astrocytomas (GII). The early uptake ratio and delayed uptake ratio were high, but retention ratio and retention index were lowest in meningiomas. The early uptake ratio and delayed uptake ratio were low, but the retention ratio and retention index were middle in metastases. Meningiomas were differentiated from other benign and malignant tumors by their high early and delayed uptake ratios, and low retention ratio and index. Astrocytomas (GII) were differentiated from glioblastomas by the delayed uptake ratio, retention ratio and retention index, and from astrocytomas (GIII) by the delayed uptake ratio. However, it was difficult for ^{201}TlCl to differentiate benign tumors from malignant ones and to evaluate histological malignancy grade, and also to differentiate malignancy grade even among the gliomas.

False negative cases were seen mostly in astrocytomas (GII) on both ^{99m}Tc(V)-DMSA and ^{201}TlCl, most likely due to their hypovascularity. But, ^{201}TlCl showed false negative in several other tumors.

CONCLUSION

Technetium-99m(V)-DMSA uptake was mainly dependent upon the tumor vascularity with no significant difference among the primary and metastatic brain tumors. Washout from the lesions was different from tumor to tumor and independent of tumor vascularity, but was closely related to tumor histology and histological malignancy. Thallium-201-chlorine uptake was also dependent on tumor vascularity, but showed no significant relationship between washout and tumor histology or histological malignancy. Therefore, differentiation between benign and malignant tumors was difficult by the uptake and retention of ^{201}TlCl. This may suggest that there should be different uptake and washout mechanisms between ^{201}TlCl and ^{99m}Tc(V)-DMSA. Technetium-99m(V)-DMSA could clearly demonstrate primary and metastatic brain tumors with a sensitivity of 93.2%, which is slightly higher than the 88.1% of ^{201}TlCl. False negative was very limited in astrocytomas (GII). Tumor histology and histological malignancy grade could also be predicted noninvasively by numerical scores, which would be very useful to determine the therapeutic methods. Technetium-99m(V)-DMSA was superior to ^{201}TlCl in imaging quality, sensitivity and specificity to tumor histology and histological malignancy of the primary and metastatic brain tumors.

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Prediction of Myelotoxicity Using Semi-Quantitative Marrow Image Scores

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Marrow radiation with resultant myelosuppression is usually dose-limiting in radioimmunotherapy (RIT). This study evaluated the relationship between a semiquantitative score of radiolabeled antibody marrow uptake obtained by imaging and subsequent decrease in peripheral blood cell counts in a patient population in whom marrow malignancy is common. **Methods:** Semiquantitative scores were assigned to lumbar marrow images of 18 patients acquired 0, 6, 24 and 48 hr after the first therapy dose of ^{131}I-Lym-1. Scores were adjusted for injected dose (GBq) and body surface area (m^2), and correlated with post-therapy blood counts. A well-defined scale, where 0 and 4 represented least to highest marrow uptake when compared to background, was used to assign marrow image scores. Injected doses of ^{131}I-Lym-1 ranged from 1.1–8.2 GBq (29–222 mCi). **Results:** Linear regression of summed marrow scores (0–24 hr after injection) versus decrease in cell counts produced correlation coefficients of 0.76, 0.44, 0.58 and 0.46 for platelets, granulocytes, white blood cells (WBC) and hematocrit, respectively. Scores for individual and other combinations of images obtained immediately up to 24 hr after injection were also predictive.

Key Words: myelotoxicity; marrow imaging; radioimmunotherapy; semiquantitative

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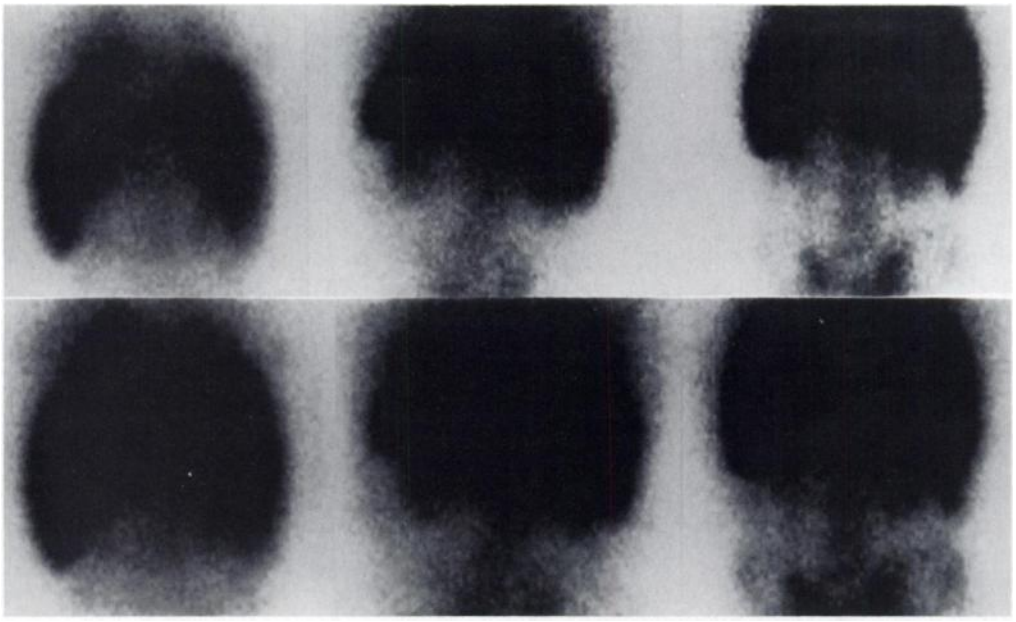

FIGURE 1. Posterior abdominal marrow images acquired 6 hr after injection demonstrating 0 (left), 2 (center) and 4 (right) scores (no, moderate and high uptake of ^{131}I-Lym-1, respectively). Image intensity was increased from baseline (upper row) to an intensity in which several pixels in the lumbar marrow were at maximum brightness (lower row).

In patients with hematologic malignancies, marrow involvement is common. Radiation dose to the marrow from radionuclides targeted to malignant cells in the marrow and skeleton can be significant (*1–3*). Several groups have described quantitative imaging methods intended to measure the contribution to marrow radiation from targeted radionuclides (*4–7*). These methods for estimation of targeted marrow radiation doses seem to be of value for prediction of myelotoxicity (*1,2,5*). Estimates of marrow radiation using imaging had a better correlation with myelotoxicity than did conventional body and blood methods for estimating radiation dose to the marrow (*1,2*). However, many factors affect the accuracy of marrow radiation dose obtained by quantitative imaging including the size, shape and placement of the marrow region of interest (ROI). Quantitative marrow methods provide information that is limited by the accuracy of the ROI representations of marrow uptake and background activity. Furthermore, quantitated, absolute marrow radiation doses can be misleading because they represent macroscopic, global values that are only remotely related to doses to normal marrow cellular elements. Finally, application of a quantitative radiation dose method is time-intensive and requires in-depth training.

Subjective interpretation of images may actually be superior to the use of quantitative data in some instances (*8*). The purpose of this study was to assess whether a semiquantitative method that is less demanding and more clinically feasible could also predict myelotoxicity.

MATERIALS AND METHODS

Patients

Fifty-four, heavily pretreated patients with advanced non-Hodgkin's lymphoma or chronic lymphocytic leukemia, in whom marrow malignancy was common, received therapeutic doses of ^{131}I-Lym-1 from 1985-1994. The amount of administered Lym-1 protein was dependent on the size of the treatment dose and the specific activity of the radiopharmaceutical preparations. The amount of protein ranged from 3–100 mg. Protein doses in this range have been shown to yield stable pharmacokinetics and were chosen to provide stability by exceeding the required threshold amount (*9*). All selected patients had bone marrow biopsies to determine the presence (positive or negative) of marrow malignancy. Eighteen patients met the following criteria: no cancer treatment 4 wk before or after RIT, no prior radiation to the lumbar spine and no increases in blood cell counts within 4 wk after RIT (decreases in blood counts were examined).

Marrow Image Score and Image Review

Images were acquired on a Siemens Orbiter camera (Hoffman Estates, IL) with a circular detector (39 cm diameter) for 1 million counts or on a Siemens Bodyscan camera with rectangular detectors (61 cm × 39 cm) for 2 million counts, or 600 sec whichever occurred sooner. All images were stopped by counts in 16 patients; in two patients that received 1.1 GBq (30 mCi) the 48 hr images were stopped by time but all earlier images were terminated by counts. To avoid bias in the semiquantitative method, the operator, who assigned scores to images, was blinded to blood counts, and to marrow radiation doses obtained using the quantitative imaging method (*1*). To standardize the method, images were displayed without subtracting background intensity and with a brightness setting at maximum for vertebral marrow pixels with greatest counts. Images acquired immediately (as soon as practical after infusion), 6, 24 and 48 hr after injection were reviewed. The semiquantitative scores for posterior abdominal images were selected from the following scale of uptake in the third and fourth lumbar vertebral marrow when compared to background regions (Fig. 1):

0 = Intensity in the region of the third and fourth lumbar vertebrae is equivalent to that of the adjacent paraspinal background.

1 = Intensity in the region of the third and fourth lumbar vertebrae is slightly greater than that of the adjacent paraspinal background, but intervertebral space cannot be discriminated.

2 = Intensity in the region of the third and fourth lumbar vertebrae is definitely greater than that of the adjacent paraspinal background so that intervertebral space can almost be seen, but vertebrae cannot be discretely outlined.

3 = Intensity in the third and fourth vertebrae is definitely greater than that of the adjacent paraspinal background, intervertebral spaces can be easily identified, and individual vertebrae can be discretely identified, but lateral margins are blurred.

4 = Intensity in the third and fourth vertebrae is definitely greater than that of the adjacent paraspinal muscle and individual vertebrae can be discretely identified with sharp margins.

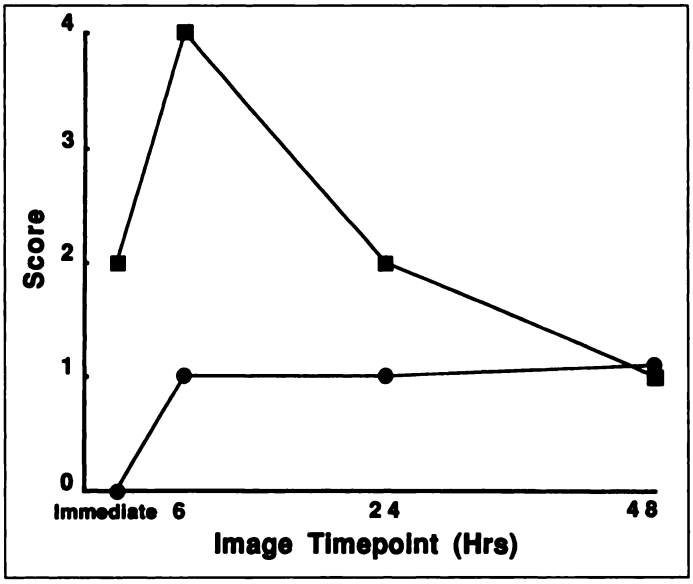

FIGURE 2. Illustrative patterns for image scores over time for a patient with little or no uptake (● = sum of 0, 6 and 24 hr scores = 2) and a patient with substantial uptake (■ = sum of 0, 6 and 24 hr scores = 8) demonstrate the usual occurrence of peak uptake 6 hr after injection of ^{131}I-Lym-1.

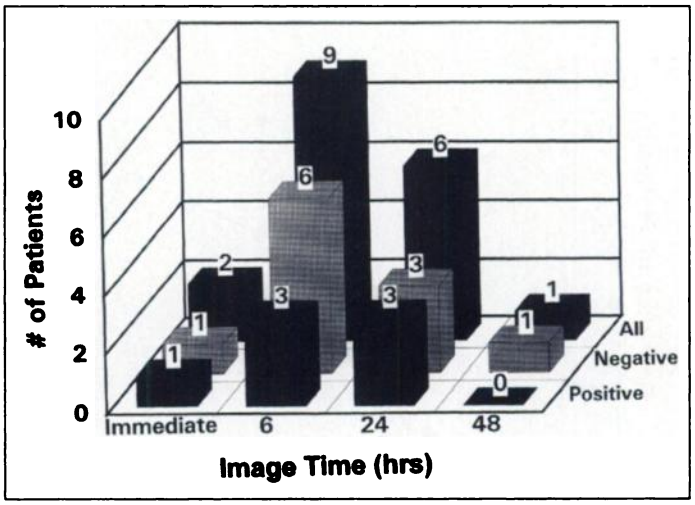

FIGURE 3. Number of patients assigned peak marrow scores for each image timepoint grouped according to whether marrow biopsy was positive (7 patients) or negative (11 patients) for lymphoma. The median sum of scores was 6.5 (range = 4–9) in patients with marrow biopsies that were positive for lymphomatous involvement and was 5 (range = 2–6) in patients with negative marrow biopsies.

If the observer felt that the score fell between two numbers, the larger number was used. Individual scores and the sum of scores for images acquired immediately, 6, 24 and 48 hr after injection of ^{131}I-Lym-1 were compared with changes in peripheral blood cell counts. In addition, intraoperator reproducibility was analyzed for a single observer's review of and scoring for lumbar marrow images. Immediate, 6, 24 and 48 hr images were scored respectively for each of the 18 patients (72 observations) on 11 occasions over the course of 2 wk. To evaluate reproducibility, coefficients of variation (CV) were determined for image scores assigned at each time-point.

Comparison of Semiquantitative Marrow Score

The relationship between the semiquantitative score and post-therapy changes in blood counts was evaluated. Marrow scores were adjusted for injected dose per body surface area by multiplying the marrow image score by the administered activity dose per m^2 (GBq/m^2. The fractional decrease in blood count was defined as the difference between the pretherapy and nadir blood count divided by the pretherapy blood count (*9*). Linear regressions were performed on plots of individual and sums of marrow scores for images acquired immediately, 6, 24 and 48 hr versus change in platelets, granulocytes, WBC and hematocrit.

RESULTS

Marrow Image Score

The median image scores were greater for 6 and 24 hr images (both medians = 2) than for immediate and 48 hr images (both medians = 1) (Fig. 2). The peak score over time was assigned to the immediate image in two patients, the 6 hr image in nine patients, the 24 hr image in six patients and the 48 hr image in one patient (Fig. 3). The median sum of scores was 6.5 (range = 4–9) in patients with marrow biopsies that were positive for lymphomatous involvement and was 5 (range = 2–6) in patients with negative marrow biopsies. Intraoperator reproducibility was good for all images particularly those acquired 6 or more hours after injection. The CV did not differ between images with high (*3–4*) or low (*0–2*) scores. The median and range of CV were 0.21 (0.00–0.50), 0.15 (0.00–0.32), 0.14 (0.00–0.20) and 0.18 (0.00–0.20), for immediate, 6, 24 and 48 hr images, respectively.

Comparison of Semiquantitative Marrow Score

For all time-points before 48 hr, correlations were best for decrease in platelets ($r \geq 0.63$, $p \leq 0.005$) and were good for WBC ($r \geq 0.46$, $p \leq 0.05$) (Table 1, Fig. 4). Correlations were not significant for granulocytes and hematocrit except for correlations between hematocrit and the sum of immediate and 6 hr scores and the sum of immediate, 6 and 24 hr scores ($r \geq 0.46$, $p = 0.05$). Correlations for platelet decrease were slightly

TABLE 1
Correlation Coefficients and Significance (p value) for Marrow Score Versus Decrease in Blood Counts*

	Image times after injection (hr)			Image times after injection (hr)			Image time after injeciton (hr)
Blood counts	Immediate	6	24	48	Immediate and 6	6 and 24	Immediate 6 and 24
Platelets	0.63; 0.005	0.65; 0.005	0.69; 0.005	0.38; ns	0.65; 0.005	0.77; 0.001	0.76; 0.001
Granulocytes	0.39; ns	0.21; ns	0.31; ns	0.16; ns	0.39; ns	0.37; ns	0.44; ns
WBC	0.57; 0.02	0.48; 0.05	0.46; 0.05	0.32; ns	0.58; 0.02	0.55; 0.02	0.58; 0.02
Hematocrit	0.44; ns	0.27; ns	0.28; ns	0.14; ns	0.47; 0.05	0.38; ns	0.46; 0.05

*Scores for 48 hr images alone or combined with other timepoints were not discriminating.
ns = not significant; $p \geq 0.1$.

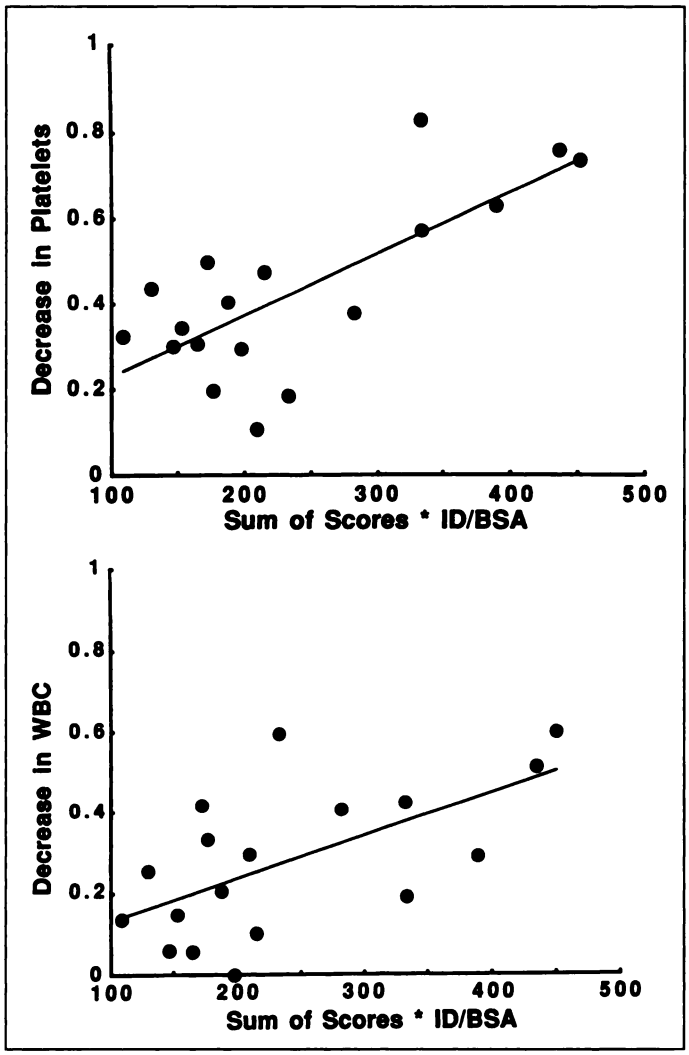

FIGURE 4. Correlation coefficients for the sum of scores for immediate, 6 and 24 hr images were better for fractional decrease in platelets ($r = 0.76$) (upper) and WBC ($r = 0.58$) (lower).

better for the sum of 6 and 24 hr and the sum of immediate, 6 and 24 hr scores ($r \geq 0.76$, $p = 0.001$) than for individual scores or the sum of immediate and 6 hr scores ($r \geq 0.63$, $p = 0.005$). Sums of immediate and 6 hr scores and immediate, 6 and 24 hr scores yielded significant correlations with decrease in platelets, WBC and hematocrit ($r \geq 0.46$, $p \leq 0.05$). Correlations of 48 hr scores with decrease in blood counts were not significant. Addition of the 48 hr scores did not improve the correlations ($r = 0.39-0.71$). For the number of patients in this study, the correlation coefficient had to be equal to or greater than 0.46 to be significant at $p \leq 0.05$ in the two-tail test for significance. Linear regression of the sum of immediate, 6 and 24 hr scores versus decrease in platelets fit the equation, $y = 0.05 + 0.002x$ and that of the 6 hr image score versus decrease in platelets fit the equation, $y = 0.12 + 0.002x$, where x is the sum of image scores multiplied by injected dose/body surface area and y is the fractional decrease in platelets. Because of the small number of patients in our study, caution should be exercised when using these equations for predicting myelotoxicity in other patient populations.

DISCUSSION

Thrombocytopenia has been the most severe manifestation of ^{131}I-Lym-1 radiation toxicity in patients with B-cell malignancies (*3*). Patients who had peripheral blood cytopenias before ^{131}I-Lym-1 treatment were more likely to experience Grade 3–4 hematologic toxicity after ^{131}I-Lym-1 treatment. In many patients, the degree of myelotoxicity could not be explained by marrow radiation contributed by blood and body ^{131}I alone (*3*). Bone marrow biopsy and imaging commonly provide evidence for marrow malignancy and concomitant additional marrow radiation from ^{131}I-Lym-1 targeting, and also for toxic effects from prior treatment (*3*).

Prediction of myelotoxicity by estimation of conventional radiation dose to marrow contributed by blood and body radioactivity has not proved to be reliable in patients with marrow malignancies (*6,10,11*), but was improved by addition of the targeted radiation dose to marrow obtained by imaging (*1*). However, absolute quantitation of targeted radiation dose to marrow is difficult, time-consuming and as yet has yielded only modest correlations for the prediction of myelotoxicity. Factors that hinder the quantitative accuracy of the targeted marrow dose, and consequently its ability to predict myelotoxicity, include the following. Insurmountable uncertainties exist for ROI definition for background subtraction and major vessels exist in the region of the marrow and background ROIs (*2*). Additionally, the conventional MIRD technique used to determine radiation dose assumes uniform distribution of radioactivity (*12*). Estimation of the macroscopic marrow radiation can be misleading because both normal and abnormal marrow is quite heterogeneous, as is radionuclide distribution, so that the microscopic radiation dose to hematopoietic cells can vary considerably from the average macroscopic dose (*13*). However, estimation of marrow radiation dose is of critical importance to radionuclide therapy so that these problems should not deter from further attempts to develop methods for accurate quantitation of the radiation dose to the red marrow. The calculated absolute dose can be used as a reference value at the least and can be related to data generated by a variety of therapists.

There have been no other reports of image scores for marrow uptake. However, others have compared marrow radiation doses from body, blood and marrow targeting with myelotoxicity and moderate predictions were found (*2,5*). In this study, a semiquantitative marrow score method was defined and investigated for accuracy in prediction of myelotoxicity. The marrow image scoring system was implemented by an experienced observer. Adequate image counts (≥1 million) facilitated assessment of uptake in vertebral marrow. When assigning scores to images, all information in the field of view of the image was considered including high activity regions, such as paravertebral masses or kidneys, that can contribute error to a rigid ROI background used to obtain an absolute value (*1*). The semiquantitative score method was also simpler and less time-intensive than the quantitative radiation dose method.

Prediction of myelotoxicity by the marrow score method was slightly better than that by the quantitative method that includes radiation doses to marrow from body, blood and marrow targeting (*1*). Correlation coefficients for the sum of scores versus change in blood counts were higher than those for marrow dose from body, blood and marrow targeting for platelets (0.76 versus 0.54), WBC (0.58 versus 0.47) and hematocrit (0.46 versus 0.11), and were similar for granulocytes (0.44 versus 0.49). Prediction of myelotoxicity obtained by the marrow score method was equivalent to that obtained by the absolute targeted radiation dose to marrow method for WBC (0.58 versus 0.54), and slightly better for platelets (0.76 versus 0.61) granulocytes (0.44 versus 0.31) and hematocrit (0.46 versus 0.20). The prediction of decrease in platelets and WBC was better for the sum of immediate, 6 and 24 hr scores ($p \leq 0.02$) but was comparable for the 6 hr image scores alone ($p \leq$

0.05). Adequate prediction by the 6 hr image score may be more applicable than scores from other images due to the fact that in over one half of the patients, uptake quantified by a lumbar ROI (*1*) as well as uptake assessed by semiquantitative image scores peaked by 6 hr. The semiquantitative scores obtained by an experienced observer for images acquired 6 hr after infusion of ^{131}I-Lym-1 proved to be a good method to predict myelotoxicity in patients with non-Hodgkin's lymphoma and chronic lymphocytic leukemia. The method may have applications for myelotoxicity prediction in multicenter RIT trials in patients likely to have marrow (or skeletal) malignancy because it is readily implemented. The marrow scores were reproducible when determined by an experienced observer.

Accurate prediction of the degree of myelotoxicity to be expected after infusion of therapeutic amounts of radiopharmaceutical is important because it identifies patients in need of closer monitoring of blood counts and facilitates earlier administration of colony stimulating factors or other blood reconstitution methods. Although therapy images were studied here, the semiquantitative image score method can be used for tracer images as well (*14*) to predict myelotoxicity before administration of the therapeutic dose. In this instance, it would be essential to accumulate sufficient image counts.

CONCLUSION

A well-defined semiquantitative marrow image score generated by an experienced observer can be used to predict myelotoxicity from RIT in patients in whom marrow malignancy may exist. Other factors that need to be investigated to enhance the prediction of myelotoxicity include previous chemotherapy and radiation therapy.

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EDITORIAL

Predicting Myelotoxicity in Radioimmunotherapy: What Does Dosimetry Contribute?

Potential radiogenic damage to the hematopoietic bone marrow is the primary dose-limiting toxicity for systemic radionuclide therapy in general and radioimmunotherapy in particular. A variety of approaches have been pursued in an effort to establish a predictive dose-response relationship for myelotoxicity (*1–7*). Although such efforts are still in their infancy, a number of tentative conclusions have emerged. First, although no such correlations have been particularly impressive, absorbed dose yields a better correlation than administered activity. Second, marrow absorbed dose appears to be a marginally better predictor of myelotoxicity than whole-body absorbed dose. Third, in an "intermediate" absorbed-dose range, myelotoxicity has been unpredictable. As noted in Lim et al. (*8*), because of time and effort required to obtain patient-specific absorbed-dose estimates and their limited use to date in predicting myelotoxicity, the development of less rigorous (i.e., nondosimetric), but simpler, approaches to the prediction of myelotoxicity warrants evaluation.

Myelotoxicity is a classic nonstochastic (i.e., deterministic) effect, characterized by a sigmoidal, rather than by a linear, dose-response relationship (Fig. 1). Such a dose-response relationship is well-behaved only for a reasonably homogeneous population. With increasing heterogeneity of the irradiated population, the biological variability of responses may confound the derivation of a meaningful (i.e., predictive) dose-response relationship. As illustrated in Figure 2, fitting a single linear function to widely dispersed data from a heterogeneous population may result in a poorly fit dose-response function that is quantitatively unreliable for managing individual patients. With stratification of patients into clinically distinct subpopulations with separate dose-response functions (illustrated in Fig. 3 as a series of separate data sets and corresponding fitted curves), the goodness of fit and, therefore, the clinical utility of such functions should be greatly improved. This rather intuitive concept becomes significant in practice only when clinically evaluable criteria for such stratification can be identified and implemented. In radioimmunotherapy, the effect of prior cytotoxic therapy and/or disease involvement on the functional capacity and radiation sensitivity of the hematopoietic marrow now appears to be

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