Pharmacokinetics, Dosimetry and Toxicity of Holmium-166-DOTMP for Bone Marrow Ablation in Multiple Myeloma


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In this Phase I clinical trial, six multiple myeloma patients who had not responded to conventional therapy and were scheduled for bone marrow transplantation received a bone-seeking radiopharmaceutical for bone marrow ablation. The pharmacokinetics, dosimetry, and toxicity of this radiopharmaceutical were studied. Methods: Patients received from 519 mCi to 2.1 Ci (19.2 GBq to 77.7 GBq) of holmium-166 (166Ho) complexed with a bone-seeking agent, DOTMP (1,4,7,10-tetraazacyclododecane-1,4,7,10-tetramethylene-phosphonic acid). The reproducibility of pharmacokinetics from multiple injections of 166Ho-DOTMP administered to these myeloma patients was demonstrated from blood ($r^2 = 0.926$) and whole-body retention ($r^2 = 0.983$), which allowed therapeutic parameters to be determined from a diagnostic study. Results: Over 50% of the 166Ho-DOTMP injected dose was excreted within 2–3 hr postinjection, increasing to 75%–85% over a 24-hr period. Rapid blood clearance resulted in a short half-life. Conclusion: All patients demonstrated severe bone marrow toxicity with a white blood cell (WBC) count <1,000 cells/μL, two patients exhibited marrow ablation (WBC count <100 cells/μL), and no other toxicity grade 2 was observed in any of the patients.

Key Words: marrow ablation; radionuclide therapy; marrow dosimetry


Chemotherapy is the standard treatment for multiple myeloma (1–3). Unfortunately, 30% of patients are resistant to standard-dose chemotherapy at the onset of the disease, and the majority of remaining patients develop resistance rapidly (4). This has led investigators to more intensive treatment regimens such as high-dose chemo-therapy (5), biologic-response modifiers (6) and total body irradiation (7), each of which has shown some success in disease control. Because these therapies are aggressive, they compromise the hematopoietic system to the level of requiring bone marrow transplantation to recover normal blood cell formation.

Bone marrow transplantation itself can be a therapeutic strategy for multiple myeloma patients aimed at achieving complete remission. This technique, called bone marrow ablation, relies on destroying all stem cells of the hematopoietic system, including the precursor stem cells of the myeloma. Following bone marrow ablation, the patient receives healthy stem cells that are capable of self-renewal and allow for marrow reconstitution (8).

In this study, an approach to bone marrow ablation using radionuclide therapy was implemented. The method employed a radiopharmaceutical that localized in the skeleton and delivered therapeutic doses to the adjacent bone marrow. Multiple myeloma patients were selected because this malignancy is largely confined to the marrow and has a steep dose-response to irradiation. Six patients with multiple myeloma were treated; after their original bone marrow was destroyed, they received a re-infusion of their own purged bone marrow.

Holmium-166 is an excellent radionuclide for therapy because with each nuclear transformation 166Ho emits a high-energy beta particle with a maximum energy of 1.85 MeV (max. range ~9 mm) and a small proportion of gamma rays (80.6 keV at 6.6% and 1.38 MeV at 0.90%) (9). Holmium-166 has a physical half-life of 26.80 hr. K-shell x-rays of 48.2 keV at 2.8% and 49.1 keV at 5.0% are also emitted (10). The choice of DOTMP as the chelating agent to deliver 166Ho to the skeleton was made based upon the mass of material to be administered. The use of enough 166Ho to expect ablation would require several milligrams of holmium target material due to the relatively low specific activity of 166Ho. Aminophosphonic acids such as EDTMP are used clinically with a ligand-to-metal molar ratio of approximately 267:1 (11). The use of EDTMP in this ablation application at similar ratios would require correspondingly large amounts of ligand relative to the mass of hol-
mium. In contrast, DOTMP aminophosphonic acid has been found to form kinetically inert complexes with samarium andholmium (12). This property has allowed the use ofDOTMP complexed with 153Ho for ablation studies in beagle dogs at a ligand-to-metal molar ratio as low as 1:5:1 (13).

A major objective of this study was to evaluate the reproducibility of multiple injections of 153Ho-DOTMP administered to each patient by determining the rate at which the injected activity was excreted from the body and the percentage of the injected activity which was retained for each injection. Multiple dose injections rather than one single dose were necessitated by 153Ho production limitations. Additional objectives of this Phase I study were estimating the radiation dose to bone marrow and evaluating the toxicity of 153Ho-DOTMP for bone marrow ablation in a small group of patients. Estimates of the absorbed dose to the tumor sites were beyond the scope of this study, particularly since they would have required estimates of the mass of uptake sites and no plans were made to biopsy these sites.

**MATERIALS AND METHODS**

**Patient Protocol**

Patients under 60 years of age with resistant multiple myeloma despite prior treatment with VAD chemotherapy (continuous infusion vincristine and adriamycin with pulses of dexamethasone) were eligible. Patients with extramedullary myeloma as the dominant site of disease were ineligible. Patients had to have a performance status on the Zubrod scale of 0 (no symptoms) or 1 (symptoms but fully ambulatory). All patients also had to have adequate organ function defined as follows: creatinine level <2.0 mg/100 ml or creatinine clearance >50 ml/min; bilirubin level ≤1.5 mg/100 ml, left ventricular ejection fraction ≥50%; FEVI or FVC ≥70% and DLCO >50% of predicted. There could be no overt infection. Finally, all patients signed an informed consent form and were registered with Data Management Services at The University of Texas M.D. Anderson Cancer Center.

A time line for bone marrow ablation with 153Ho-DOTMP is shown in Figure 1. Approximately 1500 cm³ of bone marrow cells were harvested by aspiration from the right and left iliac crests prior to therapy. The total radiopharmaceutical dose was administered intravenously over a 1-min period to each patient in four separate fractions: a 30-mCi (1.11 GBq) diagnostic dose on one day, followed by three daily therapy doses. The total amount of administered 153Ho was selected to deliver a prescribed red marrow dose of 26 Gy at the first dose level (three patients) and 39 Gy at the second dose level (three patients). Serial blood samples and all excreted urine were collected at several time intervals for 24 hr following the injection of the diagnostic dose. Whole-body gamma camera images were acquired at approximately 1, 6 and 18 hr after injection of the diagnostic dose, and 18 hr after each of the three daily therapeutic injections. The harvested bone marrow was reinfused after the mean estimated radiation dose rate within the bone marrow cavities had fallen to less than 1 cGy/hr, typically 5 to 10 days after the last dose.

**Preparation of 153Ho-DOTMP**

The radioisotope 153Ho⁺³ was supplied by the University of Missouri Research Reactor (Columbia, MO). The isotope was produced by neutron capture reaction [152Ho(n, γ) → 153Ho] using 152Ho(NO₃)₃ as the target material in a thermal neutron column (flux of 8 × 10¹³ to 2.5 × 10¹⁴ neutrons cm⁻² s⁻¹, for irradiation periods of 84 to 155 hr). Radionuclide purity was assessed by high-purity germanium (HPGe) spectrometry to be less than one part in one million, where the impurity is 154Ho. After irradiation, the target was dissolved in a sufficient amount of 0.1 N HCl to keep the holmium concentration at or below 2.42 mM. After sterile filtering, the vial was shipped overnight at ambient temperature to the M.D. Anderson Cancer Center. The quantity of 153Ho received was verified with a HPGe spectrometer and was subsequently used to cross-calibrate a reentrant-well air ionization chamber.

The 153Ho-DOTMP complex was prepared by adding 5 ml of 153Ho in 0.1 N HCl to a lyophilized, sterile, pyrogen-free evacuated vial containing 1.5 equivalents of DOTMP (18 μmole) and enough base to neutralize the hydrochloric acid. The resulting pH was >8 to ensure complexation. The degree of complexation was determined by simple cation and anion-exchange chromatography techniques. The pH was then adjusted to between 7 and 8 by the addition of sterile filtered phosphate buffer. The final radiopharmaceutical was assayed for percentage of 153Ho complexed using both cation and anion exchange chromatography techniques and was consistently >99% complexed. An aliquot of the final dose was tested for pyrogenicity and sterility.

**Pharmacokinetics of 153Ho-DOTMP in Urine**

Pooled urine samples were collected for 0–2, 2–4, 4–6, 6–8, 8–12, 12–20, and 20–24-hr periods postinjection to measure total body clearance of 153Ho. Urine samples were not collected from the first two patients. Patients 2–6 were hydrated at 75 ml/hr during the week they received 153Ho-DOTMP to accelerate clearance of radioactivity from the renal system.

**Nal Probe Measurement of 153Ho-DOTMP Whole-Body Retention**

Although urine was collected after the diagnostic injection of 30 mCi (1.11 GBq), that was considered impractical for therapeutic injections because of the large activities administered and the risk of contamination. Consequently, an alternate method was developed to measure whole-body retention with a Nal probe detection system. The probe was a 2 × 2-inch Nal scintillation detector interfaced to an MCA (Canberra Industries, Model Series 20, Meriden, CT). The Nal detector was positioned such that the central axis of the detector was 90 cm above the floor and the
detector viewed the full length and width of the erect patient. The detector was shielded from extraneous sources such as residual urine in the bathroom or radioactivity in adjacent hospital rooms with 5-cm thick lead bricks. The 50 keV and 80 keV photons emitted by $^{166}$Ho were not used to measure total body activity because they are more significantly affected by attenuation differences of bone and soft tissue. Rather, the MCA allowed us to restrict measurement to include only the 1.38 MeV photons emitted by the $^{166}$Ho in the patient. The low-energy photons were filtered by placing 4 mm of lead over the face of the detector. This permitted measurement of high integral count rates over the 1.38 MeV photon peak without operating the detection system under signal overload (deadtime).

Longitudinal dependence of the detector was evaluated by acquiring counts with a $^{60}$Co point source positioned at 10-cm increments from 0 to 2 m. Latitudinal dependence was evaluated by acquiring counts with the same source positioned 90 cm from the floor and displaced at 10-cm increments off the central axis, from 0 to 1 m. The count rate variation was within 10% of the mean value for nearly all source locations along the length of the body and within 10% of the mean value for a patient up to ±70 cm wide.

To provide an initial (t = 0) count rate, immediately following the injection of $^{166}$Ho-DOTMP and before the patient urinated, the patient stood 2 meters from the face of the detection system and photon counts were measured. The geometric mean of anterior and posterior counts were used to compensate for the effect of any source movement in the transverse (axial) plane of the patient (14). To determine the percentage of the injected activity retained in the whole body, the photon count rate measured at each time point postinjection was corrected for physical decay of $^{166}$Ho and normalized to the initial count rate.

Retention of $^{166}$Ho-DOTMP in the Whole Body from Multiple Injections

Whole-body retention was measured for all diagnostic and therapeutic injections using the NaI probe. The geometric mean of the anterior and posterior counts was calculated to yield the true count rate at each time point.

Following the first injection, the counts recorded with the probe were directly proportional to the activity retained in the body at the time of the measurement. Count rates measured with the probe following the second injection represented the summation of activity remaining from the first injection and the activity administered in the second injection. Since each patient received four daily injections of $^{166}$Ho, the detected counts from the activity remaining from previous injections was subtracted from the measured counts C$_M$. The true count rate C$_T$ at time t following the initial injection was determined by correcting the counts measured from the previous injection C$_M$(t − $\Delta t$) at time t − $\Delta t$ by applying a decay factor $e^{-\lambda\Delta t}$ and subtracting the result from the measured value at t. Mathematically, this is given by

$$C_T(t) = C_M(t) - C_M(t - \Delta t) \cdot e^{-\lambda\Delta t}.$$  \hspace{1cm} \text{Eq. 1}

Pharmacokinetics of $^{166}$Ho-DOTMP in Whole Blood

Serial blood samples were collected in heparinized tubes from each patient at 0.083, 0.25, 0.5, 1, 2, 4, and 24 hr postinjection. The activity in a 1-ml aliquot of whole blood was measured in an automatic gamma counter calibrated with two $^{166}$Ho standards prepared from a stock solution. Each patient was assumed to have a blood pool of 5 liters.

**Bone Marrow Radiation Dose Estimates**

Radiation doses to the red marrow were calculated using the MIRD formalism (15) and follow the variable model employed by Maxon et al. (16). The radiation dose to each target organ from all source organs (the S factors) was obtained using the MIRDose2 computer program distributed by Oak Ridge National Laboratory. The bone marrow dosimetry presented here follows the assumption suggested by the MIRD Committee (17) of an equal partition (50/50) of skeletal activity in the trabecular and cortical bone and neglects the dose to red marrow from activity circulating in the blood, which clears rapidly (18). The amount of activity required to deliver the prescribed radiation dose to the bone marrow and the waiting period necessary to limit the radiation dose rate to the infused marrow to an acceptable level (1 cGy/hr) for transplantation were determined as previously described (19).

**Toxicty**

The primary clinical response parameter in this Phase I trial was to achieve bone marrow ablation, i.e., complete eradication of hematopoietic cells (blood cells) of the bone marrow. Verification of bone marrow ablation is complex, and the parameters and techniques to confirm ablation are not well established. In this protocol, bone marrow ablation was evaluated clinically by measuring the peripheral white blood cell (WBC) count; ablation was considered to have been achieved when the WBCs were reduced to a nadir of 100 cells per microliter of blood. In a second method, bone marrow aspirates drawn from the iliac of the $^{166}$Ho-DOTMP patients were analyzed for hematopoietic activity. The aspirates drawn from the iliac crest of each patient were assessed for stem cell viability by visual examination. The plasma cell differential was determined both morphologically and from flow cytometry. Ablation was considered successful if the aspirate demonstrated minimal activity. Tumor cells in the marrow aspirates were also counted and expressed as a percent of all the cells.

**RESULTS**

**Urine**

The rate and magnitude of urinary excretion for Patients 3–6 are displayed as a log-linear plot in Figure 2. The cumulated urinary excretion data from a previous study of patients receiving $^{153}$Sm-EDTMP for cancer metastatic to the bone (20) are included in Figure 2 for comparison. Over 50% of the $^{166}$Ho-DOTMP injected dose was excreted within 2–3 hr postinjection, and over the period of 10 to 24 hr, the activity appears to leave the body as a single exponential. Whereas 50% of the $^{153}$Sm-EDTMP was excreted over a 24-hr period, nearly 75–85% of the $^{166}$Ho DOTMP was excreted over the same time. This difference may be attributable to the phosphonates, although animal studies with $^{166}$Ho-DOTMP (12) and $^{166}$Ho-EDTMP (21) have indicated that nearly 50% of the injected dose localized in the skeleton. The relatively low uptake of $^{166}$Ho-DOTMP observed in these multiple myeloma patients may be the result of disease involvement of the bone (22,23) and of increased skeletal uptake of $^{153}$Sm-EDTMP by the bastic bone lesions (24). In support of the latter, the 19 $^{153}$Sm-EDTMP patients exhibited a larger variation in excretion than that observed in the $^{166}$Ho-DOTMP patients; this is perhaps attributable to the wide range in the number of bone lesions noted in the $^{153}$Sm-EDTMP patients.
Validation of NaI Probe Measurements with Cumulated Urine Results

Total body retention of $^{166}\text{Ho}$-DOTMP (measured with the NaI probe) should be equivalent to the residual activity excreted in the urine, inasmuch as no other pathway for elimination of $^{166}\text{Ho}$ exists. Skeletal uptake was assumed to be equivalent to whole-body activity at 10 hr postinjection. This assumption was validated qualitatively by whole-body gamma camera images acquired at 4 hr postinjection (Fig. 3). These images show specific uptake in the skeleton, and images acquired from 18 to 66 hr postinjection indicated no detectable uptake of $^{166}\text{Ho}$-DOTMP in nonskeletal tissue.

Whole Body Retention

Whole-body retention of $^{166}\text{Ho}$-DOTMP for one patient, as measured by the NaI probe and corrected for physical decay of $^{166}\text{Ho}$, is shown in Figure 4A. The injected activity cleared the body in a two-compartment model: a rapid phase followed by a slow clearance. The rate and magnitude of whole-body clearance measured with the diagnostic study duplicated the response from the therapeutic injections at nearly every time point measured. The %ID values at 24 and 27 hr from the diagnostic dose are slightly below the values observed from therapy. This underestimation may have been due to statistical errors in the small number of counts measured with the probe 24 hr postinjection for the diagnostic study, which was not a problem for the therapeutic studies. The %ID retained in the whole body following diagnostic injection was compared to the values derived from the therapeutic injections (Fig. 4B). These results show a direct correlation ($r^2 = 0.983$) between the diagnostic and therapeutic injections; almost every therapeutic value was within 5% of the diagnostic readings for all five patients studied. The correlation between diagnostic and therapeutic injections was not evaluated for Patient 1 because hydration for this patient changed significantly during the study.

An interpatient comparison of whole-body retention of $^{166}\text{Ho}$ is depicted in Figure 4C. Each curve represents a biexponential fit of four injections for each patient; all data were corrected for physical decay of $^{166}\text{Ho}$. The interpatient correlation observed in Figure 4A differs from the interpatient variability shown in Figure 4C. Interpatient variability is demonstrated both in the magnitude of skeletal uptake and the rate of biological clearance. These results clearly show the necessity for accurate measurements of whole-body retention for each patient and demonstrate that diagnostic studies of $^{166}\text{Ho}$-DOTMP are predictive of whole-body retention for subsequent therapeutic injections.

Blood

The %ID of $^{166}\text{Ho}$ retained in whole blood following the diagnostic injection is shown for each patient in Figure 5A. All patients exhibited biexponential clearance of activity: a rapid phase (avg. $T_{1/2} = 1.5 \pm 0.6$ min) followed by a slower phase (avg. $T_{1/2} = 64 \pm 23$ min). Less than 10% of the injected activity remained in the blood pool 1 hr postinjection, and less than 2% remained after 5 hr. The clearance of $^{166}\text{Ho}$-DOTMP from whole blood expressed as the

**FIGURE 2.** Measured cumulated urinary excretion of $^{166}\text{Ho}$-DOTMP in patients receiving 30 mCi (1.11 GBq) as a diagnostic dose. Data from $^{153}\text{Sm}$-EDTMP are shown for comparison. Holmium-166-DOTMP clears slowly from the body over the 6–24-hr period.

**FIGURE 3.** Whole-body gamma camera images acquired 4 hr after the diagnostic injection of 30 mCi (1.11 GBq) of $^{166}\text{Ho}$-DOTMP administered to Patient 4. Localization is primarily in the skeleton, with minimal uptake visualized in the kidneys and bladder.
half-time for each phase was derived using an exponential stripping program (Table 1).

Data obtained from blood samples indicate that the levels of whole blood retention and clearance were qualitatively similar for all four injections. The percentage of the injected activity measured in the blood is shown for Patient 3 in Figure 5B. Small differences in blood activity between the four injections were observed until 24 hr postinjection, at which time the low activity yielded poor counting statistics. Comparison of the whole-body clearance in Figure 5B demonstrates that the amount of activity in the blood pool was negligible relative to that retained in the whole body, and that the activity was cleared from the blood much more rapidly than from the whole body.

Figure 5C depicts the reproducibility of whole blood retention from multiple injections of $^{166}$Ho-DOTMP. For Patients 1–3, blood samples were collected 0.5, 1, 4, and 24 hr postinjection for the diagnostic and all three therapeutic injections, allowing direct comparison. Analogous to whole-body retention measurements, the %ID of $^{166}$Ho in whole blood measured after therapeutic injections was found to be within 5% of the corresponding diagnostic values, with a correlation coefficient of $r^2 = 0.926$.

**Bone Marrow Radiation Dose Estimates**

The values of the parameters required to calculate $\bar{D}$ (RM) and the results are listed in Table 2. The average red marrow dose delivered from the diagnostic study was 76 ± 19 cGy. Although marrow doses at this level from $^{131}$I-labeled monoclonal antibodies have produced Grades 1–3 toxicity in Phase I clinical trials (25,26), experience with radiolabeled bone-seeking phosphonates such as $^{153}$Sm EDTMP (18,20,24,27–29) has shown that myelotoxicity at these marrow doses was reasonable. These $^{166}$Ho patients received increasing activity at each dose level, which resulted in increasing radiation dose to the bone.
TABLE 1
Whole Blood Retention of $^{166}$Ho-DOTMP Measured from the Diagnostic Injection

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Biological half-life in blood (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Phase 1</td>
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<tr>
<td></td>
<td>$T_{1/2}$</td>
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<tr>
<td>1</td>
<td>1.5</td>
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<td>2</td>
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<tr>
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</tr>
<tr>
<td>5</td>
<td>2.2</td>
</tr>
<tr>
<td>6</td>
<td>1.3</td>
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</table>

Mean values 1.5 0.6 64 23

FIGURE 6. Remaining cumulative dose rate in bone marrow following administration of $^{166}$Ho-DOTMP. Once the dose rate within the marrow cavity was below 1 cGy/hr, the remaining dose rate was considered safe for re-infusion of transplant marrow.

marrow. In this study, the third patient was the first to receive a therapeutic dose calculated from the diagnostic data (after accounting for interpatient differences in skeletal uptake and biological clearance). As a consequence of the unexpectedly low skeletal uptake and determining the injected dose on a mCi/kg basis for the first two patients, they did not receive the prescribed radiation dose in Step I of the present protocol (26 Gy). Also, the first two patients demonstrated a variation in the cGy/mCi level to the bone marrow, which can be attributed to changes in the hydration rate for these patients during therapy. In step 2 (4–6) all three patients received a radiation dose to the bone marrow near the prescribed dose of 39 Gy. The total radiation absorbed dose delivered to the bone marrow for the six patients ranged from 7.9 Gy to 41.4 Gy.

Figure 6 shows the radiation dose rate averaged over the whole bone marrow for all six $^{166}$Ho-DOTMP patients. The dose rate to the marrow decreased exponentially as a function of the effective half-life of $^{166}$Ho-DOTMP in the skeleton. Although the variation in biological clearance of $^{166}$Ho-DOTMP from the skeleton and the resultant total marrow dose are large, the range in waiting periods for a dose rate limit of 1 cGy/hr was small; consequently, all patients were eligible to receive their transplant marrow within 130 hr following the final injection of $^{166}$Ho-DOTMP. This short

TABLE 2
Radiation Dose Estimates to the Marrow from Whole-body Retention Measurements with the NaI Probe

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Dose</th>
<th>Administered activity of $^{166}$Ho (mCi)</th>
<th>Effective half-life (hr)</th>
<th>%ID in the skeleton at t = 0*</th>
<th>Bone marrow dose estimates† (cGy)</th>
<th>Relative marrow dose (cGy/mCi)</th>
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<td>—</td>
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<td>—</td>
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*Values of %ID were measured >20 hr postinjection and extrapolated back to t = 0.
†Marrow dose estimates are calculated as the mean red marrow dose using the MIRD method.


waiting period is an advantage of $^{166}$Ho, which nearly halves the dose rate delivered to the bone marrow every 24 hr.

**Toxicity**

The degree of bone marrow eradication for all patients appears in Table 3. All patients demonstrated severe bone marrow toxicity with a WBC count <1000 cells/$\mu l$, and Patients 5 and 6 exhibited marrow ablation. Examination of bone marrow aspirates produced the same results as counts of peripheral WBCs in this small group of patients. The WBC responses to $^{166}$Ho-DOTMP are shown for all patients in Figure 7. In each patient, the transplant marrow was reinfused 7–10 days following the final injection of $^{166}$Ho-DOTMP. All patients showed a similar WBC response after receiving $^{166}$Ho-DOTMP: a rapid decrease in counts, an ~14-day plateau followed by a recovery phase. All patients received a recombinant granulocyte colony-stimulating factor at a dose of 5 $\mu g/kg$ beginning on the day of the transplant and continuing until the WBC count was >5,000 cells/$\mu l$. The WBC response of Patient 4 was similar to the responses of Patients 1–3, even though the red marrow dose estimate for all three patients in the second step of the protocol (38 ± 3 Gy) was significantly greater than the estimates for the first step (15–26 Gy). Patients 5 and 6 demonstrated a more complete WBC response.

**DISCUSSION AND CONCLUSION**

The pharmacokinetics of $^{166}$Ho-DOTMP in the blood, urine and whole body of six multiple myeloma patients was investigated. The amount of activity retained in the skeleton of these patients, 15%–30% of the injected dose, was lower than expected based on experience with a similar bone-seeking radiopharmaceutical ($^{153}$Sm-EDTMP). Also, unlike the result in $^{153}$Sm-EDTMP studies, the biological half-life of $^{166}$Ho-DOTMP was not infinite. The shortest biological half-time for clearance of $^{166}$Ho-DOTMP from the skeleton was 44 hr. One possibility for the relatively low uptake is that this might be characteristic of multiple myeloma patients; proposed studies of patients with metastatic breast cancer with bone and marrow involvement may provide further explanation.

A primary objective of this research was to demonstrate reproducibility of in vivo pharmacokinetic measurements following multiple injections of $^{166}$Ho-DOTMP administered to patients. Reproducibility was demonstrated for both blood and whole-body retention for the therapeutic activities used in this study (Figs. 4B, 5C). Thus, important therapeutic information can be determined from a diagnostic injection regarding the amount of activity required to deliver a prescribed radiation dose to the marrow, waiting period to limit the radiation dose to the re-infused transplant marrow to a defined level and dose to other critical organs. Safety considerations dictate the importance of estimating these values for each patient because of the significant variability of interpatient pharmacokinetics shown here.

Interpatient differences in skeletal uptake and biological clearance produce dose rates to the marrow that differ by more than a factor of 10. These dose rates, however, are still in the region where the dose-response does not change significantly with rate and was therefore not considered significant.

Bone marrow dosimetry has been a challenge both for external beam irradiation techniques and internal dosimetry with radionuclides. Important information on a dose response model for bone marrow ablation depends on determination of the radiation absorbed doses delivered to the red marrow from $^{166}$Ho. We have developed a treatment planning strategy designed to estimate the average red marrow dose in the total marrow volume for each patient. Additional dosimetry should account for the non-uniform spatial distribution of activity within the skeleton. Appelbaum et al. (30) reported regional “cold spots” in the skeleton and Turner et al. (27) observed activity per gram

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**TABLE 3**

Analysis of Bone Marrow Ablation in Multiple Myeloma Patients Receiving $^{166}$Ho-DOTMP

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>WBC nadir ($\times 10^9$ cells/$\mu l$)</th>
<th># Days WBCs ≤300 cells/$\mu l$</th>
<th>Marrow ablation observed in aspirate</th>
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<tr>
<td>1</td>
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<td>0</td>
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<tr>
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<tr>
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<td>6</td>
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**FIGURE 7.** White blood cell response of multiple myeloma patients who received $^{166}$Ho-DOTMP. The transplant marrow was re-infused between 7 and 10 days following the final injection of $^{166}$Ho-DOTMP. Bone marrow ablation, defined as <100 white blood cells per $\mu l$ of peripheral blood, was observed in Patients 5 and 6. These patients were the only two who received red marrow dose estimates over 10 Gy for all skeletal regions.
in trabecular bone to be seven times greater than that found in cortical bone. The MIRD formalism utilizing "S" factors (17) assumes a uniform distribution of activity in each source organ and that each patient is configured as Reference Man. A more rigorous model would be useful to quantify regional radiation dose distributions delivered to bone marrow and prescribe a therapeutic dose that depends on total skeletal mass. This type of model would be necessary to assess stromal damage. Fibrosis is a consideration because of the nonuniform pattern of absorbed dose delivered to the skeletal system from $^{166}\text{Ho-DOTMP}$. Fibrosis is likely above absorbed doses of about 90 Gy. Prompt recovery of blood counts after re-infusion of the purged marrow in every patient, however, indirectly indicated that damage to the stroma was not a significant problem for this radionuclide therapy approach.

To date, nine patients who received $^{166}\text{Ho-DOTMP}$, two at the 50 Gy level, indicated a clinical response as assessed by a drop in myeloma marker protein. One of these patients has had a complete response and the protein markers indicate a greater than 90% drop 8 mo after treatment. The second patient had a partial transient fall in protein and subsequently progressed to successful autologous bone marrow transplantation.

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