

Dosimetry and Toxicity of Samarium-153-EDTMP Administered for Bone Pain Due to Skeletal Metastases

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Palliation of bone pain in patients with cancer metastatic to bone is being evaluated in several cancer centers by the administration of the bone-seeking phosphonate ethylenediaminetetramethylenephosphonic acid (EDTMP) chelated with the beta particle-emitting radionuclide ^{153}Sm . **Methods:** In this study, ^{153}Sm -EDTMP was intravenously injected into 19 patients over a 1-min period. Patients received up to four injections of 18.5 MBq (0.5 mCi) or 37 MBq (1.0 mCi) per kilogram of body weight. Skeletal retention was calculated from urinary excretion. **Results:** No uptake of ^{153}Sm -EDTMP in nonskeletal tissues was observed in whole-body gamma camera images. The mean skeletal uptake for all patients was $54\% \pm 16\%$ of the injected dose (%ID). This resulted in the bone marrow receiving $89 \text{ cGy/GBq} \pm 27 \text{ cGy/GBq}$ ($3.28 \text{ cGy/mCi} \pm 0.99 \text{ cGy/mCi}$), with calculated marrow doses ranging from 27 cGy to 338 cGy. For each patient, the estimated radiation absorbed dose to the marrow was correlated to the percent decrease in platelet number, ranging from 7.4% to 78.9%. **Conclusion:** Since the deviation of uptake between the four injections for a given patient (7.6% ID) was less than the deviation for all patients (16% ID), the initial dose may be used to estimate the skeletal uptake for the remaining doses. These radiation dose estimates permit patients at risk to be identified prior to reaching myelotoxicity and develop dose-response models. Thirteen patients (68%) reported significant pain relief from this radionuclide therapy. Bone pain appears to be alleviated by ^{153}Sm -EDTMP with limited red marrow doses and no toxic effects in other organs.

Key Words: bone marrow; ^{153}Sm -EDTMP toxicity; skeletal metastases; radionuclide therapy bone pain

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Bone metastases occur in many patients with solid malignant tumors. For example, approximately 50% of patients with breast carcinoma and 80% of patients with prostate carcinoma develop metastatic bone disease and nearly half of them experience bone pain (1). Narcotic analgesics

and external beam radiotherapy are among the most common forms of palliation for bone pain. External beam radiotherapy is less favorable when the disease has metastasized globally, because effective radiation dose can be limited by toxicity in adjacent or overlapping critical structures and organs.

Radionuclide therapy using ^{32}P , ^{89}Sr , ^{90}Y , ^{153}Sm and ^{186}Re has been proposed as an alternative modality for management of bone pain (2-4). These radionuclides are labeled to phosphonates which preferentially localize in active bone, and specifically in sites of metastases producing site-directed radiotherapy. However, canine (5-7) and human patient (8) studies show bone marrow toxicity limits the amount of radiopharmaceutical that may be administered. Radiation dose to the bone marrow depends on the amount of the injected activity that localizes in the skeleton. Turner et al. (9,10) measured skeletal uptake of ^{153}Sm -labeled EDTMP in 63 patients and found a range of 40%-95% of the injected dose (%ID). Singh et al. (11) found a mean skeletal uptake of 45% ID with a deviation of 20% in five patients.

In the Phase I/II clinical trial reported in this paper, palliation of metastatic bone pain was achieved with the beta particle-emitting radionuclide ^{153}Sm attached to the bone-seeking phosphonate ethylenediaminetetramethylene phosphonate (EDTMP). Samarium-153 emits a beta particle of 810 keV maximum energy which is desirable for treatment, photons of 103 keV at 28% which is suitable for imaging, and has a short half-life (46.7 hr). The objectives of our study were to evaluate the pharmacokinetics of repeated injections of ^{153}Sm -EDTMP in 19 patients; determine the characteristics of skeletal uptake; observe the biological response; estimate the radiation dose delivered to the red marrow and other critical organs; and establish a radiation dose versus bone marrow toxicity model for this radionuclide in man.

MATERIALS AND METHODS

Preparation of Samarium-153-Labeled EDTMP

Samarium-153 was produced by neutron capture of isotopically enriched $^{152}\text{Sm}_2\text{O}_3$ at the University of Missouri Research Reactor (Columbia, MO) and then dissolved in 0.1 M HCl. The radio-

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pharmaceutical ^{153}Sm -EDTMP was then prepared by the addition of Ca salt of EDTMP to the acidic ^{153}Sm solution; pH was adjusted with NaOH at the Bioproducts Laboratory, Dow Chemical Company (Midland, MI) and shipped frozen to ensure stability until it was prepared for injection. Quality control tests of the radiopharmaceutical prior to administration included assaying for complexation of ^{153}Sm to EDTMP (consistently >99%), pH (7.0–8.0), sterility and apyrogenicity.

Pharmacokinetics of Samarium-153-Labeled EDTMP in Humans

The radiopharmaceutical was injected intravenously over a 1-min period in a volume that was always less than 1.0 ml. Multiple doses of ^{153}Sm -EDTMP were administered at 4–6-wk intervals as tolerated to nine patients at 18.5 MBq/kg (0.5 mCi/kg) body weight and at 6–10-wk intervals for ten patients at 37 MBq/kg (1.0 mCi/kg).

Serial blood samples were collected in heparinized tubes from each patient at 0.5, 1, 2, 4 and 24 hr following the first injection. The activity in a 1-ml aliquot of whole blood was measured in an automatic gamma counter along with two standards made from the stock solution.

The activity in the blood pool at each collection time was calculated from the measured activity per unit volume in the blood samples. The blood volume of each patient was estimated to be 7% of the patient's total body weight. The total activity in the blood pool was normalized as a percent of the injected activity. The clearance of ^{153}Sm -EDTMP from blood expressed as the half-time was derived using an exponential stripping program.

Pooled urine samples were collected at 0–4, 4–8, 8–12 and 12–24 hr postinjection to measure the total body clearance by urinary excretion. All patients were hydrated for 6 hr before and after they received ^{153}Sm -EDTMP to accelerate clearance of radioactivity from the renal system. Aliquots of urine (20 ml each) were assayed in a dose calibrator (CRC-12, Capintec, Ramsey, NJ). The percent of injected dose in the total volume of urine at each time interval and the cumulated clearance of ^{153}Sm -EDTMP in urine was calculated.

The activity in the whole body was calculated as the residual of the activity excreted in urine. This is represented as:

$$A_{\text{WB}}(t) = A_0 - \bar{A}_{\text{U}}(t), \quad \text{Eq. 1}$$

where $A_{\text{WB}}(t)$ is the activity in the whole body, A_0 is the injected activity, and $\bar{A}_{\text{U}}(t)$ is the cumulated ^{153}Sm excreted in urine at time t postinjection.

The skeletal activity was assumed to be equivalent to the whole-body activity 6 hr after injection. This assumption was validated by the lack of activity in urine collected from 6 to 24 hr, and specific skeletal uptake observed in whole-body gamma camera images acquired at 24 hr postinjection. A typical whole-body gamma camera image is shown in Figure 1. Since the skeletal retention was considered to have an infinite biological half-time, the skeletal uptake was calculated by normalizing the skeletal activity to the injected activity.

The whole-body gamma camera images acquired 24–48 hr postinjection indicated no uptake of ^{153}Sm -EDTMP in nonskeletal tissue. Based on this observation, biodistribution data from the rat model (12) were used to estimate the uptake and clearance of ^{153}Sm in the stomach, small and large intestines, kidneys and liver in patients for calculating radiation doses to these organs.



FIGURE 1. Anterior and posterior whole-body gamma camera images of ^{153}Sm -EDTMP at 24 hr postinjection. The administered activity is localized in the skeleton with no visible uptake in other organs.

Radiation Dose Estimates

Radiation doses to the red marrow and other organs were calculated using the MIRD formalism (13). For bone-seeking radiopharmaceuticals that clear rapidly from the blood, each organ can be considered to receive a radiation dose from essentially two sources: the skeleton and the organ itself. The trabecular and cortical skeleton contribute an equivalent photon dose to each organ, while a "self-dose" is delivered predominantly by electrons emitted in the organ itself. Mathematically, the dose to target organ k is given by:

$$\bar{D}_k = A_0[\tau_k \cdot S_{k \leftarrow k} + \tau_{\text{Skel}} \cdot S_{k \leftarrow \text{Skel}}], \quad \text{Eq. 2}$$

where A_0 is the total activity administered and τ is the residence time in the source organ.

The radiation dose delivered to the red marrow is a special case of Equation 2: (1) there is no detectable uptake of the radiopharmaceutical in the red marrow, therefore its τ is neglected; and (2) activity in trabecular bone contributes a larger electron dose to the marrow than does activity in cortical bone, so their individual contributions to the marrow dose must be considered separately. The MIRD methodology also assumes a uniform distribution of activity within the skeleton. This is a necessary approximation since standard techniques have not been established to measure the activity concentration and distribution within each region of the skeleton and used to calculate the marrow doses. With these approximations, the red marrow dose can be calculated using:

$$\bar{D}_{\text{RM}} = A_0 \cdot \tau_{\text{Skel}} \cdot \frac{1}{2} \cdot [S_{\text{RM} \leftarrow \text{TB}} + S_{\text{RM} \leftarrow \text{CB}}], \quad \text{Eq. 3}$$

assuming an equal distribution (50/50) of skeletal activity in the trabecular bone and cortical bone and neglecting the dose to red marrow from activity circulating in the blood, which clears rapidly (9).

The common approach to bone marrow dosimetry is to assume

TABLE 1
Corrections for Differences in Skeletal Uptake*

Organ	%ID in each organ of the rat [†]	%RB activity in each organ of the rat [†]	τ {h} per % of RB activity
Liver	0.96	$\frac{0.96}{43.1} = 2.23$	0.675
Kidneys	1.74	$\frac{1.74}{43.1} = 4.04$	0.420
Large intestine	0.61	$\frac{0.61}{43.1} = 1.42$	0.149
Small intestine	0.79	$\frac{0.79}{43.1} = 1.83$	0.189
Stomach	0.39	$\frac{0.39}{43.1} = 0.90$	0.104

*From Logan et al. (12).

[†]At 15 min postinjection.

an equal partition of radioactivity in the trabecular and cortical bone. We have defined the ratio of trabecular-to-cortical bone uptake as \hat{f} , where C and m are the activity concentration and mass, respectively:

$$\hat{f} = \frac{C_{TB}}{C_{CB}} \cdot \frac{m_{TB}}{m_{CB}} = \frac{\tau_{TB}}{\tau_{CB}}, \quad \text{Eq. 4}$$

approximating the rate of uptake and release from the two bone types are equal. Thus, from Equation 3 we find the relationship:

$$\bar{D}_{RM} = A_0 \cdot \tau_{CB} \cdot [\hat{f} \cdot S_{RM \leftarrow TB} + S_{RM \leftarrow CB}]. \quad \text{Eq. 5}$$

Since the τ in the skeleton is the sum of cortical and trabecular bone, Equation 4 gives:

$$\tau_{Skel} = \tau_{TB} + \tau_{CB} = \tau_{CB} \cdot [\hat{f} + 1]. \quad \text{Eq. 6}$$

The radiation dose to the red bone marrow is therefore:

$$\bar{D}_{RM} = A_0 \cdot \tau_{Skel} \cdot \left(\frac{1}{\hat{f} + 1} \right) \cdot [\hat{f} \cdot S_{RM \leftarrow TB} + S_{RM \leftarrow CB}]. \quad \text{Eq. 7}$$

When an equal activity distribution exists between cortical and trabecular bone (i.e., $\hat{f} = 1$), the radiation dose relationship becomes:

$$\bar{D}_{RM} = A_0 \cdot \tau_{Skel} \cdot \frac{1}{2} \cdot [S_{RM \leftarrow TB} + S_{RM \leftarrow CB}]. \quad \text{Eq. 8}$$

Radiation dose estimates to the bone marrow presented here follow Equation 8. If the actual activity distribution between cortical and trabecular bone is known, Equation 7 would be more appropriate.

Differences in Skeletal Uptake

The activity localized in a given organ is usually expressed as the percent of the injected dose (%ID). In the case of bone-seeking radiolabeled phosphates, the skeleton is the only organ that exhibits preferential uptake. Activity localized in other organs is proportional to blood or urine activity, both of which result from activity outside the skeleton. The activity in each organ can be

expressed as a percentage of the activity available to the remainder of the body, RB (i.e., that which is not localized in the skeleton). If a large percentage of the injected activity is localized in the skeleton, the activity concentration in the blood will be low, and consequently the %ID in blood-containing organs will be low. The biodistribution data from the rat showed an average skeletal uptake of 56.9% ID, so that 43.1% ID was available to the RB. Because skeletal uptake differs for each patient, τ in each organ should be normalized to the %ID available in the remaining body. The second column of Table 1 shows the %ID measured in five organs of the rat at 15 min postinjection. The third column lists the percentage of activity available in the RB that is localized in the same organs. This ratio was applied to patient data so that τ in organ h of each patient was calculated from the following:

$$\tau_h(p) = \frac{\tau_h(\text{rat})}{\%ID_{RB}(\text{rat})} \cdot \%ID_{RB}(p), \quad \text{Eq. 9}$$

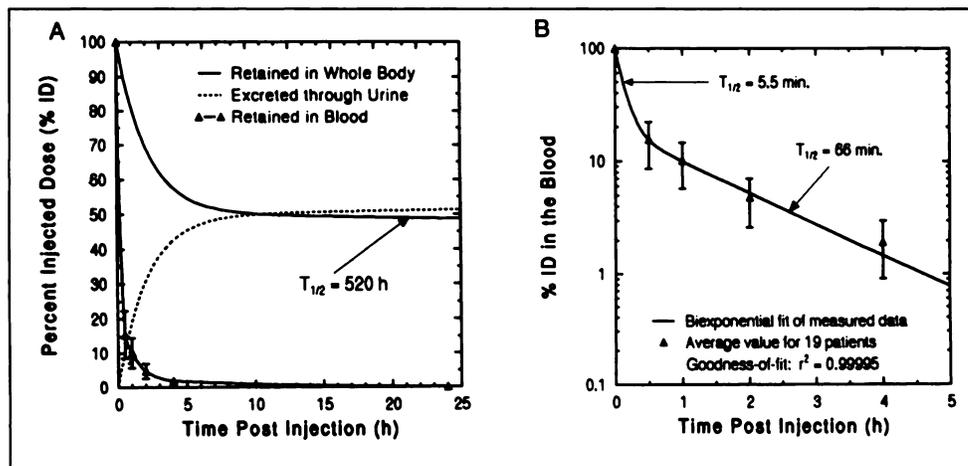
where $\tau_h(\text{rat})$ is the calculated mean τ in organ h of the rat; $\%ID_{RB}(\text{rat})$ is the mean percent injected dose available in the RB of the rat (43.1%); $\tau_h(p)$ is τ for the same organ in a patient; and $\%ID_{RB}(p)$ is the percent injected dose available in the RB of the patient. The first term in Equation 9 yields the numerical values shown in Table 1. These values were multiplied by the percentage of RB activity retained by each patient to calculate the τ in each organ.

RESULTS

Pharmacokinetics

The average pharmacokinetics of ¹⁵³Sm-EDTMP for the 19 patients is shown in Figure 2. The %ID values for the whole body, urine and blood are corrected for radionuclide decay. The clearance of activity through the urine is expressed as the cumulated activity excreted. The whole-body retention is simply the reciprocal of the cumulated urine activity. Figure 2A depicts a rapid clearance of activity from the urine and blood. The mean biological half-time of activity in the skeleton for the 19 patients was 520 hr. Since the biological half-life was ten times greater than

FIGURE 2. Average pharmacokinetics of the first administered dose of ^{153}Sm -EDTMP delivered to 19 patients. (A) The administered activity rapidly clears from the urine and blood and is retained in the skeleton with a mean biological half-time of 520 hr. (B) The blood clears biexponentially.



the physical half-life of the radionuclide, it may be considered infinite for dosimetry purposes.

The activity clearance from the blood was biexponential, as shown in Figure 2B. Over the first 30 min, the blood activity decreased rapidly ($T_{1/2} = 5.5 \text{ min} \pm 1.1 \text{ min}$) to approximately 20% ID and then cleared more slowly ($T_{1/2} = 65.4 \text{ min} \pm 9.6 \text{ min}$). The first phase was assumed to represent the activity leaving the blood pool to localize in the skeleton and the second phase was assumed to represent the activity clearing from the blood to the urine. Less than 1% ID remains in the blood at 5 hr postinjection. Since the activity in the blood cleared rapidly, the radiation dose to the red marrow from activity in the blood was considered negligible in this report.

Skeletal Uptake Characteristics

The dependence of skeletal uptake of the ^{153}Sm -EDTMP on administered activity was evaluated for the first administered dose. The first nine patients received 18.5 MBq/kg

and the measured skeletal uptake was $47.8\% \text{ ID} \pm 16.3\% \text{ ID}$. The next ten patients received 37 MBq/kg and the measured skeletal uptake was $52.5\% \text{ ID} \pm 11.7\% \text{ ID}$. Since the difference between these values was small, the %ID localized in the skeleton was considered independent of the activity injected.

The variation of skeletal uptake between patients for the first administered dose is shown in Figure 3. A broad range in skeletal uptake, Gaussian in nature, was found. The mean skeletal uptake value was $50.4\% \text{ ID} \pm 14.5\% \text{ ID}$. This correlated well with the skeletal uptake value of $52.2\% \text{ ID} \pm 18.0\% \text{ ID}$ for all four injections in all patients.

A better correlation was found between injections for individual patients. Figure 4 shows the mean skeletal uptake for each patient over the four injections. Although the uptake from patient to patient varied greatly, each patient exhibited little deviation between injections. For example, Patient 3 retained a consistently abnormal high %ID for the four injections. The large deviation in uptake exhibited by

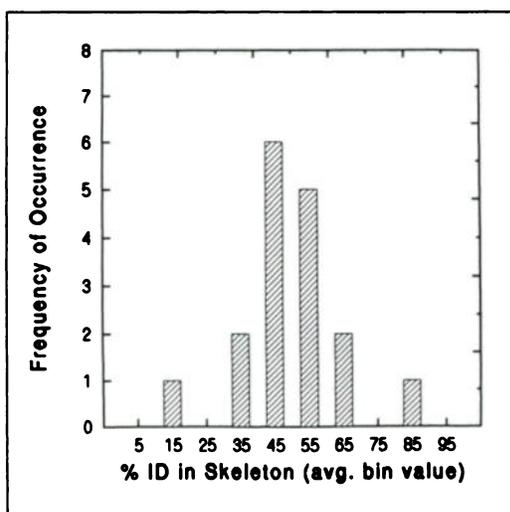


FIGURE 3. Distribution of skeletal uptake of ^{153}Sm -EDTMP in 19 patients for the first administered dose. The mean skeletal uptake was $50.4\% \pm 14.5\% \text{ ID}$.

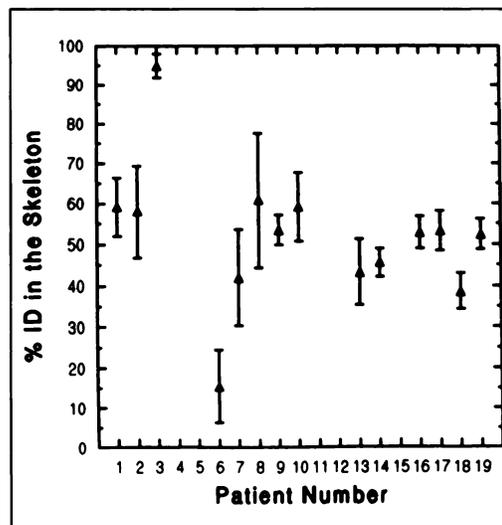


FIGURE 4. Mean skeletal uptake in percent injected dose of ^{153}Sm -EDTMP in 19 patients for all four administered doses. The pooled standard deviation between injections for a particular patient is 7.6%.

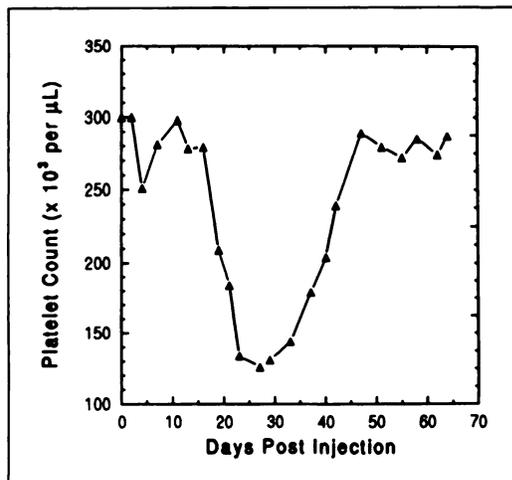


FIGURE 5. Characteristic response of myelotoxicity from ¹⁵³Sm-EDTMP expressed as platelet counts in serial blood samples. This patient achieved platelet nadir at 27 days postinjection and recovered 48 days postinjection.

Patients 2, 6, 7 and 8 may have been partially due to these patients receiving fewer injections. The pooled standard deviation between injections for a given patient (7.6% ID) was calculated by weighting the standard deviation of each patient by the number of injections that patient received.

Biological Response Characteristics

The hematological toxicity for each patient was assessed from the decrease in platelets and white blood cell count observed in serial blood samples. A characteristic platelet response is given in Figure 5. In general, a 2-wk delay in the platelet response was followed by a rapid decrease. The platelet counts were constant for the next 2 wk, and returned to the initial level 2–4 wk following the nadir. The platelet nadir for this patient occurred at 27 days postinjection and a full recovery occurred approximately 50 days postinjection. Figure 6 indicates the time lag in the expression of toxicity of ¹⁵³Sm-EDTMP for all patients enrolled in this study. On average, the platelet nadir occurred 24 ± 5 days postinjection and the white blood cell nadir occurred approximately 24 days postinjection.

Radiation Dose Estimates

The radiation dose estimates to several critical organs were calculated from Equations 2 and 9. The results from 16 patients are shown in Table 2. The results are listed in decreasing order of skeletal uptake and are for the first injection only. The activity administered to each patient is also given as is average radiation absorbed doses for all organs considered. Radiation dose to the red marrow from activity in the skeleton is five times greater than for any other organ listed. The kidneys and the urinary bladder wall also receive a significant radiation dose from activity in the urine. Radiation dose to the liver remains low due to the rapid clearance of the activity from the blood pool.

The red marrow radiation dose estimates were calculated assuming an equal partition of activity between tra-

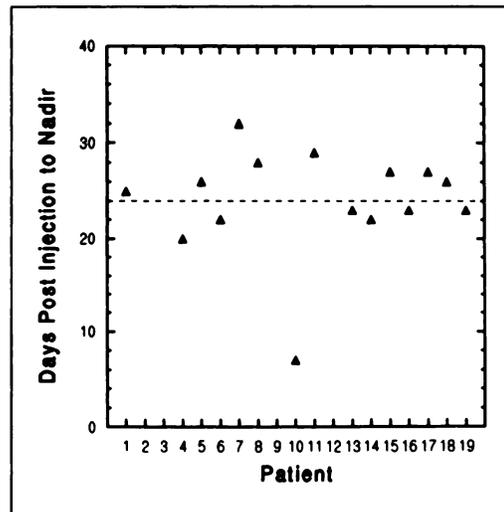


FIGURE 6. Days to platelet nadir for each patient following the first injection of ¹⁵³Sm-EDTMP. The mean platelet nadir was observed 24 ± 5 days postinjection.

becular and cortical bone (i.e., $\hat{f} = 1$). The dependence of calculated doses on this ratio is shown in Figure 7. Since the contribution of dose to marrow from trabecular bone is much greater than from cortical bone, the estimated dose increases as the fraction of activity in trabecular bone increases. The mass of trabecular bone is one-fourth that of cortical bone in standard man. If the concentration of activity in each bone type were equal, \hat{f} would be 0.25; if it were 4:1, \hat{f} would be 1. For the concentration ratio of 7:1 reported by Turner et al., \hat{f} is nearly 2. A 20% larger dose to the red marrow is predicted; this percentage would not necessarily be obtained if the activity ratio were 1, as demonstrated by Figure 7.

Bone Marrow Toxicity

The bone marrow toxicity was assessed by the percent change in platelets. Radiation dose calculations assumed a uniform distribution of activity within all the bones of the skeleton. The relationship between estimated radiation dose and the percent change in platelets is shown in Figure 8. The dose response indicates that the platelets decreased with increasing radiation dose. The calculated radiation doses range from 27 to 337 cGy, which correlated with the percent change in platelets, as they ranged from 7% to 79%.

DISCUSSION

For the 19 patients in this Phase I/II clinical protocol, approximately 50% of the ¹⁵³Sm-EDTMP administered was deposited in the skeleton and the remainder was rapidly excreted through the urine. Since the variance in skeletal uptake observed between injections for a given individual was small (i.e., 7.6% ID), pharmacokinetic data could be obtained from a diagnostic study, prior to palliative therapy, to predict toxicity. The diagnostic study could be used to prescribe a desired therapy dose for efficacy and limit the toxicity to acceptable levels.

TABLE 2
Radiation Dose Estimates to Several Organs Following the First Administration of ^{153}Sm -EDTMP to 16 Patients*

Patient number [†]	%ID in skeleton	Injected activity (GBq)	Bladder wall [‡] (cGy/GBq)	Stomach (cGy/GBq)	Small intestine (cGy/GBq)	Large intestine (cGy/GBq)	Kidneys (cGy/GBq)	Liver (cGy/GBq)	Red marrow [§] (cGy/GBq)
11	82.9	3.12	5.5	2.0	2.4	3.2	5.4	2.5	108.2
1	65.6	1.11	9.1	2.3	2.7	4.3	9.2	3.2	85.5
15	57.8	2.39	10.7	2.5	2.8	4.8	10.9	3.6	75.3
4	57.3	0.84	10.8	2.5	2.8	4.9	11.0	3.6	74.7
16	55.5	2.85	11.2	2.5	2.8	5.0	11.4	3.7	72.3
5	51.7	1.20	12.0	2.6	2.9	5.2	12.2	3.8	67.4
9	50.8	1.19	12.2	2.6	2.9	5.3	12.4	3.9	66.3
17	49.8	2.26	12.4	2.6	2.9	5.3	12.7	3.9	65.0
19	49.6	3.50	12.4	2.6	2.9	5.4	12.7	3.9	64.7
10	48.7	2.27	12.6	2.6	2.9	5.4	12.9	4.0	63.5
14	46.5	4.16	13.1	2.6	3.0	5.6	13.4	4.1	60.6
18	42.1	3.51	14.0	2.7	3.0	5.8	14.3	4.3	54.8
8	41.6	1.66	14.1	2.7	3.0	5.9	14.4	4.3	54.3
13	37.7	3.09	14.9	2.8	3.1	6.1	15.3	4.5	49.2
7	35.3	1.06	15.4	2.8	3.1	6.3	15.8	4.6	46.0
6	13.8	1.52	19.9	3.2	3.5	7.6	20.5	5.5	17.9
Average values	49.18 ± 14.35		12.5 ± 3.0	2.6 ± 0.2	2.9 ± 0.2	5.4 ± 0.9	12.8 ± 3.1	4.0 ± 0.6	64.1 ± 18.7

*Doses are listed per mCi of ^{153}Sm administered. The cumulated activity in each organ was calculated from biodistribution data obtained from a rat model (13) and weighted according to the %ID available, i.e., not taken up by the skeleton. The marrow doses are the exceptions.

[†]Urine samples not available for Patients 2, 3 and 12.

[‡]The mean residence time in the bladder was determined from estimates of urinary clearance assuming 75% voiding every 30 min.

[§]Estimated dose to the marrow assumes that skeletal activity was uniformly distributed in the bones in accordance with the MIRD approach. No specific uptake in the marrow itself was observed.

Toxicity to the bone marrow could be reduced further if the radionuclide selected for palliation emitted beta particles/electrons with a shorter range than ^{153}Sm . Such radionuclides (e.g., internal conversion and Auger electron emitters) would deposit a larger fraction of their energy in the bone tissue and a smaller fraction in the adjacent mar-

row. Since the localization of radiolabeled phosphates in sites of bone metastases is elevated and macroscopic "cold areas" within bone tumors were not observed, these short-range electron emitters would be expected to deliver a large radiation dose to the target tumor cells.

The American Association of Physicists in Medicine (AAPM) established a methodology for estimating bone marrow dose in radioimmunotherapy (14). When specific uptake of the radiolabeled monoclonal antibody in the skel-

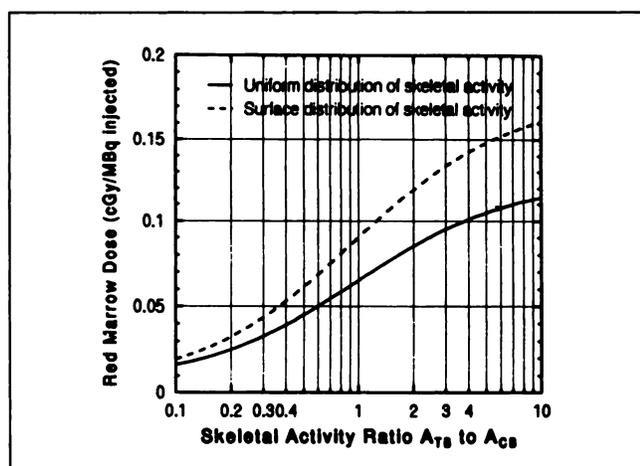


FIGURE 7. Dependence of red marrow dose estimates on distribution of ^{153}Sm within the skeleton. The activity ratio is the product of the ratio of activity concentrations and the ratio of masses between trabecular and cortical bone. Red marrow doses increase when the administered activity preferentially localizes in trabecular bone.

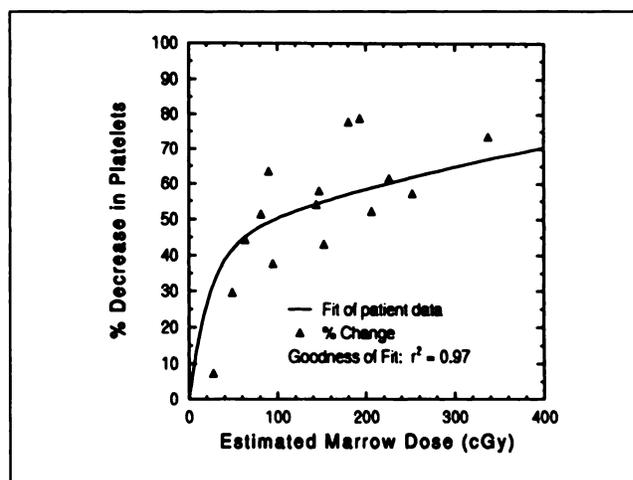


FIGURE 8. Radiation dose response model for each patient following the first injection of ^{153}Sm -EDTMP.

etal system is not detected, the cumulated activity in the marrow can be approximated from activity concentrations measured in serial blood samples. Activity in the blood can be a significant contributor of red marrow dose when the biological clearance of monoclonal antibodies from the blood pool is in the order of days.

The pharmacokinetics of ^{153}Sm -EDTMP serendipitously provides a unique model for radiation dose estimates to the bone marrow for internal emitters and establishing dose response models for bone-seeking radionuclides. The problems related to determining localization of sources in radioimmunotherapy (the amount of specific uptake in the bone marrow and the rate of clearance, the fraction of the blood pool in the marrow cavities, the concentration of activity in the marrow relative to the circulating blood, etc.) are negligible in this model. Most of the ^{153}Sm -EDTMP injected is rapidly localized and retained within the bone, while the remainder is also rapidly cleared from the blood pool by the urinary system. Prompt clearance of ^{153}Sm -EDTMP from the blood pool reduces the red marrow dose from activity in the blood to approximately 1% of the radiation dose delivered from the skeleton.

In practice, the radiation dose delivered to the bone marrow is complicated by other factors. The partition of activity between trabecular and cortical bone is not clear and Figure 7 demonstrates how this affects the dose estimates. The location of activity deposition within the bone is also important in estimating the marrow dose. Heggie et al. (15) have shown that calculations of the radiation dose to the red marrow for ^{153}Sm are underestimated by 24% if the activity is assumed to be uniformly distributed in trabecular bone, compared to a surface distribution on the trabeculae.

An additional factor in influencing dose estimates is the heterogeneity of the activity within a given bone. Applebaum et al. (8) reported spontaneous marrow recovery without marrow transplantation in a canine model, despite delivering 30 Gy to the red marrow. They concluded low uptake in the midshaft of long bones reduced the biological response for the red marrow doses estimated.

Further studies should include an escalation of administered activity for therapeutic treatment of bone lesions as well as palliation. The heterogeneity of skeletal uptake observed in this study implies significantly higher levels of activity could be administered without achieving bone marrow ablation. An accurate estimate of the distribution of radiation doses delivered to the marrow cavities is needed.

If spontaneous marrow recovery continues at higher dose levels, the kidneys and the urinary bladder wall become the critical organs reaching toxicity. However, the radiation dose delivered to the bladder wall can be reduced simply by the addition of a catheter.

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