Bone Marrow Dosimetry: Regional Variability of Marrow-Localizing Antibody

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In radiolabeled antibody therapy, imaging and biopsy-based methods are used to estimate marrow activity concentration when the administered antibody localizes to the marrow. Absorbed dose estimates obtained using such measurements may be subject to large variability due to the potential for regional differences in marrow activity concentration. This variability was examined in ten patients with leukemia after administration of ^{131}I-labeled HuM195 antibody. **Methods:** Regions of interest were drawn around the head and neck of the humerus and femur (both sides) and around lumbar vertebra 3 (L3) and 4 (L4) on a series of planar images collected at multiple times postadministration of the antibody. A single exponential fit to each attenuation-corrected, time-activity curve was obtained to estimate clearance half-life and the back-extrapolated percent injected activity. **Results:** The activity concentration in the femoral head and neck (mean and s.d. = 0.04 ± 0.02 %ID/g) was not significantly different than that measured in L3 and L4 (0.06 ± 0.02% ID/g) but was significantly lower than the concentrations measured in the humeral head and neck regions (0.07 ± 0.03 %ID/g, $p < 0.05$). Although half-life estimates differing by more than a factor of 2 were observed among different regions for individual patients, no systematic difference was observed in half-life between regions overall. S-factors were used for individual marrow regions to determine the mean absorbed dose to marrow in the femoral and humeral heads and the lumbar vertebrae (L3 and L4) which were 0.66 ± 0.3, 1.0 ± 0.3 and 2.2 ± 0.5 mGy/MBq (2.4, 3.8 and 8.3 rad/mCi), respectively. **Conclusion:** A single value is generally quoted for the absorbed dose delivered to the red marrow following marrow-localizing radiolabeled antibody administration. These results suggest that the regional marrow dose may differ significantly from the mean.

Key Words: radioimmunotherapy; bone marrow dosimetry; leukemia; iodine-123-HuM195

J Nucl Med 1996; 37:695–698

As with most systemically administered therapeutic agents, the amount of radiolabeled antibody that may be administered for treatment in radioimmunotherapy without marrow transplantation is limited by marrow toxicity (*1–4*). The potential for marrow toxicity increases significantly when the administered antibody localizes to the marrow (*4,5*). Red marrow pharmacokinetics of radiolabeled antibodies that do not specifically localize in the red marrow have already been examined by a number of investigators (*6–15*). For such antibodies, red marrow pharmacokinetics are generally obtained by sampling blood and applying a correction factor to convert the blood activity concentration to that in the marrow (*8,12*). When the administered antibody crossreacts with cellular components of the marrow, however, or when targeting hematologic disease, blood is no longer appropriate for assessing the pharmacokinetics of red marrow (*8,12,16–20*). In such cases, gamma camera imaging of the activity distribution, usually combined with a single biopsy, can be used to determine marrow kinetics. Typically, a single region of interest (ROI) is drawn around one of several marrow-rich, low-background regions in each of the planar gamma camera images (*21*). The activity concentration and time kinetics that are calculated for this region are then assumed applicable to the marrow as a whole. This approach, however, does not account for potential regional variability in marrow activity concentration that may be associated with distribution of target cells within the marrow.

In this article, we assess this regional variability in a series of leukemia patients who received the administered ^{131}I-labeled HuM195 (Anti-CD33) antibody (*20*). S-factors that are available in the MIRDOSE3 dose calculation software (*22,23*), were used to calculate absorbed doses in individual regions. Several different strategies for determining a mean absorbed dose over the whole marrow are also evaluated.

METHODS

Imaging data obtained from patients with acute myelogenous leukemia during a Phase I trial of humanized M195 (HuM195), anti-CD33 antibody were used in this study (*20*). Each patient received 300 MBq ^{131}I-HuM195. Anterior and posterior images were obtained on the day of the injection and daily for the next 3 days on a dual-headed gamma camera. High-energy, high-resolution collimation was used with a 20% energy window (364 keV) for the ^{131}I. Image acquisition for each anterior-posterior image set ranged from 10 to 20 min. Contours within each ROI were background corrected by subtracting the counts obtained in an adjacent ROI. The geometric mean of background-subtracted anterior and posterior counts was then calculated. The resulting values were converted to activity using the geometric mean of background-subtracted anterior and posterior counts from a 6- to 7-cm diameter standard typically containing 2–3 MBq ^{131}I. Contours were drawn around the following regions: liver, spleen, thyroid, whole body, head and neck of each femur, head and neck of each humerus and lumbar vertebrae 3 (L3) and 4 (L4). These marrow regions were chosen because there was minimal anterior and posterior overlying tissue which reduced background activity. Regional contours for each patient were drawn manually using the third or fourth day images, as the red marrow was best visualized in these later images (*20*). Regional contours were then superimposed upon the corresponding regions in the remaining images. Typical marrow ROIs used in this study are illustrated in Figure 1. Since transmission images were not available for these patients, attenuation correction factors were obtained for each marrow region using body thicknesses obtained from a cross-sectional anatomy atlas (*24*). Body thickness over the femoral head was adjusted according to patient sex; patient-specific adjustments in body thickness were not performed for the other marrow regions.

The red marrow volume corresponding to each of the marrow regions was obtained by scaling the "reference man" values (*25*)

Received Feb. 14, 1995; revision accepted Aug. 17, 1995.
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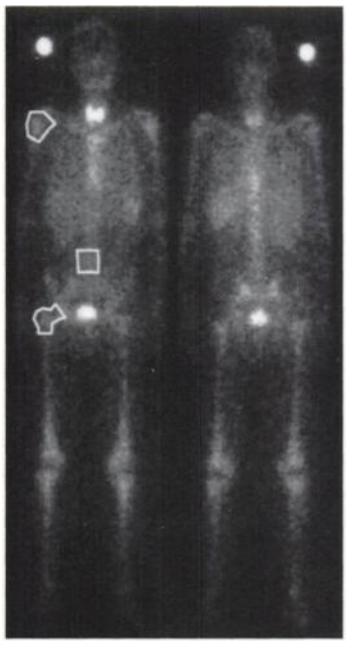

FIGURE 1. Anterior (right) and posterior (left) planar images of a patient. ROIs used for dosimetry are illustrated in the anterior view.

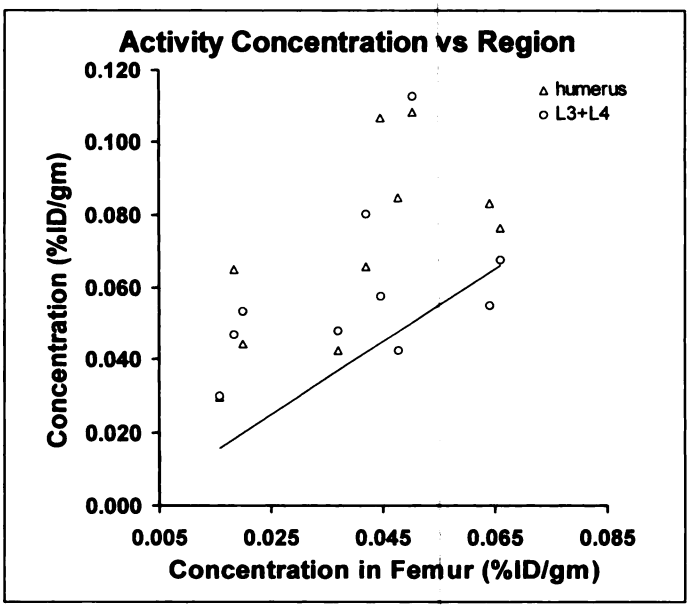

FIGURE 2. Activity concentrations in the humerus and lumbar vertebrae 3 and 4 (L3+L4) plotted against the femur concentration. All values represent back-extrapolated, initial activity concentration obtained by fitting the clearance data. The solid line represents the line of identity for the activity concentration in the femur.

according to each patient's body weight. The activity concentration was expressed as the percent injected dose per gram of tissue (%ID/g). The clearance half-time and back-extrapolated %ID/gm were obtained for each region by fitting each time-activity curve to a single exponential. The significance of differences in the mean concentration and half-life between regions was assessed using Tukey's HSD test (*26*).

Estimates of the absorbed dose to each region were obtained by multiplying the cumulated activity in each region by the appropriate regional S-factors in the MIRDOSE3 dose calculation software (*22*). The cumulated activities were obtained by integrating the fitted analytical expression for each tissue. The whole-body (wb)-to-red marrow (rm) contribution was also added to give the total dose to each marrow region (rg) according to the following equation:

$$D_{rg} = \tilde{A}_{rg} \times S_{rg \leftarrow rg} + \tilde{A}_{wb} \times S_{rm \leftarrow wb}. \qquad \text{Eq. 1}$$

Table 1 lists the recently released regional S-factors, the nominal red marrow mass in each ROI and the mass-adjusted regional S-factors used for these calculations. Further details regarding this general approach to internal emitter dosimetry may be found in MIRD Committee publications (*27*).

To assess the effect of different approaches, we calculated the mean absorbed dose to the red marrow in three different ways:

1. The cumulated activity concentration in the femur was assumed to be representative of whole marrow.
2. A volume-weighted average of the regional cumulated activity concentrations was taken to be representative of whole marrow.
3. A weighted average of the regional doses was used.

The absorbed dose contributions from the liver, spleen and thyroid, as well as the rest of the body were included in calculations 1 and 2; the S-factors from MIRD Pamphlet No. 11 were used (*28*). A whole-body term was also included in calculation 3 to estimate regional doses. Individual organ contributions were not considered separately since S-factors for each organ-to-target region are not currently available.

RESULTS

The activity concentration in the humerus and in L3 and L4 relative to the concentration in the femur is depicted in Figure 2. In the 10 patients examined, the mean and s.d. of the activity concentration in the femur, lumbar and humeral regions was 0.04 ± 0.02, 0.06 ± 0.02 and 0.07 ± 0.03 %ID/gm, respectively. As also seen in Figure 2, however, a wide variability in activity concentration was observed between patients and also between the different regions in a given patient. The mean activity concentration in the femoral versus the humeral regions was significantly different ($p < 0.05$). Figure 3 depicts a comparison of the regional clearance half-times. The clearance half-times for the whole body and for the slower-clearing blood component are also shown on this plot for comparison. The following mean half-times and s.d.'s were obtained for the femoral, lumbar and humeral regions and for the blood and whole-body, respectively: 50 ± 20, 50 ± 20, 50 ± 10, 37 ± 9

TABLE 1
Self-Dose S-Factors and Nominal ROI Masses Used in Dose Calculations

Region	Mass* (g)	S-factors* (mGy/MBq-sec)	ROI	Mass† (g)	Modified S-factors (mGy/MBq-sec)
Legs, upper	37.5	1.69×10^{-4}	Femoral heads	39.8	1.59×10^{-4}
Arms, upper	25.6	2.43×10^{-4}	Humeral heads	19.9	3.12×10^{-4}
Spine, lower	110	1.67×10^{-4}	L3+L4	47.9	3.83×10^{-4}

* From MIRDOSE3.
† ICRP Task Group on Reference Man (see ref. 25).

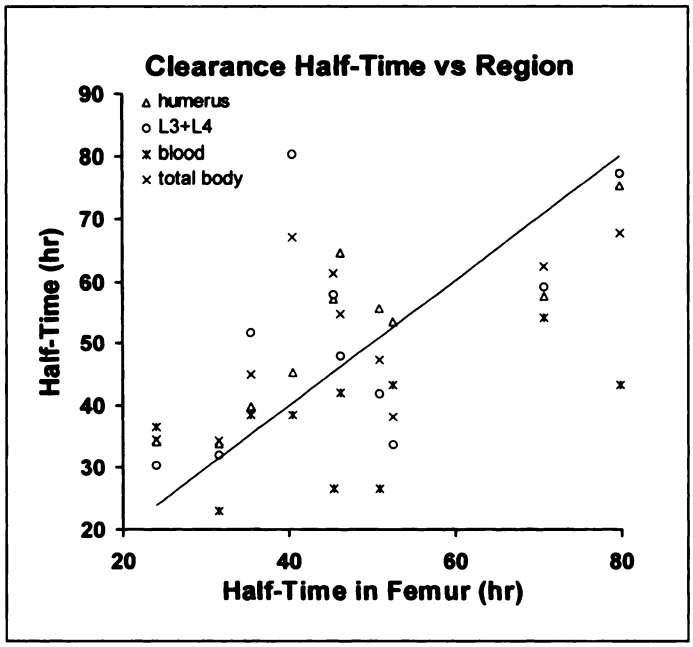

FIGURE 3. Clearance half-times in the humerus, lumbar vertebrae 3 and 4 (L3+L4), blood and whole body plotted against femur concentration. Solid line represents the line of identity for the half-time in the femur.

and 50 ± 10 hr (no two groups were significantly different). Although wide inter- and intrapatient variability are also observed in the marrow region half-lives, no systematic difference between the three different marrow regions is evident. As expected of a marrow-targeting antibody, the clearance half-time in the marrow is generally greater than that in blood. The whole-body clearance half-time is approximately the same as that in the marrow, possibly indicating that whole-body kinetics are dominated by clearance of antigen-bound HuM195 antibody (*20*) (The mean clearance half-times in liver and spleen were 38 ± 9 and 40 ± 10 hr).

The absorbed dose to each marrow region is depicted in Figure 4, which demonstrates that the activity concentrations and clearance half-times, alone, may not be used to arrive at conclusions regarding the absorbed dose distribution in marrow. The mean absorbed dose to the lumbar region (2.2 ± 0.5 mGy/MBq; 8.3 rad/mCi), for example, is greater than the absorbed dose to the humeral region (1.0 ± 0.3 mGy/MBq; 3.8 rad/mCi) and approximately a factor of three greater than the dose to the femoral region (0.66 ± 0.3; 2.4 rad/mCi). This ranking is different from that obtained for activity concentration

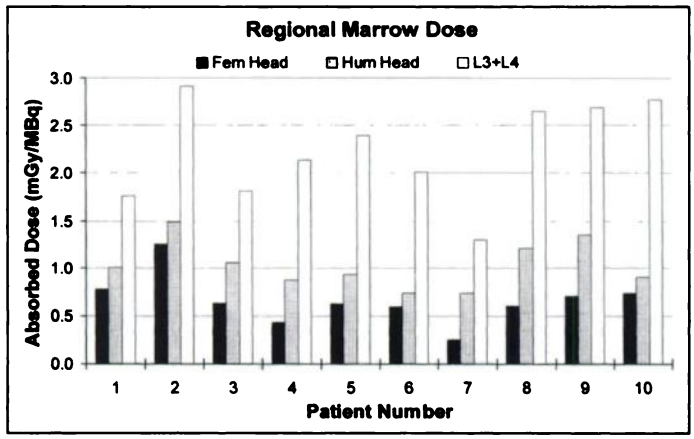

FIGURE 4. Absorbed dose to the femoral heads (Fem Head), humeral heads (Hum Head) and lumbar vertebrae 3 and 4 (L3+L4) for each patient. Values may be converted to rad/mCi by multiplying by 3.7.

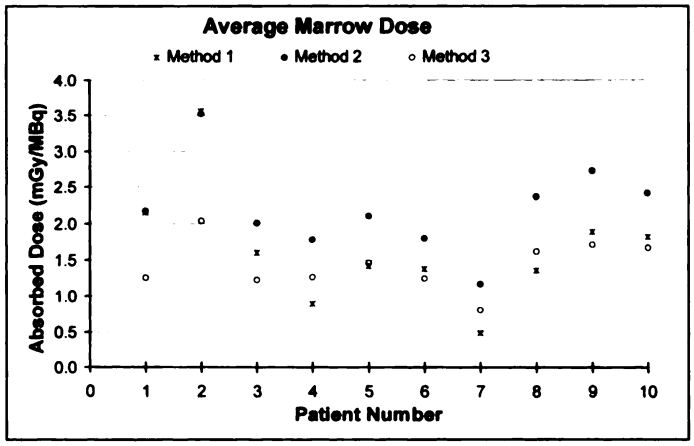

FIGURE 5. Average absorbed dose to the red marrow for each patient. Method 1: cumulated activity concentration in the femur was used. Method 2: volume-weighted average of the cumulated activity concentration in each region was used. Method 3: weighted average of the regional absorbed doses was used. Values may be converted to rad/mCi by multiplying by 3.7.

and depends considerably upon the region volumes and volume-adjusted S-factor values listed in Table 1.

Figure 5 depicts the mean absorbed dose to the red marrow calculated in three different ways. In the first approach, the cumulated activity concentration in the femoral head and neck is assumed to be representative of whole-body red marrow (Method 1). The mean and s.d. of the red marrow absorbed dose using this assumption is 1.7 ± 0.8 mGy/MBq (6.1 rad/mCi). Using a weighted-average of the cumulated activity concentration in each region (Method 2), the corresponding value is 2.2 ± 0.6 mGy/MBq (8.2 rad/mCi). A weighted average of the absorbed dose to each region (Method 3) yields 1.4 ± 0.3 mGy/MBq (5.3 rad/mCi). S-factors obtained from MIRD Pamphlet 11 (*28*) were used for the first two calculations, while the recently released MIRDOSE3 regional S-factors were used for the third approach. The discrepancy between the absorbed dose estimates of Method 2 versus Methods 1 and 3 observed in some patients reflects the lower activity concentration measured in the femoral region (Method 1) and also the lower marrow-to-marrow S-factor values used for Method 3 compared to the MIRD Pamphlet 11 values used in Methods 1 and 2. The recently revised S-factors reflect more recent estimates of the red marrow absorbed fractions for electrons (*22,29*).

DISCUSSION

The large inter- and intrapatient variability differences observed in this study suggest that dosimetry based upon the activity concentration at a single site may not adequately assess the potential for marrow toxicity in any given patient.

It is important to note that approximately 7% of whole-body red marrow volume was accounted for in the regions used to assess red marrow activity concentration. It is difficult to evaluate additional ROIs by planar imaging alone, since activity from overlying and underlying tissues becomes a problem. The significance of variability in terms of marrow toxicity within this 7% is difficult to evaluate. In leukemia, such variability most likely represents the patient-specific distribution of antigen-positive cells within the marrow. In this case, red marrow dose is primarily indicative of target cell dose. Other sources of variability may include differences in both target cell antigen expression and the regional population of cell types (i.e., antigen-expressing target cells, cross-reacting cells and normal cells).

Since the experience with external beam irradiation suggests that specific sites may be depleted of red marrow without

associated morbidity (*30,31*), the regional absorbed dose may not be as much of a concern as the average absorbed dose over the whole marrow. The average dose is a more conservative assessment of potential toxicity since it is not possible to obtain a low mean dose if all marrow regions receive high doses. Given the experience with external beam irradiation, the latter condition is required for overall marrow toxicity. The converse is not true, however—a high mean dose will not always lead to toxicity since one or two high-dose regions will increase the mean dose estimate without affecting overall marrow toxicity. If marrow ablation is the objective (*5*), then the minimum regional dose to the red marrow is important.

The three approaches used in this study to assess mean absorbed dose over the red marrow were included to demonstrate the effect of different assumptions regarding activity distribution and also to compare these values with values obtained when the regional absorbed doses, obtained using recently released regional S-factors, were used to calculate the mean red marrow absorbed dose. The revised marrow S-factors are derived from Monte Carlo calculations which account for the intricate marrow geometry (*29*) better. More recently, Monte Carlo calculations have been performed which examine the increase in absorbed fraction in the marrow cavity due to electron backscatter from bone (*32*).

CONCLUSION

Red marrow dosimetry is important only if it provides a better index of potential marrow toxicity than other more easily determined parameters, such as whole-body absorbed dose or administered activity. Marrow dose estimation is critical since the biological clearance rate, fractional uptake in marrow, radionuclide half-life and emission characteristics are accounted for in assessing absorbed dose. Additional information is required, however, about marrow radiosensitivity, its regional variability and the effect of prior treatment before absorbed dose estimates can be related directly to complication probability.

ACKNOWLEDGMENTS

The authors thank Michael G. Stabin, PhD, and Keith F. Eckerman, PhD, The Oak Ridge Institute for Science and Education, for providing the regional S-factor values prior to their release. This work was supported in part by National Institutes of Health grants U01 CA58260 and R01 CA62444 and Department of Energy grant DE-FG02-86ER-60407.

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