Marrow Toxicity and Radiation Absorbed Dose Estimates from Rhenium-186-Labeled Monoclonal Antibody

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Estimates of radiation absorbed dose to the red marrow (RM) would be valuable in treatment planning for radioimmunotherapy if they could show a correlation with clinical toxicity. In this study, a correlation analysis was performed to determine whether estimates of radiation absorbed dose to the bone marrow could accurately predict marrow toxicity in patients who had received ^{186}Re-labeled monoclonal antibody. **Methods:** White blood cell and platelet count data from 25 patients who received ^{186}Re-NR-LU-10 during Phase I radioimmunotherapy trials were analyzed, and the toxicity grade, the fraction of the baseline counts at the nadir (percentage baseline) and the actual nadir were used as the indicators of marrow toxicity. Toxicity was correlated with various predictors of toxicity. These predictors included the absorbed dose to RM, the absorbed dose to whole body (WB) and the total radioactivity administered. **Results:** Percentage baseline and grade of white blood cells and platelets all showed a moderate correlation with absorbed dose and radioactivity administered (normalized for body size). The percentage baseline platelet count was the indicator of toxicity that achieved the highest correlation with the various predictors of toxicity ($r = 0.73$–0.79). The estimated RM absorbed dose was not a better predictor of toxicity than either the WB dose or the total radioactivity administered. There was substantial variation in the blood count response of the patients who were administered similar radioactivity doses and who had similar absorbed dose estimates. **Conclusion:** Although there was a moderately good correlation of toxicity with dose, the value of the dose estimates in predicting toxicity is limited by the patient-to-patient variability in response to internally administered radioactivity. In this analysis of patients receiving ^{186}Re-labeled monoclonal antibody, a moderate correlation of toxicity with dose was observed but marrow dose was of limited use in predicting toxicity for individual patients.

Key Words: radioimmunotherapy; radiation absorbed dose; myelotoxicity; rhenium-186; monoclonal antibody

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Estimates of the radiation absorbed dose to normal organs would be valuable in the management of patients undergoing radioimmunotherapy (RIT) if the dose estimates could be correlated with radiation toxicity. In Phase I RIT dose escalation trials, bone marrow was the first organ to demonstrate toxicity clinically. This occurred in trials with ^{131}I, ^{90}Y and ^{177}Lu and in our own trials with ^{186}Re-labeled antibodies, whether they were administered systemically or intraperitoneally (*1-10*). We performed an analysis to determine whether the observed toxicity with one of the ^{186}Re-labeled antibodies could have been predicted by the absorbed dose estimates.

Peripheral blood count data from patients on a dose escalation trial of ^{186}Re-labeled murine monoclonal NR-LU-10 were examined as indicators of bone marrow toxicity. We used these data to assess whether the toxicity correlated with radiation absorbed dose estimates to the red marrow (RM), so as to determine whether RM absorbed dose estimates could be useful in patient management. These indicators of toxicity were also compared to the whole-body (WB) absorbed dose and administered radioactivity to determine whether the bone marrow dose estimates (based primarily on the concentration of radioactivity in the blood) were more valuable in predicting toxicity than either the WB dose or the radioactivity administered.

Prior treatment with myelotoxic agents increases the apparent sensitivity of the bone marrow to radiation exposure by partially depleting the regenerative reserve, the stem cells. Thus, the maximum tolerated dose to radiolabeled antibodies is lower for patients who have received prior myelosuppressive chemotherapy (*3,7*) or radiation therapy to marrow-bearing areas (*11*). We compared the predictors of toxicity with the observed toxicity in the patients who had normal bone marrow reserves, i.e., patients without prior therapy to those patients who had received myelotoxic therapy to assess whether the predictions of toxicity could be improved in patients with normal marrow reserves.

MATERIALS AND METHODS

Data were evaluated from 25 patients who had received a single dose of 40 mg of NR-LU-10 murine monoclonal antibody labeled with ^{186}Re. NR-LU-10 is a pancarcinoma antibody that reacts with a 40-kDa glycoprotein that is expressed on most carcinomas. Patients with metastatic disease from colorectal (12 patients), lung (6 patients), ovary (3 patients), breast (1 patient), renal cell (1 patient), ampulla of Vater (1 patient) and gastroesophageal junction carcinoma (1 patient) were treated. Thirteen of the patients were on a Phase I ^{186}Re dose escalation trial, and the administered ^{186}Re dosage ranged from 45 to 297 mCi (*7*). Twelve patients received 45 mCi/m^2 ^{186}Re-NR-LU-10 in a study assessing the value of cyclosporin A in reducing human antimouse antibody formation (*12*). Eight of the 25 patients had not received prior myelosuppressive therapy. No patients received bone marrow transplantation. These studies were approved by the Institutional Review Board of Virginia Mason Medical Center, and written informed consent was obtained from all patients.

The predictors of toxicity were:

1. The amount of radioactivity administered; and
2. The radiation absorbed dose.

The radioactivity administered was expressed as total activity (i.e., mCi of ^{186}Re), activity corrected for body surface area (BSA) (i.e., mCi of ^{186}Re/m^2) or activity corrected for lean body mass (LBM) [i.e., mCi of ^{186}Re/LBM (kg)]. [For men, LBM = $(2.04 \times 10^{-3})\cdot$(height/cm^2); for women, LBM = $(1.75 \times 10^{-3})\cdot$(height/cm^2).]

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Time-activity curves were constructed for source organs of interest, including the liver, kidneys, lungs, thyroid gland and remainder tissues, from quantitative planar gamma camera measurements. Residence times were calculated for each source organ and for the RM (*13*). Radiation absorbed dose estimates were calculated using models and methods recommended by the Medical Internal Radiation Dose (MIRD) Committee of the Society of Nuclear Medicine (*14–18*) and by the American Association of Physicists in Medicine (AAPM) task group on dosimetry of radionuclide therapy (*19*).

Red Marrow Radiation Absorbed Dose

Individualized marrow specific dosimetry from direct bone marrow biopsy was not available. Bone marrow radioactivity was not visible on the gamma camera images in any of these patients and, thus, bone marrow was not considered a source organ. Residence time ($T_{R,RM}$) in the marrow for each patient was calculated from measurements of the time-activity curve determined for ^{186}Re in the serum ($T_{R,S}$) and accounted for the patient's hematocrit (Ht). The following formula was used:

$$T_{R,RM} = T_{R,S} \times (1 - Ht) \times M_{RM} \times F,$$

where M_{RM} is the MIRD mass of the RM and F is the concentration of radioactivity in the RM (*13*). F was assumed to be a value that was 0.25 times the concentration of radioactivity measured in the blood for all patients. This factor was based on the AAPM conclusion that the concentration of intact monoclonal antibodies in the bone marrow is 0.2–0.4 times that in the circulating blood (*19*). We used 0.25 to make a consistent, reasonable model assumption to correlate with response. The RM absorbed dose was estimated with marrow S values used in ICRP Publication 30 (*20*) and implemented in MIRDOSE2 software (Oak Ridge Associated Universities). The major contributor to RM dose was circulating ^{186}Re. Also contributing to the marrow dose was the ^{186}Re activity in the major source organs and remainder body tissues.

Whole-Body Radiation Absorbed Dose

Whole-body activity was determined from daily WB counts from the gamma camera. Radiation absorbed dose estimates to the WB were determined using standard MIRD techniques, corrected for individual patient mass (*18*).

As a clinical indicator of marrow toxicity, weekly peripheral blood counts were analyzed. Only patients with peripheral blood count data available for at least 6 wk were considered. The indicators of toxicity were:

1. Toxicity grade of platelet count and white blood cell (WBC) count of 0–4 and a combined toxicity grade from platelet plus WBC grades of 0–8;
2. The nadir count compared with pretherapy count (percentage baseline); and
3. Platelet and WBC count nadir at 4–5 wk.

The platelet and WBC grades and percentage baseline counts plotted against the predictors of toxicity are shown in Figures 1–4. Correlation coefficients were derived between the parameters predicting toxicity and the peripheral blood count indicators of toxicity. Using the percentage baseline platelet and percentage baseline WBC data, a multiple linear regression analysis was also performed to determine whether the RM or WB dose estimates added value to the prediction of marrow toxicity above that using the administered radioactivity corrected for BSA alone.

RESULTS

The correlation coefficients are shown in Table 1. Of the parameters studied, the WBC grade, the combined grade and the percentage baseline platelet counts were the indicators of toxicity that showed the greatest correlation with the various predictors of marrow toxicity. The correlation coefficients (r values) ranged from 0.69 to 0.80. The nadir counts of both platelets and WBC were the least useful indicators of toxicity, with the r value ranging from 0.47 to 0.64. The corresponding p values for all data analyzed, as performed by the paired Student's t-test, reached a significance of $p < 0.001$, except for the correlation of WBC nadir with RM dose and the correlations of platelet nadir with most of the predictors. When the radioactivity administered was normalized for patient size, [mCi/m^2 or mCi/LBM (kg)], the correlation coefficients consistently improved compared with the total radioactivity administered alone (mCi). There was no single predictor that consistently achieved the highest correlation for each indicator. Using the grade as the indicator of toxicity, the WB dose provided a higher correlation than the RM dose, whereas when using the percentage baseline as the indicator, the RM dose showed a higher correlation than the WB dose. Overall, this analysis showed that both normalized activity and absorbed dose could be considered as moderate or moderate-to-strong predictors of toxicity.

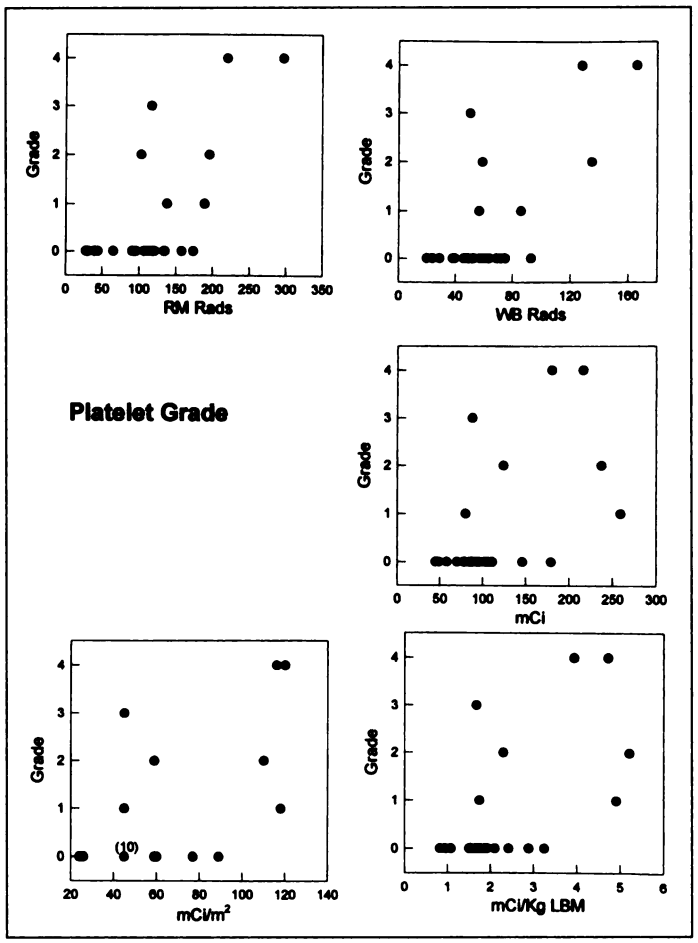

FIGURE 1. Comparison of platelet grade with predictors of toxicity. Grade 1 = 75–99 × 10^3/mm^3 platelets; Grade 2 = 50–74 × 10^3/mm^3 platelets; Grade 3 = 25–49 × 10^3/mm^3 platelets; Grade 4 < 25 × 10^3/mm^3 platelets.

Multiple linear regression showed that there was no increased use from either the RM or WB absorbed dose estimates above that of the normalized total administered activity (mCi/m^2). One would expect that absorbed dose indicators are superior predictors of toxicity compared with administered activity because patient variability in uptake and clearance is accounted for in the calculation of absorbed dose. Hence, we performed two additional analysis steps for these patients in an attempt to

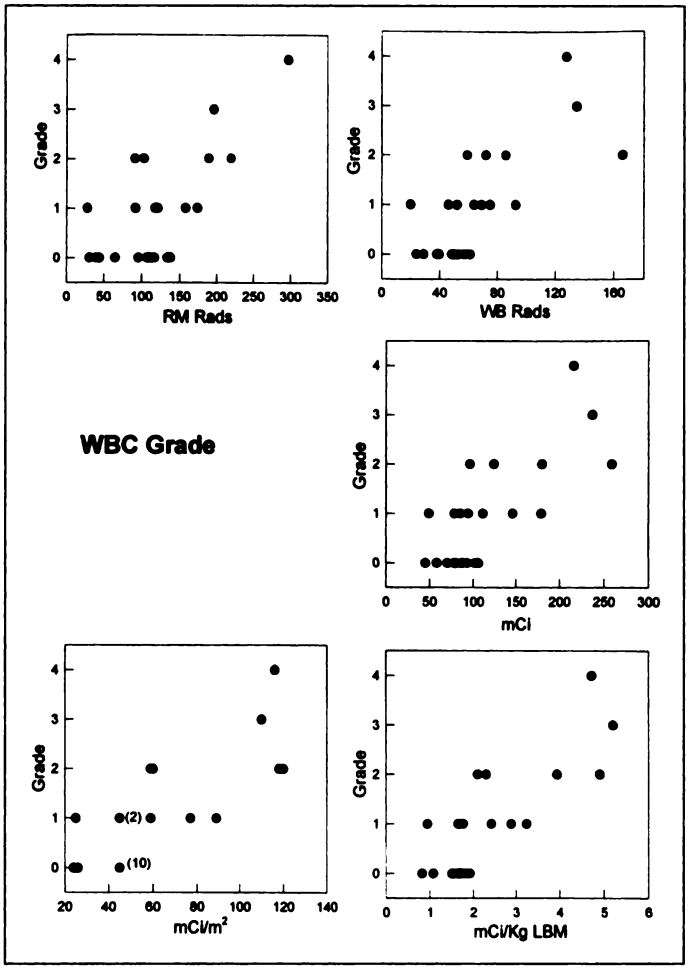

FIGURE 2. Comparison of white blood cell (WBC) grade with predictors of toxicity. Grade 1 = 3.0–3.9 × 10^3/mm^3 WBCs; Grade 2 = 2.0–2.9 × 10^3/mm^3 WBCs; Grade 3 = 1.0–1.9 × 10^3/mm^3 WBCs; Grade 4 < 1.0 × 10^3/mm^3 WBCs.

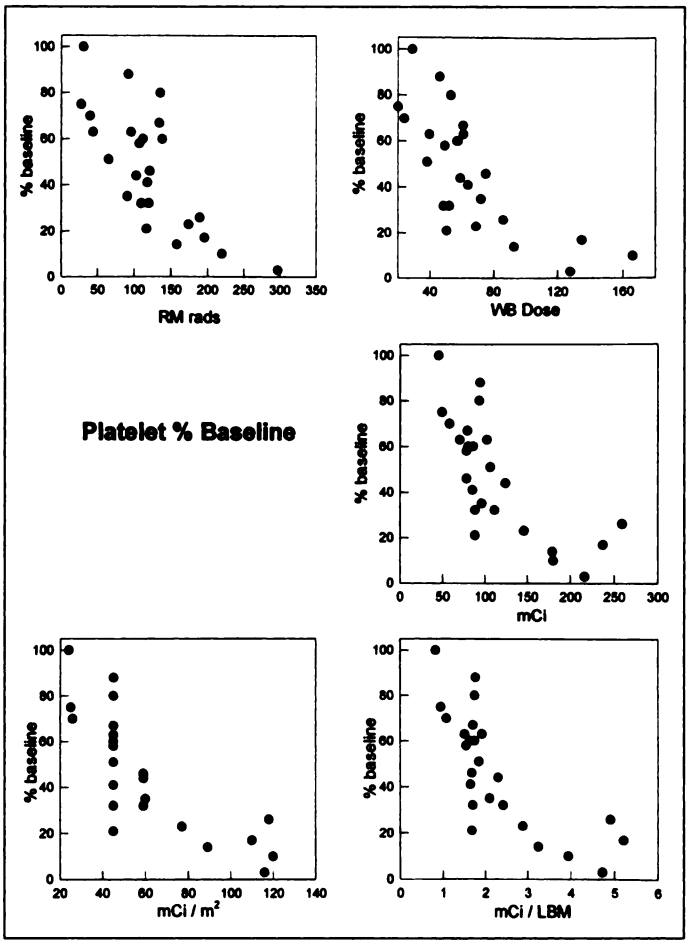

FIGURE 3. Comparison of percentage baseline platelet count with predictors of toxicity.

further define this result. We separated patients into pretreated and nonpretreated groups and, then, we distinguished patients with fast clearance from those with slow clearance of radiolabeled antibody from the blood.

Correlation coefficients were derived using the percentage baseline platelets for 17 patients with and 8 patients without prior myelosuppressive treatment. This was done to assess whether the correlation coefficients could be improved in the patients with normal marrow reserves. These correlation coefficients are shown in Table 2. The correlation coefficient for WB dose in previously untreated patients was found to be 0.87. However, the correlation with RM dose or activity administered was similar to that in the pretreated patients (Figs. 5 and 6).

The serum clearance half-times varied from 17 to 43 hr. We divided the patients into those with the slowest and fastest clearances to determine whether the variation in serum clearance half-times had any statistical effect on resulting correlation coefficients for toxicity versus administered activity or absorbed dose. The patients in the fast clearing group (n = 8) had serum half-times ranging from 17 to 24 hr, and the slow clearers (n = 6) had half-times ranging from 33 to 43 hr. A strong correlation coefficient (r = 0.91) was determined for fast clearers, whereas a weaker correlation coefficient (r = 0.61) was computed for the slower clearers, using marrow absorbed dose as predictor (Fig. 7). The same result was found for a similar analysis performed with normalized administered activity as the second variable (data not shown).

DISCUSSION

The maximum tolerated dose of internally administered radionuclides depends on the radioisotope, the stability of the chelate used in the labeling process and whether the antibody is cross-reactive with normal bone marrow tissue. Red marrow absorbed dose from radiolabeled antibodies without specific uptake of the radionuclide in the marrow is commonly estimated using methods based on measurements of blood activity as recommended by the AAPM Task Group. With data now available from several Phase I RIT trials, it is important to re-examine the resulting dose estimates. We have looked at the correlation of absorbed dose estimates with hematological toxicity and have found that both absorbed dose and normalized administered activity were moderately useful predictors of marrow toxicity. Although we recognize that the peripheral blood counts may not be a precise indicator of marrow toxicity, these were the data available to evaluate hematological toxicity in all of our patients in the clinical trials. Bone marrow samples were not evaluated for stem cell and stromal cell function.

Although we have studied several antibodies with ^{186}Re, our most complete dataset (25 patients) is with the murine monoclonal antibody NR-LU-10. RM absorbed dose was not calculated using blood activity as the primary contributor of dose to RM for our earlier studies. We did have WB dose and toxicity data from patients who received a ^{186}Re-labeled chimeric antibody and a ^{186}Re-labeled F(ab')$_2$ fragment. When we included these patients (n = 47) and examined the WB dose and percentage baseline platelets, the correlation coefficient was r = 0.69. This value was similar to that described above, suggesting similar correlation of absorbed dose with toxicity

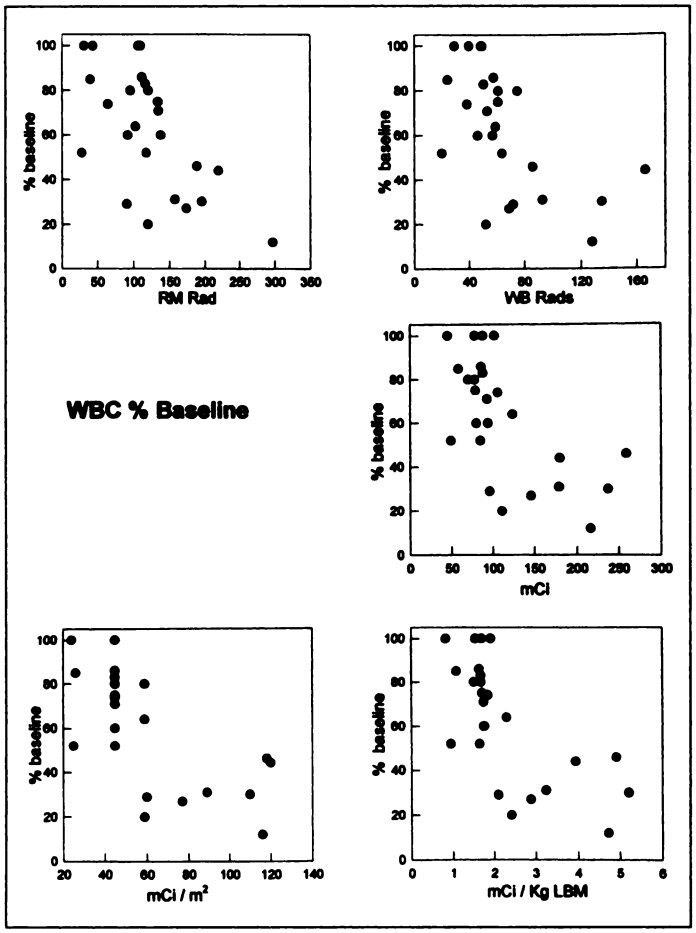

FIGURE 4. Comparison of percentage baseline white blood cell count with predictors of toxicity.

with other ^{186}Re-labeled antibodies when the mercaptoacetyl-glycylglycyl-gamma-aminobutyrate chelate is used.

Rhenium-186 emits a beta particle with a maximum energy of 1.07 MeV. There are abundant 137-keV gamma photons (9%) and also higher-energy (702-keV) gamma photons of low abundance (0.05%). A small fraction of the marrow dose is due to low-energy photons below 137 keV. Most of the bone marrow exposure would be expected to result from the nonpenetrating beta radiation deposited by circulating ^{186}Re activity, which was found to account for ~85% of the dose. The remainder of the body activity contributed ~15%. Without bone marrow biopsies, we cannot be certain that there was no ^{186}Re deposited on bone surfaces. However, the absence of antibody cross-reactivity with bone marrow elements and the absence of detectable activity on the images and in the preclinical studies (*21*) suggest that any ^{186}Re associated with bone or bone marrow could only account for a small fraction of the activity.

Several investigators have attempted to correlate toxicity with radiation absorbed dose estimates to the bone marrow with ^{131}I-labeled antibodies (*6,22–24*). The correlation of hematological toxicity with dose from ^{131}I-labeled antibodies has been weak to moderate. Because more of the emitted ^{186}Re radiation energy is attributable to the nonpenetrating beta component than with ^{131}I, we anticipated that this method of radiation absorbed dose estimation might provide a higher correlation with ^{186}Re-labeled antibody toxicity than that reported for ^{131}I-labeled antibody studies. All the parameters did show higher correlation coefficients compared with those reported for ^{131}I.

In situations in which there is specific uptake in the bone marrow, as demonstrated by bone marrow localization on the gamma camera images, it is necessary to consider the bone marrow as a source organ, and estimates of radioactivity from regions of interest over the sacrum or lumbar spine have been used to determine the RM dose. Increased localization causes increased marrow toxicity, and methods to quantitate this are being evaluated (*25*). Correlation of toxicity with RM dose for ^{90}Y-labeled antibodies has not been found in the literature. The variable release of ^{90}Y from an ^{90}Y-DTPA chelate and its accumulation on bone surfaces makes the correlation of bone marrow toxicity with RM dose estimates from serum clearance unreliable as a predictor of toxicity.

Of the parameters we examined, the percentage baseline platelet count, although not a standard measure of toxicity, appeared to be the best indicator of radiation damage.

The platelet grade was a weak indicator of marrow radiation damage because of the wide range in baseline platelet counts in patients with cancer. Thrombocytosis (counts of >400,000 platelets) occurred in six patients. Of these patients, four had Grade I or II white cell toxicity with no platelet toxicity. Thus, the thrombocytosis appeared to mask the effect of the radiation on the platelet count. The combined grade also was affected by this factor.

It was likely coincidental that the WBC grade and not the percentage baseline WBC counts showed the higher correlation.

The indicators of toxicity did not show an improved correlation with the radiation absorbed dose to the RM compared with the dose to the WB or with the total administered activity corrected for body size. At doses below the maximum tolerated dose, a variation in response of the marrow to radiation was observed (e.g., see the 15 patients with <50 mCi/m^2 ^{186}Re), even in patients with normal marrow reserves. This variation in response was also observed by DeNardo et al. (*26*) with

TABLE 1
Correlation Coefficients from All Patients

	Correlation coefficients				
	Red marrow radiation absorbed dose	Whole-body radiation absorbed dose	Total activity	Activity/body surface area	Activity/lean body mass (kg)
WBC grade	0.69	0.74	0.76	0.79	0.80
Platelet grade	0.67	0.71	0.56	0.64	0.61
Combined grade	0.76	0.80	0.72	0.79	0.78
% baseline WBC	0.63	0.58	0.64	0.67	0.67
% baseline platelets	0.75	0.73	0.73	0.79	0.75
WBC nadir	0.59	0.60	0.57	0.64	0.62
Platelet nadir	0.59	0.54	0.47	0.55	0.52

WBC = white blood cell.

TABLE 2
Comparison of Correlation with Percentage Baseline Platelet Count in Patients With and Without Prior Myelosuppressive Therapy

	Correlation coefficients				
	Red marow rads	Whole-body rads	Total activity	Activity/body surface area	Activity/lean body mass (kg)
All patients	0.75	0.73	0.73	0.79	0.75
No prior treatment	0.75	0.87	0.75	0.82	0.77
Prior treatment	0.74	0.72	0.79	0.81	0.70

^{131}I-Lym-1 antibody. Although microscopic tumor deposits in the marrow could influence the marrow response, there was no clinical evidence of this, and marrow biopsies were not performed to definitely exclude this. Thus, using the correlation between biological toxicity and absorbed dose as a means of verifying accuracy of the absorbed dose estimates was complicated by the patient-to-patient variation in response to the same exposure.

Previously, in a study of 31 patients treated with the ^{186}Re-labeled F(ab')$_2$ fragment of anti-CEA monoclonal antibody NR-CO-02, we reported that the degree of toxicity in patients who had received prior myelosuppressive therapy was higher than that in the minimally pretreated patients (*7*). In the group of patients treated with ^{186}Re NR-LU-10 at doses below the maximum tolerated dose, the patient-to-patient variation and the level of toxicity were no greater in the heavily pretreated patients than in the minimally pretreated patients. The correlation of RM absorbed dose with toxicity did not improve in the minimally treated patients, as would have been expected, and as was shown by Sgouros (*22*), although a high correlation coefficient of WB dose with percentage baseline platelets (0.87) was observed. A strong correlation coefficient was also observed for both marrow absorbed dose and administered activity versus percentage baseline platelets for the patients with fast serum clearance. We are unable to explain this finding at present. One could hypothesize that it may be due either to variations in dose rate with time, or possibly, that the use of a fixed marrow-to-blood ratio is less applicable to prolonged biological half-times.

CONCLUSION

In these patients undergoing RIT with ^{186}Re-NR-LU-10, the RM dose estimates were moderately predictive of marrow toxicity. However, the moderate correlation of toxicity with bone marrow absorbed dose as currently estimated from blood clearance (r = 0.75) was not higher than the correlation of toxicity with normalized administered radioactivity or with WB radiation absorbed dose.

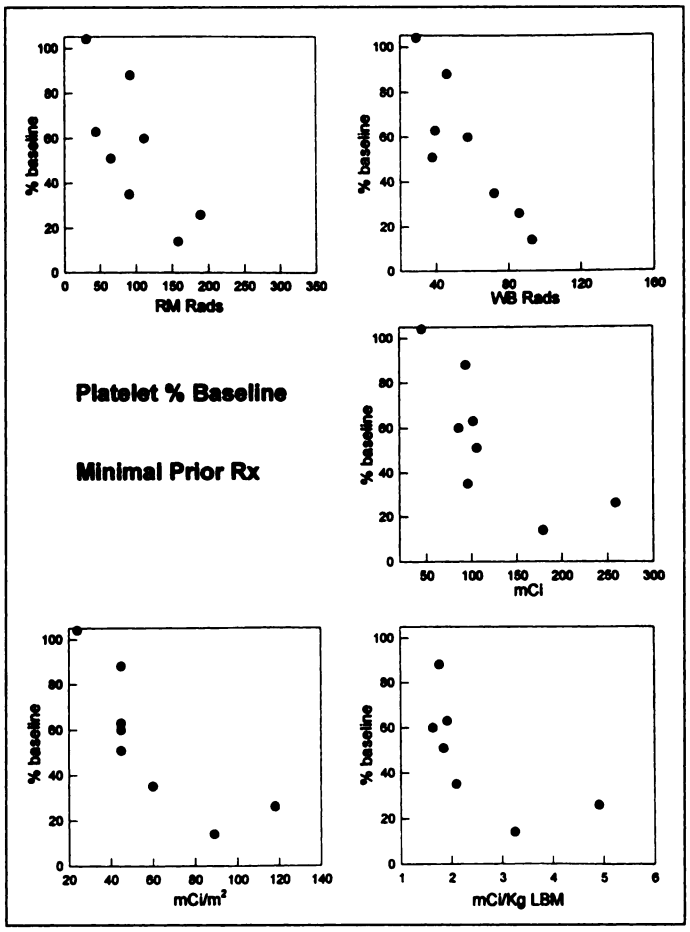

FIGURE 5. Comparison of percentage baseline platelet count with predictors of toxicity in patients without prior myelosuppressive therapy.

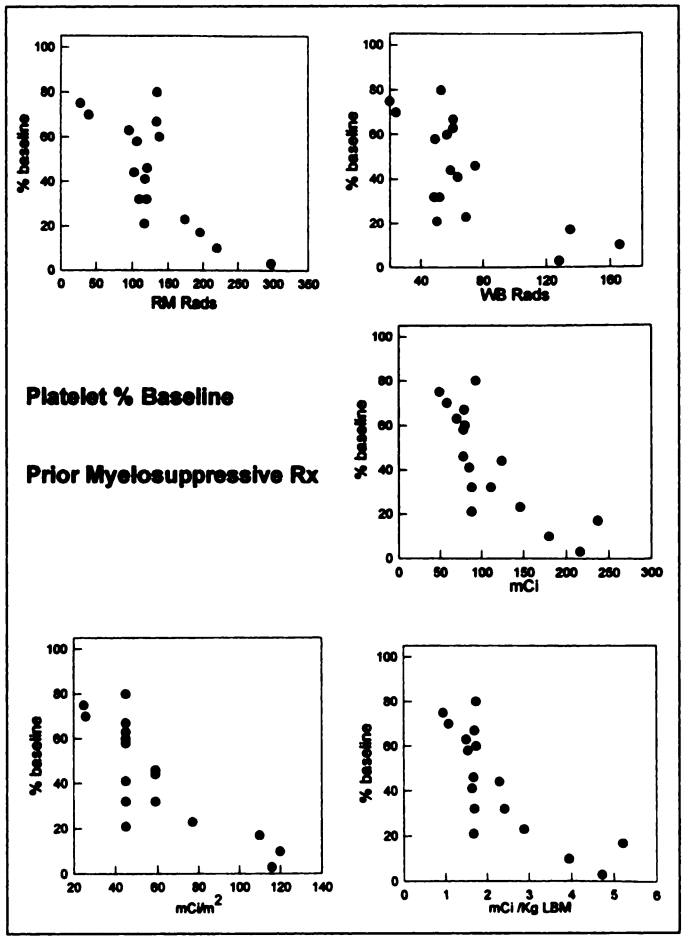

FIGURE 6. Comparison of percentage baseline platelet count with predictors of toxicity in patients who have received prior myelosuppressive therapy.

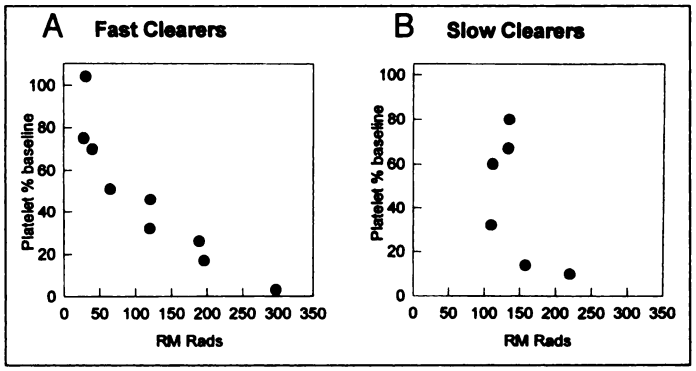

FIGURE 7. Comparison of percentage baseline platelet count with red marrow absorbed dose in patients with (A) fast and (B) slow serum clearance of radiolabeled antibody.

The dosimetry estimates for normal organs were useful in assessing biodistribution of the radiommunoconjugate. However, the radiation absorbed dose to RM was of limited value for predicting the toxicity to individual patients. This was partly due to the substantial variation in the response of the bone marrow to low-dose rate radiation, even in patients assumed to have normal bone marrow reserves.

Methods to refine the dosimetry estimates by more detailed consideration of the absorbed fraction of radioactivity in bone have been developed (*27*) and are being used in RIT trials. However, if the percentage baseline platelet count is a true measure of marrow toxicity, this analysis suggests that, because of the wide patient to patient variation in response to low-dose rate radiation, it will be difficult to predict toxicity even if absorbed dose estimates are shown to be accurate.

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