Radioimmunotherapy of Human B-Cell Lymphoma with $^{90}$Y-conjugated Antidiotype Monoclonal Antibody


Abstract

We report the first case of $^{90}$Y-conjugated monoclonal antibody (MoAb) administration for human radioimmunotherapy. Ten mCi $^{90}$Y-labeled antidiotype (anti-Id) MoAb were administered to a patient with B-cell lymphoma whose tumor successfully imaged with $^{111}$In-labeled anti-Id MoAb. No significant toxicities were observed. More than 2 g of unlabeled anti-Id MoAb were administered while clearing the circulating IgM idiotype prior to administration of the $^{90}$Y-MoAb. Transient partial regression of disease was observed. Serial fine needle aspirations of a malignant lymph node documented in vivo anti-Id penetration into a site that did not image by radioimmunoscintigraphy. The radiosensitivity of B-cell lymphoma, the tumor specificity of anti-Id, the antitumor activity of anti-Id alone, and the safe administration of 10 mCi $^{90}$Y-labeled anti-Id MoAb in this report suggest further investigation of this radioimmunoconjugate for therapy of B-cell lymphoma is warranted.

Introduction

Antidiotype monoclonal antibodies are tumor-associated reagents for B-cell lymphoma, a monoclonal proliferation of B-cells derived from a single original transformed cell (1, 2). Each lymphoma expresses a surface immunoglobulin which has a unique idiotypic variable region and is distinct from lymphomas of other patients and from the surface immunoglobulin on normal lymphocytes. The first patient treated with anti-Id$^3$ MoAb underwent a complete and durable remission (3). An additional 16 patients with large tumor burdens who failed conventional therapy have been treated with anti-Id MoAbs (4, 5). Eleven of these patients had clinically significant responses (2 complete responses, 7 partial responses, 2 minimal responses). In 2 patients who relapsed after anti-Id therapy, the residual lymphoma cells expressed surface immunoglobulin but did not react with the anti-Id (6). Further investigation suggested that idiotype-negative variants arose as a result of somatic mutation in the variable region of active immunoglobulin genes (7). Anti-Id therapy exerts a strong selective force against idiotype-positive cells, but the emergence of idiotype-negative variants and the observation of minimal response in some patients suggests that the combination of anti-Id MoAb with other reagents will improve therapeutic efficacy.

Anti-Id MoAb when combined with α-interferon in a murine lymphoma model resulted in a synergistic antitumor response (8). Based on this observation, a clinical trial of anti-Id plus α-interferon in 11 evaluable patients with B-cell lymphoma revealed 2 complete responses and 6 partial responses (5). The response rate of the combination was greater than either agent alone; however, idiotype-negative escape at disease progression remained a problem.

The inherent radiosensitivity of B-cell lymphoma, the relative immunological tumor specificity of anti-Id MoAb, and the antitumor response shown in human trials (3–5) suggest that radiolabeled anti-Id, in addition to unlabeled anti-Id, may provide enhanced therapeutic efficacy by killing idiotype-positive and idiotype-negative variant bystander cells. In the T-cell murine lymphoma model, $^{131}$I-labeled anti-Thy-1.1 delivered apparently curative therapy and appeared to eliminate small numbers of variant Thy-1.1-negative tumor cells (9). Human clinical trials utilizing $^{111}$In-labeled Lym-1 MoAb in B-cell lymphoma (10), $^{131}$I-T101 MoAb in T-cell lymphoma (11), and $^{111}$In-ferritin polyclonal antibodies in hepatoma (12) and Hodgkin's disease (13) have shown promising antitumor responses.

Antibodies labeled with $^{111}$In are not ideal for radioimmunotherapy because of in vivo dehalogenation, a half-life of 8 days (longer than the period of maximum tumor uptake), and γ-irradiation resulting in total body exposure and necessitating shielding (14). $^{90}$Y, a "pure" β-emitter, when chelated to antibodies offers the advantages of stability in vivo, half-life of 2.7 days, cytotoxic irradiation range of 9 mm, and no requirement of shielding (14–16). $^{111}$In-labeled MoAbs have similar kinetics and biodistribution properties as $^{90}$Y-labeled MoAbs (17) and can be utilized for concurrent radioimmunoscintigraphy and dosimetry calculations. A phase I study of $^{90}$Y-labeled polyclonal antiferritin in 5 patients with advanced Hodgkin's disease has shown complete responses in 2 evaluable patients (15). Dosimetry performed on a pelvic mass in one patient suggested a calculated dose of 2700 rads.

The radiosensitivity of B-cell lymphoma, the tumor activity of anti-Id MoAb, and the advantages of $^{90}$Y for radioimmunotherapy have led to the initiation of this pilot investigation of $^{90}$Y-anti-Id MoAb in patients with B-cell lymphoma. Results with the first patient are reported here.

Case History of Patient G. K.

This patient was a 43-year-old woman who presented in 1983 with follicular small cleaved cell lymphoma expressing surface immunoglobulin, IgMx, stage IVB, with cervical, retroperitoneal adenopathy and bone marrow involvement. In 1985, she required 3000 cGy whole abdomen irradiation for a 13-cm retroperitoneal mass and ascites. In 1986 she had a partial remission when treated with cyclophosphamide–vincristine–prednisone for progressive adenopathy and thrombocytopenia. One year later she relapsed with pulmonary nodules and hilar and mediastinal adenopathy. Subsequently, she was treated with 2 cycles of Esorubicin, 2 cycles of cyclophosphamide–doxorubicin–vincristine–prednisone, and 3 cycles of cyclophosphamide, etoposide, and dexamethasone. Because of progressive disease, she was enrolled on the $^{90}$Y-anti-Id protocol. Autologous bone marrow was harvested prior to protocol enrollment. For several months prior to protocol entry, a circulating idiotype IgM level of 10–25 μg/ml was detectable. Repeat staging at the time of enrollment confirmed persistent pulmonary, mediastinal, retroperitoneal, bone marrow, and peripheral nodal disease.

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3 The abbreviations used are: anti-Id, antidiotype; MoAb, monoclonal antibodies; SDS-PAGE, sodium dodecyl sulfate-polyacrylamide gel electrophoresis; HRP, horseradish peroxidase; HAMA, human anti-mouse antibody.
Materials and Methods

Patient Eligibility and Protocol. Patient G. K. was required to have: (a) a diagnosis of low-grade B cell non-Hodgkin’s lymphoma for which an antiidiotype MoAb had been generated; (b) serum idiotype level <50 μg/ml; (c) satisfactory chelation and labeling of the anti-id MoAb; (d) immunoreactivity of the labeled MoAb of >60%; (e) no chemotherapy for at least 3 weeks; (f) measurable disease; (g) capability of giving informed consent. The protocol design was first to document tumor targeting with 111In-anti-Id. Following successful imaging, 90Y-anti-Id was to be administered beginning at 10 mCi and escalating every 6–8 weeks with 5-mCi increments. As described in “Results and Discussion,” unlabeled anti-Id was first infused prior to the administration of radiolabeled anti-Id. Serum samples were monitored for 111In and 90Y clearance, idiotype, and anti-id levels. Radionuclide scans were performed repeatedly during 72 h. Serial fine needle aspirations were performed on a peripheral malignant lymph node to assess in vivo anti-Id binding and saturation. This protocol was approved by the Committee on Investigations Involving Human Subjects of the UCSF School of Medicine.

Antiidiotype MoAb Preparation. Anti-id MoAb was prepared in collaboration with IDEC Pharmaceuticals Corp. as described previously (5, 18). Mouse hybridoma clones were screened by enzyme-linked immunosorbent assay for anti-id specificity, i.e., the absence of cross-reactivity with other human immunoglobulins including isotype-matched controls. A murine monoclonal antiidiotype MoAb, isotype IgGl, was generated for patient G. K. against the idiotype isolated from a lymphoma biopsy and reacted comprehensively with >99% of κ-positive B-cells by two color immunofluorescence. This anti-id-producing hybridoma clone was grown in vitro using hollow fiber bioreactors (19). Crude antibody containing supernatant was purified using NH4SO4 precipitation and ion-exchange chromatography. The antibody was >90% pure IgG determined by SDS-PAGE and passed general safety, sterility, and endotoxin testing. The preparation was found to be free of adventitious viruses.

Preparation of 111In-Anti-Id and 90Y-Anti-Id. The chelation of the anti-id to 111In and 90Y was performed in collaboration with Hybritech, Inc., as described previously (16). Immunoreactivity of the chelated anti-id was in excess of 65% based on the fraction of radiolabeled antibody capable of binding to idiotype protein bound to solid phase beads. Biodistribution studies in normal CD-1 mice confirmed the stability and similarity of the behavior of the 111In and 90Y conjugates in vivo. The specific activity of the conjugates was 1.25 mCi/mg for 111In-anti-id and 30 mCi/mg for 90Y-anti-id on the day of calibration.

Administration of Unlabeled and Labeled Anti-Id. Unlabeled anti-id MoAb was diluted in 500 ml of normal saline and infused at 20 mg/h or as stated in the text. 111In-anti-id (0.4 or 4 mg) diluted in 6.5 ml aqueous buffer solution containing normal human serum albumin was administered i.v. as a bolus over 5 min. 90Y-anti-id (0.33 mg) in 2.5 ml aqueous solution containing human normal serum albumin was administered as i.v. bolus over 5 min.

Immunological Monitoring. Serum idiotype levels were assayed by an ELISA in which microtiter plates were coated with the mouse anti-id at 10 μg/ml for at least 2 h. Patient sera and idiotype protein of known concentration were serially diluted and incubated for 30 min. HRP conjugate of either goat anti-human κ or anti-human λ, as appropriate, was added as a 1:10,000 dilution. The plates were developed with o-phenylenediamine substrate with the absorbance of each well read at 490 nm on a Vmax Kinetic Microplate Reader (Molecular Devices, Palo Alto, CA). Curves were generated for each serum sample and compared to the standard curve. Mouse IgG levels were measured with microtiter plates coated with goat-anti-mouse IgG (Tago, Inc., Burlingame, CA) diluted 1:50 in carbonate buffer. Serial dilutions of patient sera and standards with 1% bovine serum albumin were incubated for 30–60 min. A HRP-conjugated goat anti-mouse IgG antibody diluted 1:5000 was added for 30 min and the plate was developed with o-phenylenediamine substrate solution, as described above. HAMA was assayed by coating plates separately with normal mouse IgG and the treatment mouse MoAb. Patient sera and a positive control were serially diluted and incubated for 1 h. Goat anti-human κ chain-HP and goat anti-human λ chain-HP in a 1:10,000 dilution each (Tago, Inc.) were added separately to detect HAMA. When using the treatment mouse MoAb, the HRP-conjugate to the light chain which is opposite to the tumor idiotype protein must be used to differentiate HAMA from serum idiotype. Substrate development and analysis were performed as above. HAMA was assayed prior to protocol enrollment and serially after each treatment and before retreatment with 90Y-anti-id. Direct and indirect immunofluorescence staining was performed as described (20). Flow cytometry was performed on the Coulter EPICS Profile Instrument (Coulter, Hialeah, FL).

Pharmacokinetic Studies. Serum samples were obtained at times specified following injection of the 111In-anti-id or 90Y-anti-id for assay of blood clearance. Samples were assayed for radioactivity by counting 1 ml of serum from each time point at which blood was drawn and counting it against a standard made from the injected material. The patient’s blood volume was taken from lean body mass nomograms and the activity in 1 ml of serum was extrapolated to the total plasma volume. Since all of the radioactivity was associated with the serum, the absolute values in the serum became the total activity in the vascular compartment at each time point. Estimates of plasma volume from lean body mass were ±10% for humans near their ideal weight. We estimate our assessment to be within these limits since our patient was at ideal body weight.

Radioimmunoscintigraphy. Following administration of 111In-anti-id, serial radionuclide scans were performed at times specified on a dedicated gamma camera (Electromed). The adequacy of tumor imaging was determined by review of imaging scans obtained with knowledge of known sites of disease by conventional radiography and physical examination.

Lymph Node Fine Needle Aspirations. Serial fine needle aspirations of a malignant peripheral lymph node were performed by multiple passes with a 22-gauge needle. Two to 10 million cells were obtained per time point and a portion was submitted for routine cytology. Flow cytometry was performed for idiotype positivity and for bound murine anti-id MoAb. For in vitro saturation studies, the amount of fluorescent-conjugated anti-mouse IgG bound was compared with and without the addition of saturating amounts of in vitro mouse anti-id. Mean intensity of fluorescence (log scale) determined by flow cytometry was used to quantitate the relative saturation.

SDS-PAGE. The patient’s serum immediately following radiolabeled MoAb infusion and the 111In-anti-id injected material were studied by standard nonreducing SDS-PAGE. Molecular weights were determined by running molecular weight standards stained with Coomassie Blue in parallel lines. Radioactivity was determined by cutting the gels into nine 1-cm slices and counting the slices in an Auto-Gamma well counter. The counts in each slice were calculated as a percentage of the total radioactivity in all slices.

Animal Biodistribution Studies. BALB/c mice were given i.v. injections in groups of 5. Some groups received the radiopharmaceutical alone while other groups received serum obtained from the patient at time 0 (immediately after injection of the radiopharmaceutical). The mice were sacrificed 4 h after injection by cervical dislocation. The organs indicated in Fig. 5 were washed in H2O, blotted dry, weighed on an analytical balance, and counted in an Auto-Gamma well counter against standards made from the injected material. The data are presented as average percentage injected dose per organ. The radioactivity in the kidney, urine, spleen, lung, and intestine came from direct measurement of the entire organ radioactivity while the total organ uptake in blood, bone, and skin were estimated from the total body weight by assuming that blood, bone, and skin constitute 7, 15, and 15%, respectively, of total body weight.

Results and Discussion

Previous studies have shown that circulating tumor idiotype interferes with effective anti-id MoAb therapy (4). Administration of 90Y MoAb in this patient was accomplished after successful tumor targeting by addressing the problem of high circulating tumor idiotype levels.
Our patient had 22 ng/ml circulating IgM tumor idiotype at the time of initial imaging (Fig. 1). She received 50 mg unlabeled antibody over 2 h prior to 0.5 mCi (0.4 mg) $^{111}$In-anti-Id. Serial idiotype levels documented a fall from 22 μg/ml to 7 μg/ml in 1 h but a rebound to 20 μg/ml at 24 h and 32 μg/ml at 48 h (Fig. 1). The rebound may have been due to a combination of factors including rapid production by the tumor, or reequilibration of idiotype from the extravascular compartment to the intravascular compartment. Serum murine anti-Id MoAb levels reached 2 μg/ml at 1 h but were undetectable at 24 and 48 h (Fig. 1). A rapid disappearance of $^{111}$In from the heart and blood pool with uptake into the liver was observed by radioimmunoscintigraphy (Fig. 24), consistent with rapid immune complex formation and clearance. In addition, 50 mg of unlabeled anti-Id administered over a 2-h period was insufficient to clear the circulating idiotype, and no tumor was imaged by 72 h (Fig. 2B). The blood disappearance curve of $^{111}$In appeared to follow a two-compartment model (Fig. 3); however, only a few time points were measured.

SDS-PAGE of the murine $^{111}$In-anti-Id injectate was compared to the patient’s serum immediately following injection (Fig. 4A). The radioactivity from the injected material migrated with a molecular weight similar to that of IgG, as expected. However, only a portion (38%) of the patient’s serum radioactivity migrated at the molecular weight of IgG with the majority migrating at a lower molecular weight, possibly reflecting degradation of immune complexes (Fig. 4A). Animal biodistribution studies of the injected material and the patient’s serum revealed deposition of 10% of the radioactivity of the injected material into the mouse liver in comparison to 48% of the serum radioactivity deposited in liver (Fig. 5A). This observation suggests that in the presence of 22 μg/ml circulating idiotype, infusion of $^{111}$In-anti-Id after 50 mg unlabeled anti-Id led to immediate idiotype-anti-Id immune complex formation as assayed by deposition in the mouse liver.

An attempt to overcome the circulating idiotype level and to target tumor successfully was undertaken by administration of large amounts of unlabeled anti-Id (>1200 mg) over 4 days (Fig. 6). The serum idiotype level became undetectable after 590 mg unlabeled antibody was administered over 30 h; however, after a 12-h period without antibody infusion, the idiotype level began to rise [h 32 to 42 (Fig. 6)]. Therefore, a continuous infusion of 600 mg unlabeled antibody was administered over a 30-h period resulting in maintenance of undetectable serum idiotype levels and attainment of a serum mouse anti-Id level of 130 μg/ml (Fig. 6). Two mCi $^{111}$In-anti-Id (4 mg) were administered as an i.v. bolus. An additional 50 mg unlabeled anti-Id were infused over 20 h after the labeled antibody; however, by the end of the infusion, serum idiotype had risen from undetectable to 20 μg/ml. Radioimmunoscintigraphy at 2 h documented increased radioactivity in the blood and heart pools (Fig. 7A) compared to that observed with 0.5 mCi $^{111}$In-anti-Id and 50 mg of unlabeled MoAb (Fig. 2A) consistent with delayed clearance. Tumor targeting was observed at 70 h in the mediastinum, pulmonary parenchyma, and retroperitoneum (Fig. 7B) where the patient was known to have disease (Fig. 7, C and D, radiographic evidence of retroperitoneal disease not shown). Palpable peripheral malignant lymph nodes and some peripheral pulmonary nodules, however, did not image. The blood clearance curve of 2 mCi $^{111}$In-anti-Id following the larger MoAb mass differed from the clearance of $^{111}$In-anti-Id with the smaller MoAb mass and had a $t_2$ prolonged to 4 h (Fig. 3).
Fig. 3. Blood disappearance curves are shown following injection of 50 mg anti-id plus 0.5 mCi $^{111}$In-anti-id, 600 mg anti-id plus 2 mCi $^{111}$In-anti-id, and 600 mg anti-id plus 10 mCi $^{90}$Y-anti-id.

Fig. 4. SDS-PAGE of 0.5 mCi (A) or 2 mCi (B) $^{111}$In-anti-id injected material to serum immediately following injection of $^{111}$In after infusion of 50 mg (A) or 600 mg (B) unlabeled anti-id clearing dose. Molecular weight (MW) markers are shown. Pt, patient.

Fig. 5. Activity biodistribution studies in 5 mice sacrificed 4 h following injection of the 0.5 mCi (A) or 2 mCi (B) $^{111}$In-anti-id injected material compared to patient's (Pt) serum immediately following $^{111}$In injection after a 50 mg (A) or 600 mg (B) clearing dose of unlabeled anti-id. Standard deviations for blood and liver determinations in A and B were 3–24% of the mean value.

Fig. 6. Infusion of unlabeled anti-id i.v. in amounts (mg total) and at rates (mg/h) shown. Interruptions in the infusions are depicted by bars. $^{111}$In (2 mCi) administration time (D), and serum idiotype and antiidiotype levels are shown. Arrows, time of fine needle aspiration.

Fig. 8, 10 mCi $^{90}$Y-anti-id (0.33) were administered as an i.v. bolus followed by 500 mg unlabeled anti-id infused over 40 h. Circulating serum idiotype was suppressed as long as the infusion was administered at 22 mg/h but rose slowly when the infusion was decreased to 10 mg/h. The resulting blood disappearance curve of $^{90}$Y-anti-id revealed a $t_\text{half}$ prolonged to 7.2 h (Fig. 3), possibly reflecting the additional 500 mg unlabeled antibody administered after the labeled antibody. The idiotype...
Fig. 7. Radioimmunoscintigraphy was performed at 2 h (A) and 70 h (B) following 2 mCi \(^{111}\)In-anti-Id after 600 mg unlabeled anti-Id. Liver (L) uptake was observed. Tumor (T) was imaged. C \(\times\) R, posterior-anterior (C) and lateral (D) views document pulmonary nodules.

Fig. 8. Infusion of unlabeled anti-Id i.v. in amounts (mg total) and at rates (mg/hr) shown. Hours are continuous with those graphed in Fig. 6. Interruptions in the infusion are shown by bars. \(^{90}\)Y (10 mCi) administration time (\(\bullet\)), and serum idiotype and antiidiotype levels are shown. Arrows, time of fine needle aspiration.

level was prevented from rising for 40 h (Fig. 8) unlike the rise in idiotype level observed at 18 h after the 2-mCi \(^{111}\)In dose (Fig. 6). This greater amount of unlabeled antibody administered following the radiolabeled antibody may serve to bind additional free idiotype, which may enter the vascular compartment, resulting in prolongation of the blood clearance of the radiolabeled antibody.

Serial fine needle aspirations of a left femoral malignant lymph node were performed before \(^{111}\)In imaging and before and after \(^{90}\)Y therapy as shown by arrows in Figs. 6 and 8. All IgM \(\kappa\)-positive B-cells were idiotype positive in the 3 aspirations confirming persistence of idiotype-positive lymphoma with no detectable idiotype-negative component (Table 1). Immunofluorescence analysis and flow cytometry were performed to determine \textit{in vivo} binding of anti-Id. Addition of mouse anti-Id added \textit{in vitro} allowed a determination of the maximum percentage of idiotype-positive cells that could be saturated, as shown in Table 1. Prior to the injection of \(^{111}\)In-anti-Id and following 1190 mg unlabeled antibody over 70 h, the serum murine anti-Id level reached 130 \(\mu\)g/ml and 71% idiotype-positive cells had anti-Id bound \textit{in vivo}. However, the mean intensity of fluorescence increased from channel 54 to channel 129 (log scale) by additional anti-Id added \textit{in vitro}. Prior to the infusion of \(^{90}\)Y-anti-Id and 72 h following discontinuation of unlabeled anti-Id (Fig. 8), the percentage of idiotype-positive cells with bound anti-Id fell to 10% and increased to 30% 48 h later after 900 mg unlabeled antibody had been administered. At each time point, however, \textit{in vivo} bound anti-Id could be

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<tr>
<th>Time of</th>
<th>Serum mouse IgG ((\mu)g/ml)</th>
<th>% Id* Cells bearing anti-Id</th>
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<td>lymph node aspiration</td>
<td>(\mu)g/ml</td>
<td>% Id*</td>
<td>in vivo</td>
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<td>130</td>
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<td>54</td>
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<td>24-h Post-(\gamma)Y, 218 h</td>
<td>5</td>
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* By immunofluorescence.
* MIF (mean intensity of fluorescence) by channel number.
detected but was not saturating as determined by further administration of antibody in vitro (Table 1). Although anti-Id was documented bound in vivo on cells from a malignant left femoral node, the node did not target by radioimmunoscinogra phy. Imaging may underestimate antibody penetration of tumor secondary to factors of tumor size, vascularity, or antigenic concentration. The relative contribution of these and other factors will require further investigation.

Follow-up evaluation of the patient revealed minimal toxicity. Mild thrombocytopenia (83,000; normal, >140,000) occurred at 6 weeks and resolved by 8 weeks. Repeat staging at 3.5 weeks revealed partial tumor regression in the right lower lobe (Fig. 9) which may reflect either the effect of 10 mCi 90Y or the effect of >2300 mg unlabeled anti-Id administered over 10 days with a peak serum anti-Id level of 130 µg/ml. By 8 weeks after therapy, progressive disease developed in association with idiotype levels of 150–200 µg/ml. She received combination chemotherapy in an attempt to control her disease. Should her idiotype level be controlled, further dose increments of 90Y-anti-Id may be administered.

In summary, we have investigated the kinetics of circulating tumor idiotype in response to the infusion of anti-Id MoAb in a patient with B-cell lymphoma. As a result of this investigation, we overcame the problem of high circulating idiotype and successfully imaged tumor with 111In-anti-Id MoAb. This patient was not an ideal subject because of high circulating idiotype levels and a high secretory rate of tumor idiotype. Future patients with B-cell lymphoma selected as candidates for 90Y-anti-Id therapy should have low or undetectable idiotype levels.

In conclusion, we report the first case of 90Y-labeled MoAb administered for human radioimmunotherapy. We successfully administered 10 mCi 90Y-labeled antiidiotype MoAb to a patient with B-cell lymphoma whose tumor imaged successfully. Mild thrombocytopenia was observed. More than 2 g of unlabeled anti-Id MoAb were required to clear the circulating IgM idiotype prior to administration of the 90Y. Transient partial regression of disease was observed. Serial fine needle aspirations of a malignant lymph node documented in vivo anti-Id penetration that was nonsaturating. Further investigation of 90Y-labeled anti-Id MoAb for therapy of B-cell lymphoma is warranted based upon the radiosensitivity of B-cell lymphoma, the antitumor activity of anti-Id alone, and the safe administration of the radiopharmaceutical in this patient.

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Note Added in Proof

A second patient with bulky B-cell lymphoma who had no detectable circulating idiotype has been treated with 90Y-anti-Id resulting in at least a partial response with minimal residual radiographic abnormalities.

References

RADIOIMMUNOTHERAPY OF B-CELL LYMPHOMA

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