. Leichner, manuscript in preparation.
Second-line treatment (including high-dose chemotherapy/radiation, followed by BMT) is expected to be curative for one-third of these patients, leaving less than 2000 patients per year requiring third-line treatment. In this heavily pretreated patient population, radiolabeled AF appears to be able to target HD and provide a high tumor response rate at a low toxicity cost. A normal tissue antigen like ferritin is able to act like a tumor-associated antigen. The ferritin concentration is higher in tissues containing HD, and presumably tumor ferritin is more accessible than ferritin in normal tissues due to the leaky capillaries of tumor neovascularure. In these studies, $^{90}$Y has shown stronger antitumor effects than $^{131}$I. The most disappointing experience in the reviewed clinical studies is the failure of intact mouse monoclonal antiferritin to target HD. Further preclinical animal studies are needed. F(ab')$_2$-stabilized fragments of monoclonal AF appear to have greater promise for HD patients than intact monoclonal AF (12).

The experience obtained in HD with RIT indicates that a low amount of radiolabeled protein (<5 mg) can induce a tumor response. This argues in favor of a radiation effect and against an immunological effect of the radioimmunoconjugate. In addition, the interstitial location of tumor-associated ferritin will prevent the occurrence of immune-mediated cellular cytotoxicity or complement-dependent cytotoxicity on tumor cells. The range of $^{90}$Y $\beta$ emissions is on average over 5 mm in tissue and corrects, to some degree, for uneven deposition of the radioimmunoconjugate in the tumor and the risks for “cold” spots in the tumor. Techniques for tumor dosimetry depend on quantitative information obtained from whole-body and single photon emission computed tomography scans after In-AF administration. This information will only be predictive for Y-AF if the biodistribution and pharmacokinetics of AF is the same for the indium- and the yttrium-labeled conjugate. With the use of the proper chelation chemistry and specific activity, this appears to be the case. A positive correlation between tumor dose and response has not been found yet. Higher tumor doses could be obtained with improved monoclonal Y-90 AF and facilitate the elucidation of a dose-effect curve for RIT in HD. $^{131}$I-labeled AF given at activities over 30 mCi per patient will necessitate temporary inpatient management for radiation safety reasons. $^{131}$I-labeled AF will cause lower and less homogeneous tumor doses than $^{90}$Y. It was not feasible for the clinical studies reported to compare $^{131}$I- and $^{90}$Y-labeled AFs at equal tumor doses. $^{90}$Y-labeled AF causes less toxicity and higher response rates and thus has an improved therapeutic ratio over $^{131}$I-labeled AF.

The design of clinical RIT protocols has been improved on the basis of the reviewed studies in HD: (a) a more precise prescription method: mCi/kg; (b) delay of toxicity/dose escalation studies until the radioimmunoconjugate is optimized (see also 15); (c) higher tumor response rates in early clinical studies than commonly seen in chemotherapy studies; (d) low-toxicity, low-cost, outpatient studies by administration of In-AF first (In-AF followed by Y-AF); and (e) selection of patients with measurable disease for single-agent studies (i.e., RIT only).

The data in Tables 3 and 5 appear to indicate that B symptoms in patients or radioimmunoconjugates with higher specific activities cause third spacing (larger volume of distribution) of the radioimmunoconjugate. A possible explanation for the latter is radiation damage to normal endothelial structures by the higher specific activity that promotes leaking of the intravascular radioimmunoconjugate into the interstitial space. The activity escalation in the most recent HD RIT study was adjusted. The 0.4 mCi Y-AF/kg demonstrated a high response rate but less radiolysis and third spacing than 0.5 mCi Y-AF/kg. This again underlines the need for new sequential development studies for RIT agents that are different from the classical Phase I, II, and III studies as developed for chemotherapeutic agents (15). Further RIT studies that include BMT can be postponed until the radioimmunoconjugate and its administration has been optimized (e.g., monoclonal AF in a fractionated schedule). The timing of the administration of hemapoietic cells after RIT is crucial and should be delayed until the dose rate in the bone marrow has decreased to 1 cGy/h or less (6). The lack of a strong anti-antibody response in HD patients is due to their disease and treatment-induced immunodeficiency. Anti-antibody formation occurs in less than 5% of HD patients and facilitates the analysis of cyclic RIT in this patient population.

The variables in clinical RIT remain daunting. However, a combination of mouse and dog studies has provided information that appears to be helpful and predictive for subsequent RIT studies in HD (6). Predictive translational research in preclinical animal models is essential for progress in clinical RIT studies. Although HD does not have a counterpart in veterinary oncology, nude mice with xenografted human hepatoma cells can provide a ferritin-positive in vivo human target. Normal tissue toxicity is best analyzed in a larger animal model such as beagle dogs. In mice, RIT will be close to total body irradiation, whereas in dogs, the same normal tissue dose gradients as experienced by human patients can be reproduced. The execution of preclinical RIT research remains an organizational and financial challenge due to the many talents/specialties required for the proper execution of such research. For the time being, this will limit preclinical RIT research to larger academic institutions. Fractionation of RIT and monoclonal AF appear to be the most pressing issues for preclinical analysis.
The advantages of RIT over most other cancer therapies are selectivity and quantification (µCi/g in tumor and normal tissues can be determined over time by noninvasive methods). Selective and quantitative approaches remain necessary for further development of RIT to maintain and further enhance the therapeutic ratio of RIT. HD has several interesting characteristics that make HD once more a good paradigm for improvement in another new cancer treatment modality. The scientific community and the authors of this communication are indebted to the courage, enthusiasm, and willingness of HD patients and their caregivers to participate in the described RIT studies.

References

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