Radioimmunotherapy of Patients with Cutaneous T-Cell Lymphoma Using an Iodine-131-Labeled Monoclonal Antibody: Analysis of Retreatment Following Plasmapheresis

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Radioimmunotherapy retreatment of patients receiving radiolabeled murine monoclonal antibodies is difficult because of the human antimurine antibody (HAMA) formation. Retreatment therapy was initiated in three patients at the time of disease progression using a radioiodinated monoclonal antibody (T101). The clinical protocol consisted of a two day plasma exchange (4–6 L) to reduce HAMA titers. Immunoimaging was performed with 5 mCi ^{131}I-T101 (10 mg). Gamma scintillation images were obtained 18 hr postinfusion, and radiation dosimetry estimates were performed. At 24 hr postinfusion, each patient received a 100-mCi ^{131}I-T101 (10 mg) therapy dose. Results obtained after plasmapheresis showed a significant reduction, ranging from 28%–61%, in HAMA titers. Blood clearances were markedly different between initial therapy and retreatment therapy for patient with high HAMA titers, reflecting immune complex formation. Two patients responded to retreatment therapy with responses lasting 1 to 2 mo. Minimal acute and no chronic toxicities were observed during the retreatment protocol.

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Immunotherapy with radioiodinated polyclonal antibodies was initiated by Beierwaltes (*1*), who treated a patient having malignant melanoma with ^{131}I-labeled polyclonal antibodies. Since then, radioimmunotherapy with radiolabeled monoclonal and polyclonal antibodies have been reported in patients with solid tumors and hematologic malignancies (*2–7*). Our laboratory has conducted initial immunodiagnostic and immunotherapy trials using ^{131}I-T101 in six patients having cutaneous T-cell lymphoma (CTCL) (*8*). T101, an IgG_2a murine monoclonal antibody (MoAb), recognizes a 65,000-D antigen present on both normal and neoplastic T-cells (*9–11*). All patients demonstrated a clinical response lasting from a few weeks to 3 mo after a single immunotherapy dose. In addition, all patients developed human antimurine antibodies (HAMA) following initial treatment (*8*). Each patient received plasmapheresis prior to retreatment in an attempt to reduce HAMA levels. This report summarizes the retreatment of three patients at the time of disease progression, including the utility of plasmapheresis and the effect of residual HAMA on antibody clearance rates and subsequent response to retreatment.

MATERIALS AND METHODS

Antibody Radiolabeling

Sterile and pyrogen-free monoclonal antibody T101 (Hybritech, Inc., San Diego, CA), an IgG_2a isotype, was used at a concentration of 3 mg/ml. Radiolabeling was performed using sterile conditions in a shielded laminar flow hood. All glass-

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ware and tubing were sterile and pyrogen-free. Monoclonal antibody radioiodination (I/MoAb ratio = 1) and subsequent purification were achieved as previously described (*8*). Whenever appropriate, unlabeled T101 was added to bring the total quantity of MoAb to approximately 10 mg.

Quality Control Procedures

Free iodide levels of radiolabeled MoAb preparations were measured using instant thin layer chromatography-silica gel (Gelman Scientific, Ann Arbor, MI) and 0.9% NaCl (*12*). In addition, size exclusion high performance liquid chromatography was utilized to detect radiolabeled MoAb breakdown products. Only radioiodinated monoclonal antibody preparations having a radiochemical purity > 95% were utilized for patient infusion.

Radioimmunoreactivity, at infinite antigen excess, was measured using the method outlined by Lindmo et al. (*13*). A constant amount of radioiodinated MoAb (0.5–1 ng) was added to increasing concentrations of live cells (2–10 million/ml) bearing specific antigen (T8402). The suspension was rotated for 120 min at room temperature, centrifuged, and washed three times with PBS. After final centrifugation, the cells were counted for radioactivity using a NaI(Tl) gamma scintillation detector and multichannel analyzer. Nonspecific binding was measured by adding an excess of unlabeled T101 to live cells. After a 120-min incubation, the suspension was centrifuged and washed three times with PBS. After the final wash, radioiodinated T101 was added and cell binding determined as mentioned above.

For each specific concentration, four replicate samples were analyzed and statistical analysis performed. The data were graphically expressed with inverse cell binding on the ordinate and inverse cell concentration on the abscissa. The immunoreactive fraction, at infinite antigen excess, was determined by linear extrapolation (linear regression analysis) to the ordinate.

Biological quality control procedures were performed on the final radiolabeled MoAb preparation. Fluid thioglycollate and soy-casein digest medium were used to test for sterility following standard USP procedures. Pyrogenicity testing was performed using limulus amebocyte lysate (Mallinckrodt, St. Louis, MO).

Patients Retreatment Protocol

Radioimmunotherapy retreatment was initiated in three patients between 3 and 4 mo after initial immunotherapy treatment. Minor or partial clinical responses were measured in these patients lasting 2–3 mo after initial radioimmunotherapy treatment (*8*). Retreatment was given at the time of disease progression. All patients treated under the initial protocol developed human anti-murine antibodies (HAMA) which were detected within 14 days after initial treatment (*8*). In order to reduce HAMA titers, each patient had a 4–6-l plasma exchange in a 48-hr period prior to retreatment. Replacement fluids consisted of Plasmanate (Armour Corp., Kankakee, IL) and 0.9% NaCl. Blood samples were collected prior to and after pheresis. Patients received Lugol's solution prior to and up to 14 days after infusions.

Radioimmunodiagnostic Studies

Radioimmunodiagnostic studies were performed by administering approximately 5 mCi ^{131}I-T101 (10 mg) by slow infusion over a 30–120-min time period through HSA pretreated tubing. Multiple anterior and posterior images (5 min per image) were obtained at 18 hr postinfusion with a large-field-of-view scintillation camera with a medium energy collimator interfaced to a computer system. Blood samples were collected at 10, 30, 60, and 120 min and also at 18 hr postinfusion from two patients and at 10, 30, 60, 120, min and also at 4, 8, and 18 hr for Patient 3. Whole-body retention of radioactivity was measured initially and 18 hr after infusion using a gamma scintillation detector.

Radioimmunotherapy Studies

At 24 hr after initial infusion, patients received ~100 mCi ^{131}I-T101 (10 mg) by slow infusion over 30–120 min as described previously. Patients were isolated until whole-body activity levels reached 30 mCi, at which time, multiple anterior and posterior gamma images were obtained as described. Blood samples were obtained at 10, 30, 60, and 120 min after infusion and daily thereafter for 7 days. Whole-body radioactivity levels were measured daily as described previously. Biopsy of skin lesions and skin nonlesions were obtained 24 hr after infusion.

Clinical Effects and Toxicity

Anti-tumor responses were classified according to the World Health Organization criteria. Under this classification, a partial response was defined as a reduction in the sum or the size of the individual lesions of at least 50%. A minor response was defined as a decrease in lesion sum or size of <50%. Cross-sectional diameters of lymph nodes and skin lesions, including photographs, were taken following immunotherapy retreatment. Time of progression was measured from the date of patient retreatment. Complete blood counts, electrolytes, renal function, hepatic function, and urinalysis were measured weekly while patients were on study.

Radiation Dosimetry

Radiation doses and skin lesion absorbed doses were calculated by procedures similar to those used in initial immunotherapy treatments (*8*). Microdosimetric considerations were not addressed in this work.

Sample Analysis

Blood samples from patient infusions were centrifuged and plasma aliquots removed and counted for radioactivity using a NaI(Tl) well detector interfaced to a multichannel analyzer. Tissue biopsy samples were washed to remove any excess blood, weighed, and counted for radioactivity as described above. A radioactive standard was counted in order to correct relative counts to absolute counts (μCi/gm).

In order to assess the effect of plasmapheresis on HAMA titers, pre- and post-plasmapheresis plasma samples (0.5 ml) were incubated at room temperature for 30 min with known amounts of radioiodinated T101 (2.5–25.6 μg). Radiochemical analysis of samples was assessed using size exclusion high performance liquid chromatography (HPLC) consisting of a Rainin isocractic HPLC system (Rainin Instrument Co., Woburn, MA) and a gamma scintillation detector interfaced to a multichannel analyzer. Chromatographic separation of radiolabeled immune complex and radiolabeled T101 was accomplished using a 300 × 7.5-mm Bio-Sil TSK-250 molecular weight sizing column (Bio-Rad Labs, Richmond, CA). Samples were eluted in phosphate buffered saline (pH 7.0) at a flow rate of 1.5 ml/min. Eluted radioactivity was monitored with a multichannel analyzer using multichannel scaling (one

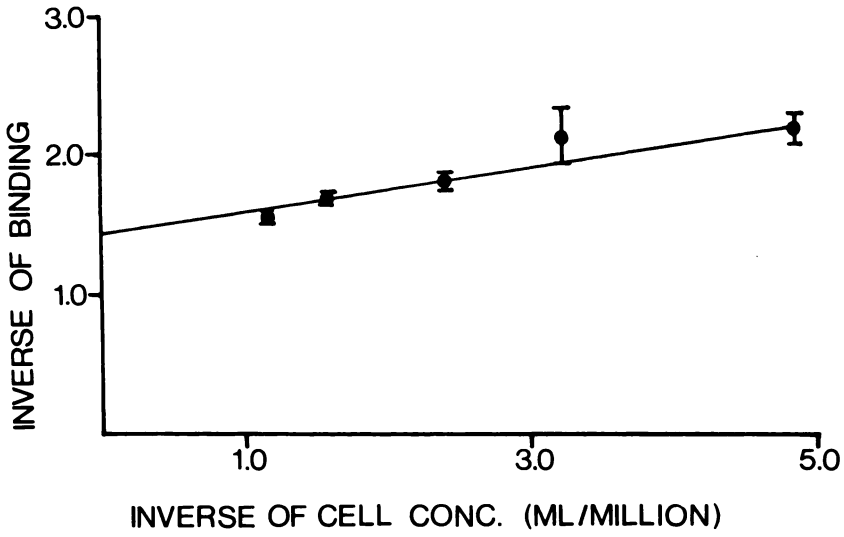

FIGURE 1
Radioimmunoreactivity plot of ^{131}I-T101. Each point is the mean of four replicate samples with standard deviation bars.

second interval). Radioactivity associated with each specific radiochemical component was measured by calculating specific areas under generated radiometric elution profiles. The results were expressed as μg T101 complexed per ml of patient plasma. The percent radioactivity recovered was determined by comparing the total eluted radioactivity to the initial radioactivity applied.

RESULTS

All three patients received between 5.2 and 5.9 mCi ^{131}I-T101 for radioimmunoimaging and between 98.3 and 105.5 mCi ^{131}I-T101 for immunotherapy retreatment. Greater than 95% of the radioactivity was associated with the radioiodinated monoclonal antibody with <2% free iodide. The immunoreactive fraction of the radiolabeled MoAb was greater than 0.5 throughout the study. A typical radioimmunoreactivity plot of ^{131}I-T101 is shown in Figure 1. For this particular radiolabeled MoAb preparation, the radioimmunoreactive fraction, at infinite antigen excess, was 0.70.

HPLC radiometric elution profiles of pre- and post-plasmapheresis plasma samples for patient 2 are shown in Figure 2. The elution profiles clearly distinguished between radioiodinated immune complex (peak a), radioiodinated T101 (peak c), and free iodide (peak d). In addition, an intermediate molecular weight radiolabeled component was also visualized (peak b). A reduction in radiolabeled immune complex formation was observed for Patient 2 following plasmapheresis (Fig. 2B). HPLC elution profiles of pre- (A and C) and post-plasmapheresis (B and D) plasma samples from patient 1 are shown in Figure 3. Elution profiles 3A and 3B were obtained using 2.5 μg T101 and elution profiles 3C and 3D were obtained using 25.6 μg T101. With a lower concentration of T101, only radioiodinated immune complex formation was observed (3A and 3B), even following plasmapheresis, indicating high HAMA plasma titers. This peak corresponds to peak a of Figure 2. With higher levels of T101 (Fig. 3C and Fig. 3D), all four radioiodinated components were visualized. For each HPLC elution run, > 90% of the initial injected radioactivity was recovered.

The effect of plasmapheresis on HAMA titers, as expressed in in vitro radioimmune complex formation, is shown in Table 1. High HAMA levels were measured for patient 1 (33.9 μg T101 complexed/ml plasma), and lower levels were observed for Patients 2 and 3 (2.6 and 1.6 μg T101 complexed/ml plasma, respectively), prior to plasmapheresis. Significant reductions in HAMA levels, ranging from 28%–61%, occurred as a result of plasmapheresis. Even with this reduction, HAMA levels remained high for Patient 1 (13.3 μg T101 complexed/ml plasma).

Table 2 compares plasma clearances of the retreated patients with the plasma clearances of these patients following initial therapy. Faster plasma clearances were observed for all three patients following radioimmunoimaging when compared to initial radioimmunodiagnostic studies. The most rapid clearance was observed for Patient 1, who also had the highest HAMA levels and the slowest plasma clearance was observed for Patient 3, whose HAMA levels were the lowest. Following radioimmunotherapy retreatment, plasma clearances of radioiodinated T101 were significantly faster for Patients 1 and 2 and comparable to the initial radioimmunotherapy procedure for Patient 3.

The radioactivity in lesion and nonlesion skin biopsies obtained 24 hr after radioimmunotherapy are shown in Table 3. Higher activities were measured in skin lesions of Patients 2 and 3, resulting in lesion/nonlesion ratios of 5.1 and 3.8, respectively. For Patient 1, low lesion radioactivity was measured resulting in a low lesion/nonlesion ratio of 1.1.

Patient response data, including acute and chronic toxicities, and calculated absorbed radiation doses fol-

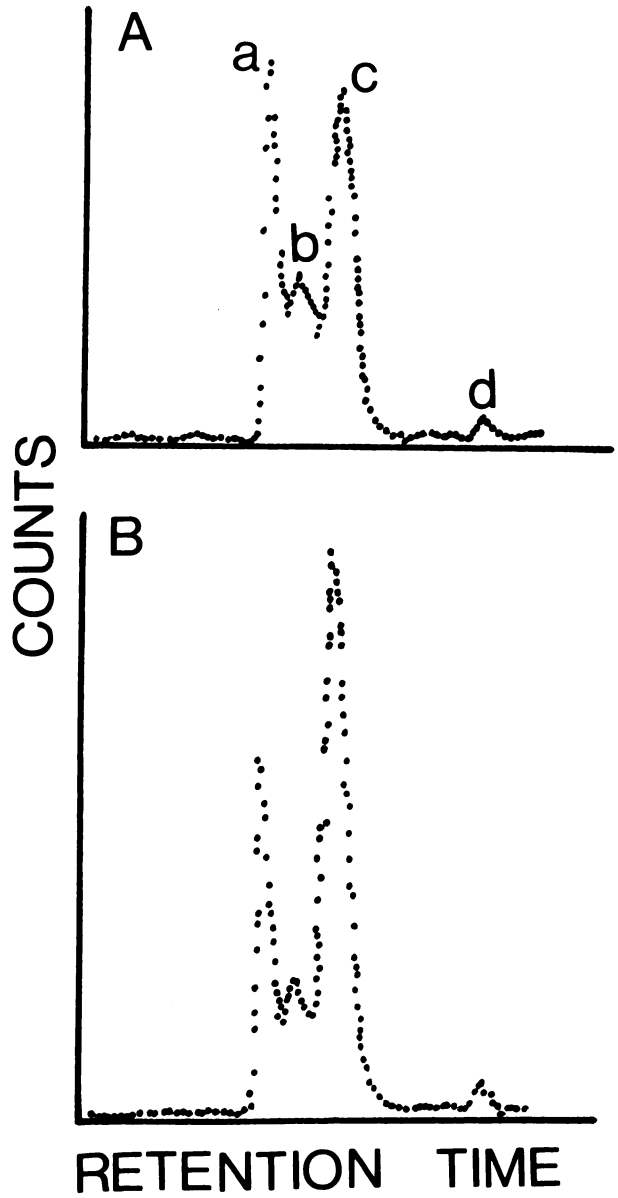

FIGURE 2
High performance liquid chromatography radiometric elution profiles of pre- (A) and post-plasmapheresis (B) plasma samples for Patient 2: a = radiolabeled immune complex; b = intermediate molecular weight radiolabeled component, c = ^{131}I-T101; d = free radioiodine.

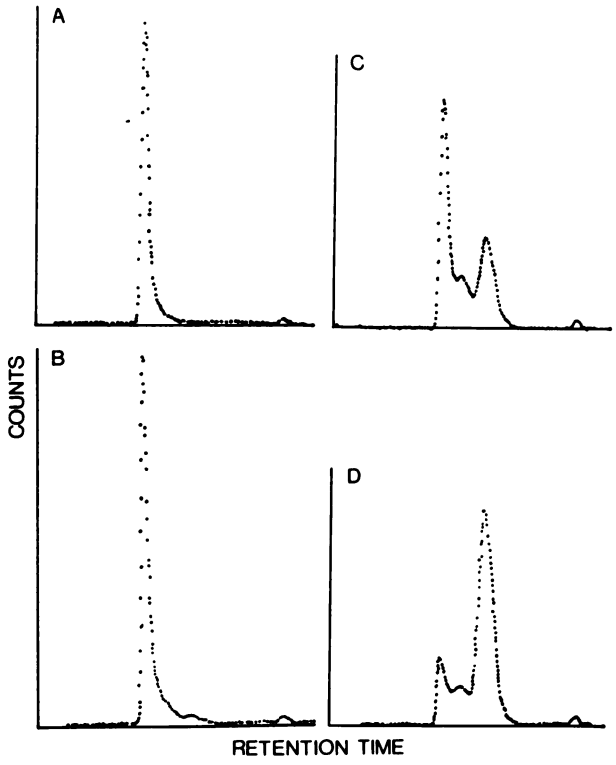

FIGURE 3
High performance liquid chromatography radiometric elution profiles of pre- (A and C) and post-plasmapheresis (B and D) plasma samples for Patient 1. Elution profiles A and B were obtained using 2.5 μg of monoclonal antibody T101 and elution profiles C and D were obtained using 25.6 μg T101.

lowing radioimmunotherapy retreatment have been published (*8*). No response was observed for Patient 1. For Patient 2, a partial response was observed lasting ~1 mo. A minor response, lasting ~2 mo, was observed for Patient 3. Acute toxicities included fever and pruritis. These side effects were controlled with acetaminophen and diphenhydramine hydrochloride. Myelosuppression was not witnessed, however, Patient 2 received alternative therapy at the time of disease progression with resultant pancytopenia.

The lymphocyte counts prior to and following radioimmunotherapy retreatment are shown in Table 4. In two out of three patients, lymphocyte numbers did not decrease as a result of retreatment. A 63% reduction in lymphocyte counts was observed for Patient 2 following retreatment. This response was transient, as lymphocyte numbers returned to pretreatment levels one week later.

Representative pictures demonstrating a response to therapy retreatment in Patient 2 are shown in Figure 4. The pictures were taken just prior to (Fig. 4A) and 1 mo after (Fig. 4B) radioimmunotherapy retreatment with ^{131}I-T101.

An anterior whole-body gamma scintillation image,

TABLE 1
Effect of Plasmapheresis on In Vitro Immune Complex Formation with ^{131}I-T101

Patient	Plasma sample	^{131}I-T101 Complexed (μg/ml plasma)	% Reduction
1	Pre-plasmapheresis	33.9	-
	Post-plasmapheresis	13.3	61
2	Pre-plasmapheresis	2.6	-
	Post-plasmapheresis	1.9	28
3	Pre-plasmapheresis	1.6	-
	Post-plasmapheresis	0.7	56

TABLE 2
^{131}I-T101 Monoclonal Antibody Plasma Clearances from Initial and Retreatment Studies

Patient	Study	Plasma disappearance time (hr)*
1	Diagnostic study	16.0
	Diagnostic retreat	0.1
	Therapy study	17.0
	Therapy retreat	0.2
2	Diagnostic study	23.0
	Diagnostic retreat	5.8
	Therapy study	28.5
	Therapy retreat	18.5
3	Diagnostic study	15.5
	Diagnostic retreat	11.5
	Therapy study	20.0
	Therapy retreat	20.0

* Biological half-life.

obtained 4 days after therapy retreatment of Patient 3, is shown in Figure 5. Inguinal nodes were readily visualized. In addition, thyroid, stomach, and bladder activity were visualized indicating in vivo dehalogenation. For Patient 1, no nodal and lesion activities were visualized on gamma scintillation images obtained after therapy retreatment.

DISCUSSION

During the initial radioimmunotherapy trials, all six patients treated with radioiodinated T101 had clinical responses lasting up to 3 mo. Minor acute toxicities, including fever and pruritis, were observed. Myelosuppression was witnessed in patients receiving high doses of ^{131}I-T101 (150 mCi). However, blood counts returned to normal within 8–10 wk post-therapy. Human antimurine antibodies were detected at 14 days post-therapy for all patients treated (*8*).

Radioimmunotherapy retreatment was initiated in three patients. Clinical responses were measured in two of three patients, lasting 1 and 2 mo, respectively. Minor acute toxicities were observed during retreatment and myelosuppression was not witnessed.

TABLE 3
Radioactivity of Skin Biopsy Samples Obtained 24 hr After ^{131}I-T101 Radioimmunotherapy Infusion

Patient	Activity in biopsy samples (μCi/g)		Ratio
	Lesion	Nonlesion	Lesion/nonlesion
1	0.52	0.43	1.2
2	3.75	0.73	5.1
3	2.04	0.54	3.8

TABLE 4
Lymphocyte Counts in Patients Prior to and Following Radioimmunotherapy Retreatment

Patient	Lymphocytes/ml blood		
	Pre-retreatment	Post retreatment	
		Week 1–2	Week 3–4
1	1485	1407	1344
2	540	200	657
3	1350	1136	1020

No clinical response was measured in patient 1, which may be attributable to high HAMA titers. Post-plasmapheresis plasma samples from Patient 1 (Table 1), were able to complex 13.3 μg ^{131}I-T101/ml plasma. If these data were extrapolated to a standard man (80 kg) with a plasma volume of 3,040 ml, ~40 mg of radioiodinated T101 was complexed. Since only 20 mg of ^{131}I-T101 was administered within a 24-hr time period (immunodiagnostic and immunotherapy study), it would appear that most, if not all, of the radiolabeled T101 was complexed and then rapidly removed from circulation. This was confirmed by comparing plasma disappearance curves and also skin lesion activity from Patient 1. Rapid plasma clearances were measured during retreatment (Table 2) and, in addition, a low skin lesion/nonlesion ratio of 1.1 was calculated for Patient 1.

Applying the same in vivo assumptions, as mentioned above, to Patients 2 and 3 would result in the complexing of 5.7 and 2.1 mg ^{131}I-T101, respectively. This would indicate faster blood clearances for the initial immunodiagnostic retreatment study (10 mg ^{131}I-T101 administered) and somewhat similar blood clearances for the immunotherapy retreatment study when compared to initial studies. In fact, faster plasma clearances were observed during the immunodiagnostic retreatment study for Patients 2 and 3. During immunotherapy retreatment, plasma clearances were somewhat faster for Patient 2 and similar for Patient 3 to initial immunotherapy studies indicating minor in vivo immune complex formation. Higher skin lesion/nonlesion ratios were also calculated for Patients 2 and 3.

HAMA titers, as expressed in in vitro immune complex formation, was effectively reduced from 28%–61% by plasmapheresis (Table 1). Previous data indicate that the most significant reduction may be in the IgM component (*8*). All radioimmunotherapy procedures were initiated within 48 hr after plasmapheresis and no additional HAMA titers were measured prior to immunotherapy.

Inguinal and axillary nodes, spleen, and some cutaneous lesions were visualized on gamma scintillation images following immunotherapy retreatment. The majority of cutaneous lesions were not visualized, however, increased radioactivity was measured in these lesions.

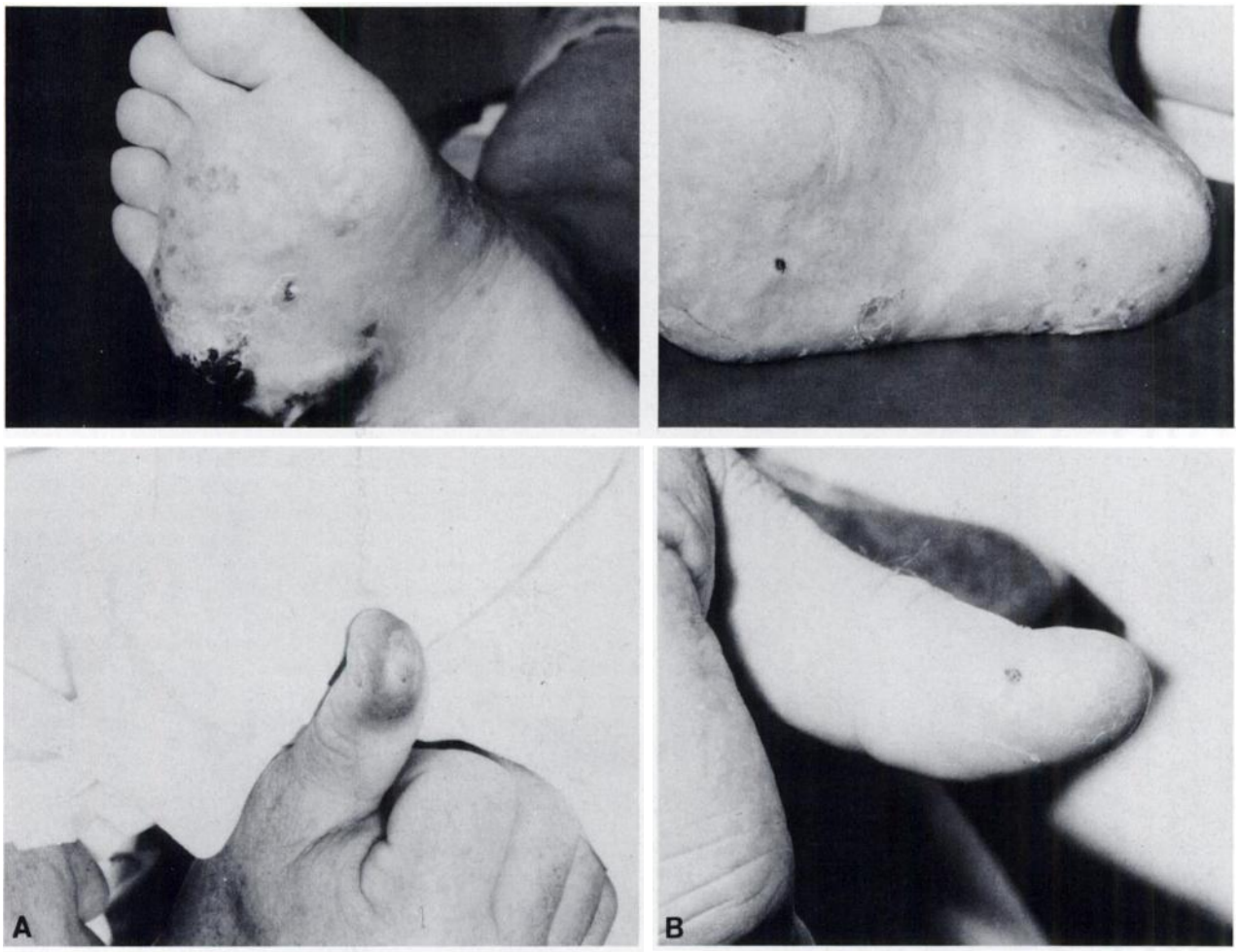

FIGURE 4
Pictures taken prior to therapy retreatment (A) and 1 mo after ^{131}I-T101 retreatment (B) of Patient 2.

Thyroid, gastrointestinal, and bladder activity were also visualized indicating in vivo dehalogenation, which is a common phenomena for radioiodinated monoclonal antibodies.

The tumor killing effects of radiolabeled antibodies have been extensively debated (*14–16*). Low human tumor localization of radiolabeled monoclonal antibodies have resulted in relatively low tumor radiation doses (*14*). In our immunotherapy treatment (*8*) and retreatment study, clinical responses were measured, lasting up to 3 mo, even though calculated radiation doses to lesions were low. Preliminary data (*17*) in animal models suggest that radiation from radiolabeled monoclonal antibodies is more effective in retarding tumor growth than a nominally equivalent dose from external beam radiation. Microdosimetry was not performed in this study. However, in two of the three patients retreated, lymphocyte numbers did not decrease as a result of ^{131}I-T101 administration. A transient reduction on lymphocyte counts was observed for Patient 2. This patient also experienced a partial response to retreatment, lasting ~1 mo. Flow cytometric analysis of peripheral blood obtained 24 hr after initial radioimmunodiagnostic procedures suggested antigenic modulation of T-cells which occurred as a result of internalization of the T65 antigen. At 7 days postinfusion, reexpression of the T65 antigen was observed. Internalization of radioiodinated T101 has been reported previously (*18*) and may result in enhanced killing of modulated cells. This phenomena is described in detail in our previously published paper (*8*).

A major problem in immunotherapy retreatment is the development of HAMA in patients following initial treatment with murine monoclonal antibodies. With the HPLC procedures outlined in this study, patient HAMA levels were quantified by molecular size separation of radioiodinated immune complex (peak a in Fig. 2) from radioiodinated T101 and intermediate molecular weight components (peak c and b, respectively). Overlapping of the various radioiodinated fractions presents some difficulties in quantification; however, these problems have been addressed previously (*19*).

Although plasmapheresis is effective in reducing pa-

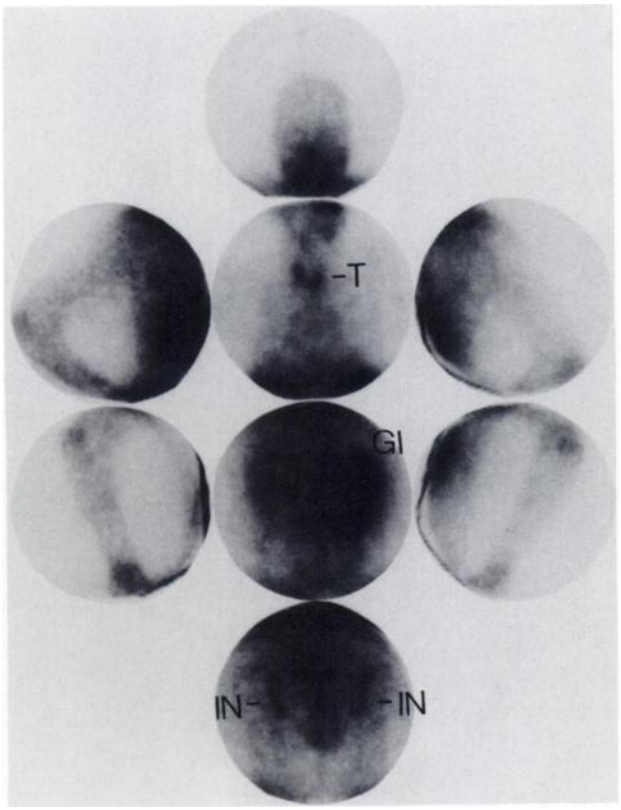

FIGURE 5
Anterior gamma scintillation images of Patient 3 obtained 4 days after therapy retreatment with ^{131}I-T101 monoclonal antibody (98.3 mCi). Note localization in inguinal nodes (IN), thyroid (T), and gastrointestinal tract (GI).

tient titers, elevated levels of HAMA were still detected in one of three patients retreated in this study. It is possible that more aggressive plasmapheresis and other measures including tolerance induction, immunosuppression, and the use of human monoclonal antibodies may reduce the problem of HAMA response.

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REFERENCES

1. Beierwaltes WH. Radioiodine-labeled compounds previously or currently used for tumor localization with radioactive agents. IAEA Advisory Group on Tumor Localization with Radioactive Agents, Vienna, IAEA-MG-50/2, 1974: 47–56.
2. Ettinger DS, Order SE, Wharam MD, et al. Phase I-II study of isotopic immunoglobulin therapy for primary liver cancer. *Cancer Treat Rep* 1982; 66:289–297.
3. Lenhard RE Jr, Order SE, Spunberg JJ, et al. Isotopic immunoglobulin: a new systemic therapy for advanced hodgkin's disease. *J Clin Oncol* 1985; 3:1296–1300.
4. Carrasquillo JA, Krohn KA, Beaumier P, et al. Diagnosis of and therapy for solid tumors with radiolabeled antibodies and immune fragments. *Canc Treat Rep* 1984; 68:317–378.
5. DeNardo SJ, DeNardo GL, O'Grady LF, et al. Radioimmunotherapy of patients with B-cell lymphoma using I-131 Lym-1 Mab [Abstract]. *J Nucl Med* 1986; 27:903.
6. Spies SM, Zimmer AM, Spies WG, et al. Initial experience with radioimmunodetection and radioimmunotherapy of cutaneous T-cell lymphoma using murine monoclonal antibodies [Abstract]. *J Nucl Med* 1986; 27:903.
7. Epenetos AA. Clinical results with regional antibody guided irradiation. *Br J Cancer* 1985; 52:641–669.
8. Rosen ST, Zimmer AM, Goldman-Leikin RE, et al. Radioimmunodetection and radioimmunotherapy of cutaneous T-cell lymphomas utilizing and ^{131}I-labeled monoclonal antibody. *J Clin Oncol* 1987; 5:562–573.
9. Dillman RO, Shawler DL, Dillman JB, et al. Therapy of chronic lymphocytic leukemia and cutaneous T-cell lymphoma with T101 monoclonal antibody. *J Clin Oncol* 1984; 2:881–891.
10. Wormsley SB, Collins ML, Royston I. Comparative density of the human T-cell antigen T65 on normal peripheral blood T-cells and chronic lymphocytic leukemia cells. *Blood* 1981; 57:657–662.
11. Foon KA, Schroff RW, Bunn PA. Monoclonal antibody therapy for patients with leukemia and lymphoma. In: Morgan AC, Jr, Foon KA, ed. *Monoclonal antibody therapy of human cancer.* Hingham, MA: Martinus Niejhoff, 1985:85–101.
12. Kazikiewicz JM, Zimmer AM, Spies SM, et al. Rapid miniaturized chromatography procedures for iodinated monoclonal antibodies: comparison to gel exclusion chromatography. *J Nucl Med Technol* 1987; 15:129–132.
13. Lindmo T, Boven E, Cuttitta F, et al. Determination of immunoreactive fraction of radiolabeled monoclonal antibodies by linear extrapolation to binding at infinite antigen excess. *J Immunol Methods* 1984; 72:77–78.
14. Vaughn ATM, Bradwell AR, Dykes PW, et al. Illusions of tumour killing using radiolabeled antibodies. *Lancet* 1986; ii:1492–1493.
15. Begent RHJ, Ledermann JA, Searle F, et al. Letter to the editor. *Lancet* 1986; iii:580.
16. Vaughn A, Chapman C, Dykes PW, et al. Antibody-targeted therapy of cancer. *Lancet* 1986; 3:860.
17. Neacy WP, Wessels BW, Bradley E, et al. Comparison of radioimmunotherapy (RIT) and 4 MV external beam radiotherapy of human tumor xenografts in athymic mice [Abstract]. *J Nucl Med* 1986; 27:902–903.
18. Boven E, Lindmo T, Mitchell JB, et al. Selective cytotoxicity of ^{125}I-labeled monoclonal antibody T101 in human malignant T cell lines. *Blood* 1986; 67:429–435.
19. Snyder LR, Kirkland JJ. Quantitative and trace analysis. In: *Introduction to modern liquid chromatography.* New York: John H Wiley and Sons; 1979:542–570.