

High-Dose ^{166}Ho -DOTMP in Myeloablative Treatment of Multiple Myeloma: Pharmacokinetics, Biodistribution, and Absorbed Dose Estimation

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Thirty-two patients with multiple myeloma were treated with high doses of ^{166}Ho -1,4,7,10-tetraazacyclododecane-1,4,7,10-tetramethylene-phosphonic acid (DOTMP) and were a subset of patients enrolled in a multicenter phase I/II dose escalation myeloablative trial. ^{166}Ho with β -emission (half-life, 26.8 h; β -particle energies, 1.85 MeV [51%] and 1.77 MeV [48%]; γ -photons, 80.6 keV [6.6%] and 1.38 MeV [0.9%]) was complexed to DOTMP, a macrocyclic tetraphosphonate. Pharmacokinetics, dosimetry, and biodistribution were studied. **Methods:** Patients were treated at escalating dose levels of 20, 30, and 40 Gy to the bone marrow in combination with high-dose melphalan, with or without total-body irradiation, to evaluate toxicity and efficacy. After infusion with 1,110 MBq (30 mCi) of ^{166}Ho -DOTMP for evaluation of biodistribution and dosimetry calculation, patients received the calculated amount of radioactivity for therapy in a single administration based on estimated dose calculations. **Results:** Thirty-two patients participated in the study and were then treated. The average amount of administered radioactivity was 74.3 GBq (2,007 mCi) (range, 21.5–147.5 GBq [581–3,987 mCi]) of ^{166}Ho -DOTMP. **Conclusion:** ^{166}Ho -DOTMP has physical and pharmacokinetic characteristics compatible with high-dose myeloablative treatment of multiple myeloma.

Key Words: β -emitters; radionuclide therapy; myeloablation; dosimetry; myeloma

J Nucl Med 2002; 43:1383–1390

Multiple myeloma is an aggressive plasma cell malignancy with ultimately fatal outcome. The 5-y survival rate is less than 30% and has remained unchanged for more than 3 decades (1). High-dose chemoradiotherapy, with or without stem cell rescue, was introduced in an effort to improve patient survival and to mitigate the problem of drug resistance seen in these patients (2,3). Total-body irradiation

(TBI) has been the mainstay of these protocols. However, because of concern about the high incidence of systemic toxicities seen with regimens using TBI, higher doses of melphalan were tried for this purpose and had similar efficacy and lower toxicity. The need to consolidate the results of current transplantation protocols and to exploit the efficacy of radiation prompted evaluation of skeletal targeted radiotherapy using bone-seeking radiopharmaceuticals. Because myeloma is a disease primarily of the bone marrow, bone-seeking radiopharmaceuticals can be used in conjunction with melphalan to deliver marrow-ablative radiation doses. These agents can deliver substantial radiation to sites of active bone turnover, such as trabecular bone, as well as adjacent bone marrow. Because of their specificity for bone localization and absence of retention in other organs, they may lack severe systemic toxicities. Although several clinically useful systemic bone-seeking agents are available (4–10), ^{166}Ho -1,4,7,10-tetraazacyclododecane-1,4,7,10-tetramethylene-phosphonic acid (DOTMP) has higher β -particle energies and, thus, greater particle range and was expected to be more effective in marrow ablation at high doses (11,12). Further, the 26.8-h half-life of ^{166}Ho balances the time required before decay to safe levels for stem cell infusion and the ability to deliver required ablative doses (13).

^{166}Ho has 2 principal β -emissions (half-life, 26.8 h; β -particle energies, 1.85 MeV [51%] and 1.77 MeV [48%]; γ -photons, 80.6 keV [6.6%] and 1.38 MeV [0.9%]). The energetic β -particle emission has a mean range of 4 mm in soft tissue and can deliver high levels of radiation to the trabecular bone and the marrow. The 81-keV photon is convenient for imaging whole-body biodistribution for estimation of radiation absorbed dose in the normal organs. DOTMP forms kinetically inert complexes with holmium, localizing in the bone (14), and requires a ligand-to-metal ratio as low as 1.5:1 (11). ^{166}Ho -DOTMP has selective skeletal uptake and rapid urinary elimination of the remainder of the activity, resulting in minimal residual activity in other tissues (10,11). Earlier studies have established that the biodistribution of ^{166}Ho -DOTMP is similar to that of other radiolabeled chelate phosphonates, such as ^{153}Sm -

Received Nov. 9, 2001; revision accepted May 21, 2002.

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DOTMP, ^{153}Sm -ethylenediaminetetramethylenephosphonate (EDTMP), and ^{166}Ho -EDTMP (6,10,15). An earlier report presented the results of a study using single-agent ^{166}Ho -DOTMP in the preparatory regimen for myeloablative therapy performed on 6 patients with refractory multiple myeloma (16). This report described the administration, biodistribution, pharmacokinetics, and radiation-absorbed-dose evaluation of ^{166}Ho -DOTMP for myeloablative therapy in a phase I/II dose escalation trial using a single large marrow-ablative dose in combination with high-dose melphalan, with or without TBI for treatment of multiple myeloma.

MATERIALS AND METHODS

Patients

The protocol required that all patients entering this study have multiple myeloma responding to conventional-dose therapy or considered primary refractory, be eligible for autologous hematopoietic stem cell transplantation, and be between the ages of 18 and 70 y. They were required to have a Zubrod performance scale of 2 or less; normal hematologic, renal, and liver function; and prior external-beam radiation (if any) not exceeding 20% of marrow volume or 30 Gy to the spinal cord. Patients with significant extramedullary myeloma were excluded. This trial was performed with the approval of the Human Subjects and Radiation Safety committees at the University of Washington and the Fred Hutchinson Cancer Research Center. All patients signed an informed consent form and were registered according to protocol requirements. All patients had peripheral blood stem cell mobilization and were eligible to undergo transplantation according to the requirements of existing protocols.

Radiopharmaceutical Preparation and Quality Control

^{166}Ho was produced at the Missouri University Research Reactor (Columbia, MO) by neutron irradiation of ^{165}Ho [^{165}Ho (n, γ) \rightarrow ^{166}Ho] and was supplied by NeoRx Corp. (Seattle, WA). The ^{166}Ho -DOTMP complex was prepared using a technique described elsewhere (16), except that doses were scaled to larger amounts for administration in a single dose rather than up to 3 daily doses. The results of the following quality control tests were reviewed for all injected doses before they were approved for patient administration: pH (7–8), radiochemical purity ($\geq 99\%$ with high-performance liquid chromatography, instant thin-layer chromatography, and cation-exchange chromatography), and pyrogenicity (negative).

Biodistribution Studies

A trace dose of ^{166}Ho -DOTMP, 1,110 MBq (30 mCi), by slow infusion into a central (Hickman) line was given to all patients for the purpose of biodistribution study and radiation absorbed dose calculation for treatment. Patients were hydrated with intravenous fluids at 200 mL/h, beginning 3 h before the infusion. Vital signs, including arm blood pressure and pulse, were monitored for 3 h after the infusion. Serial background-subtracted whole-body counts were obtained at 0.2, 0.5, 1, 2, 3, 24, 30, and 48 h after injection. A shielded detection probe, with a 7.62-cm (3 in.) NaI scintillation crystal, interfaced to a multichannel analyzer (model 261; Ludlum Corp., Sweetwater, TX) was used to obtain anterior and posterior whole-body counts, with the detector viewing the full height and width of a patient standing 4.5 m (15 ft) away. The geometric mean of the whole-body counts was used to calculate whole-body retention, correcting for any patient movement in the

transaxial planes. Whole-body counts were then corrected for physical decay using a ^{166}Ho -DOTMP standard aliquot and were normalized to obtain the percentage dose of the injected activity. Longitudinal and latitudinal dependence of the probe was evaluated periodically. Anterior and posterior whole-body images were obtained at 2–3, 24, and 48 h. A dual-head gamma camera (Maxxus; General Electric Medical Systems, Waukesha, WI) with a dedicated computer (StarCam; General Electric Medical Systems) or a variable-geometry camera (Millennium; General Electric Medical Systems) with an integrated computer system was used for image acquisition. The imaging photopeak setting was centered over 81 keV with a 15% window, using a medium-energy collimator and a scanning speed of 17 cm/min. Patients had to have $\geq 15\%$ skeletal uptake at time zero to qualify for the therapy dose.

Pharmacokinetics

After infusion of the ^{166}Ho -DOTMP trace dose, serial blood samples were obtained at 0.2, 0.5, 1, 2, 3, 24, 30, and 48 h by Hickman catheter. Serum was separated at 2,000 rpm in a centrifuge. For each time period, an aliquot was obtained from the continuous urine collection, which was initiated after the test dose infusion and continued for 48 h. Patients kept a record of the total volume of urine and saved a sample aliquot from each void.

The ^{166}Ho -DOTMP activity in samples of plasma, urine, and a standard aliquot of the infusion was measured with a γ -counter (Cobra; Hewlett-Packard Co., Canberra, IL) to calculate the percentage injected dose in the blood and the cumulative activity eliminated in the urine.

Estimation of Radiation Absorbed Dose

Serial whole-body counts with background subtraction were used to generate time–activity curves of whole-body retention. The initial steep slope of the curve represented rapid disappearance from the blood and soft tissue, and the slow second phase of the curve represented disappearance from the skeleton. The Y intercept of the extrapolated second part of the curve was used to estimate skeletal uptake at time zero. The residence time in the skeleton, estimated from the slope of the slow disappearance curve, was used as the input data to calculate the absorbed dose of radiation to major organs. A table of S values from MIRDOSE3 was used for these estimations. No corrections were made to adjust for actual organ masses. Skeletal uptake was divided between the trabecular and the cortical bone at a ratio of 0.62:0.38 of the total skeletal surface in accordance with the recommendations of the International Commission on Radiological Protection (Stockholm, Sweden) (17). The urinary bladder dose was calculated for the noncatheterized bladder assuming 30 min of urine retention within the bladder cavity.

Treatment

Patients were treated in groups, with escalating bone marrow dose levels in 10-Gy increments beginning at 20 Gy and reaching a maximum of 40 Gy, to determine toxicity. Three patients who were treated at the 40-Gy level underwent continuous Holter cardiac monitoring for 3 h after the dose infusion, and their serum ionized calcium was determined before and after therapy to see whether Ho-DOTMP induces changes in serum calcium levels.

All treatment infusions took place in lead-lined rooms, where the patients remained in isolation overnight. All patients received intravenous hydration at 200 mL/h, and their urinary bladders were catheterized with 3-lumen Foley catheters. Continuous saline irrigation at a rate of 200 mL/h continued until 9 h after the dose had

been infused. The urinary catheters remained in place until the patients were discharged the following morning.

The amount of ^{166}Ho -DOTMP for therapy, contained in a 30-mL plastic syringe with 1-cm plastic shielding, was infused by Hickman catheter at a constant rate during 10 min using a syringe pump. This infusion was followed by a saline flush of the syringe and the tubing. The average volume of the therapy dose was 13.9 mL (range, 8.8–27.5 mL). Calcium gluconate (0.465 mol/L Ca^{2+}) for intravenous use was readily available for emergency administration in the event of acute, chelate-induced hypocalcemia. Vital signs were monitored for 3 h after administration of the therapy dose. Serial blood samples after the therapy dose were obtained for the first 20 consecutive patients for calculation of disappearance of radioactivity from the blood. Radiation exposure at 1 m from the patient was measured, and the room surveyed, with a handheld dose-rate meter (Victoreen Corp. Cincinnati, OH) immediately after the infusion. Patients were discharged from the hospital the following morning, when the exposure dose rates at 1 m from the patient were less than 7 mR (0.07 mSv)/h. Posttreatment whole-body images were obtained at the time of patient discharge. All patients subsequently received high-dose melphalan (phenylalanine mustard), 140 or 200 mg/m². Seven patients additionally received 8 Gy of TBI in 4 daily fractions using external-beam techniques before autologous stem cell transfusion. The marrow was considered engrafted when the absolute neutrophil count of 500 was sustained for 3 d.

RESULTS

Thirty-two patients who participated in the full biodistribution studies were treated with ^{166}Ho -DOTMP as part of a multicenter phase I/II myeloablative treatment protocol between August 1998 and September 2000. These patients represent a subset of the patients enrolled in this multicenter trial. There were 16 men and 16 women. Their average age was 53 y (range, 39–69 y). All patients had multiple myeloma, which had previously been treated with combination chemotherapy. Patients were treated in groups that received escalating doses to the bone marrow: 3 patients at 20 Gy, 10 patients at 30 Gy, and 19 patients at 40 Gy.

Biodistribution Data

The administered dose disappeared rapidly from the serum, with an average of 5.2% of the injected dose remaining in the serum at 4 h after infusion (Figs. 1 and 2). The disappearance was identical in each patient after the test and therapy doses (Fig. 3). Average cumulative urinary excretion was 61.2% by 4 h (Fig. 4). Average extrapolated percentage skeletal uptake at time zero was 31.2% (range, 16%–54%). Calculated skeletal residence time averaged 7.82 h (range, 3.7–12.9 h). Correlation was good between whole-body retention of ^{166}Ho -DOTMP (100% minus the 24-h cumulative urinary excretion) and whole-body counting data. A typical biexponential whole-body residence curve for a patient is shown in Figure 5, and whole-body gamma camera images at 19 h are shown in Figure 6.

Radiation Dosimetry

The average amount of administered activity for dosimetric evaluation was 1,110 MBq (30 mCi) (range, 821–1,280 MBq [22.2–34.6 mCi]). The average radiation absorbed dose to the bone marrow was 0.021 Gy/37 MBq (2.06 rad/mCi), and the range was 0.01–0.04 Gy/37 MBq (1.00–3.46 rad/mCi). The average radiation absorbed dose to the urinary bladder mucosa, based on the noncatheterized model, was 0.02 Gy/37 MBq (2.07 rad/mCi), and the range was 0.017–0.024 Gy/37 MBq (1.79–2.43 rad/mCi). Mean values for absorbed dose to various organs are given in Table 1. The average effective half-time of disappearance was 17.3 h (range, 2.6–24.6 h) for the skeleton and 2.4 h (range, 0.3–4.1 h) for the blood. The estimated cumulative dose to the bone marrow and other normal organs is given in Table 2.

Patient Treatment

^{166}Ho -DOTMP for therapy was administered without problems to the 32 patients. They received an average radioactivity amount of 74.3 GBq (2,007 mCi), with a range of 21.5–147.5 GBq (581–3,987 mCi). No patient showed

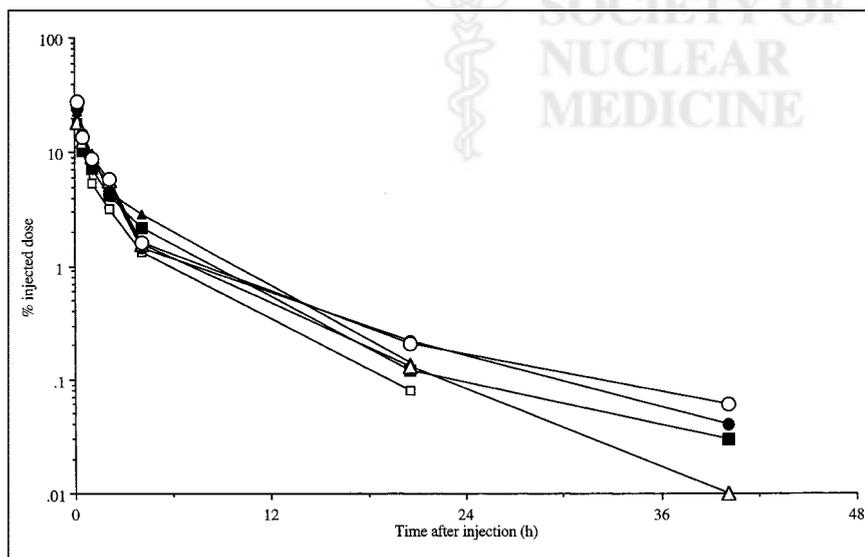


FIGURE 1. ^{166}Ho -DOTMP serum disappearance after test dose.

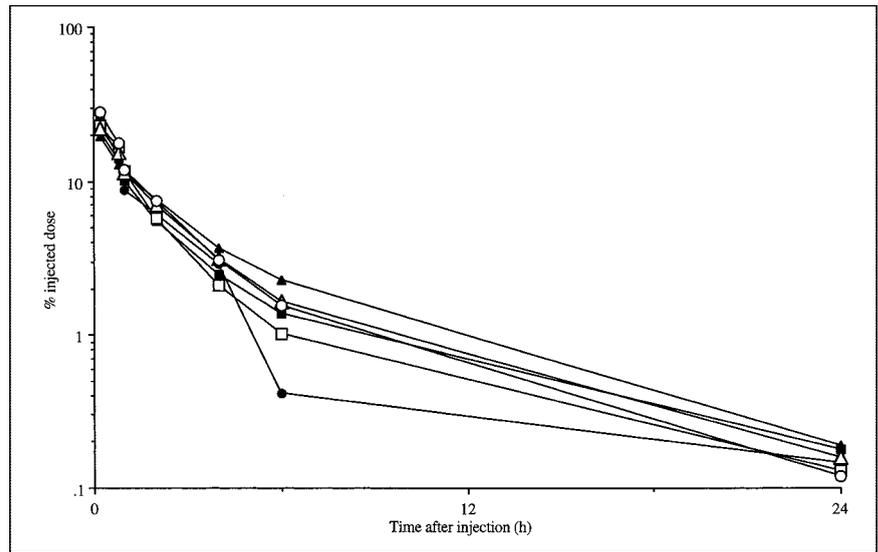


FIGURE 2. ^{166}Ho -DOTMP serum disappearance after therapy dose.

significant changes in vital signs or development of hypocalcemia during or after the therapy dose. Three patients underwent cardiac Holter monitoring after treatment, and no abnormalities were found. Radiation exposure at 1 m after treatment at the various dose levels is shown in Table 3.

Patient Outcome

Bone marrow recovery after autologous stem cell transplantation was indicated by a sustained absolute neutrophil count of ≥ 500 for 3 d. The mean engraftment time was 14 d (range, 9–25 d) for patients who received ^{166}Ho -DOTMP and TBI, 14 d (range, 12–17 d) for patients who received ^{166}Ho -DOTMP and 140 mg of melphalan, and 13 d (range, 9–13 d) for patients who received ^{166}Ho -DOTMP and 200 mg of melphalan.

Two patients (6%) showed signs of bladder toxicity. In 7 of 13 patients (54%), signs of renal dysfunction developed

(creatinine > 17.6 mmol/d [2.0 g/24 h]) at a median of 325 d (range, 178–448 d) after therapy.

DISCUSSION

The pharmacokinetics and biodistribution of ^{166}Ho -DOTMP in the blood, urine, and whole body were investigated. Rapid uptake into the skeleton and excretion by the kidneys resulted in selective targeting of the bones. This characteristic is shared with other bone-seeking radiopharmaceuticals such as ^{153}Sm -EDTMP.

Earlier animal and human studies using ^{166}Ho -labeled phosphonates have indicated that myelosuppression was the only toxicity observed in treated subjects (11,18) and could be reversed by bone marrow rescue. However, the dose required to produce irreversible toxicity to the bone marrow stroma was found to be higher than with external radiation

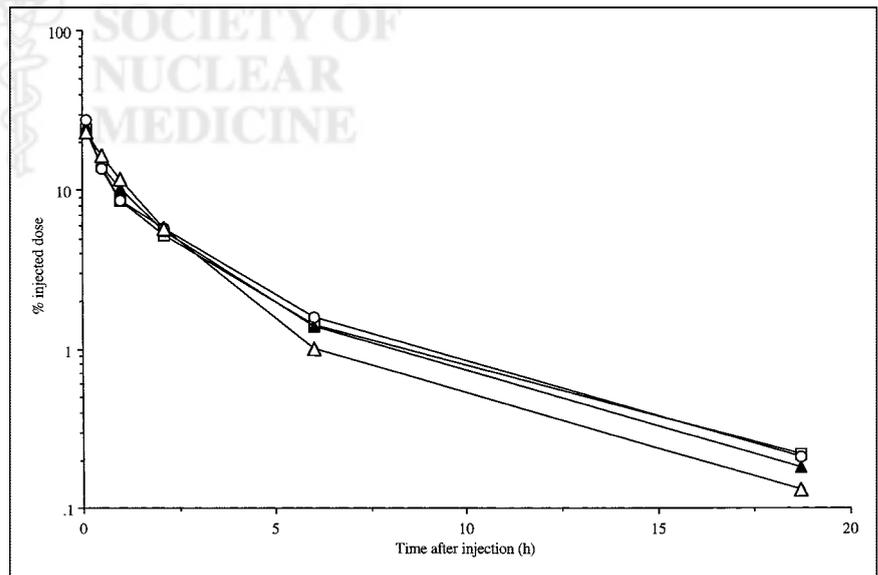


FIGURE 3. ^{166}Ho -DOTMP serum disappearance: test dose vs. therapy dose for 2 patients.

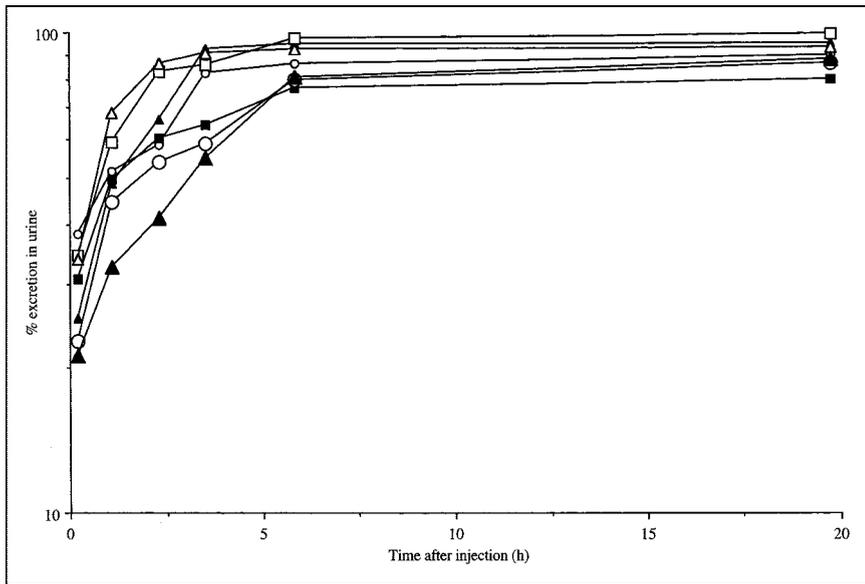


FIGURE 4. Cumulative urinary excretion of ^{166}Ho -DOTMP after test dose.

used in TBI. Doses as high as 40 Gy in 8 patients and 20 Gy in animals were given in these studies. In our study, escalating doses in 10-Gy increments were administered (maximum of 40 Gy to the marrow) to 32 patients. All patients had peripheral-blood stem cell transfusion, and engrafting occurred without delay and without any signs of irreversible bone marrow failure caused by radiation-induced fibrosis.

No significant drop in serum ionized calcium levels was observed in the 3 patients who underwent serial blood sampling for this purpose. A low mass of DOTMP in the ^{166}Ho -DOTMP complex is the likely explanation for this result (12,16). For the same reason, treatment doses with a higher mass content did not result in any appreciable cardiac toxicity.

Because ^{166}Ho -DOTMP is primarily excreted by the kidneys, the urinary bladder will receive a substantial radiation

dose if the bladder is not irrigated. The actual bladder dose delivered to our patients was probably lower than our conservative estimate of cumulative radiation dose to bladder mucosa (average, 33 Gy), calculated using the noncatheterized model, because all patients in our study had urinary bladder catheterization and continuous irrigation after therapy. This procedure is expected to probably reduce radiation dose to the bladder mucosa. It is estimated that bladder irrigation reduced radiation exposure to the bladder mucosa by 60% or more. Although most of the administered activity is excreted during the first few hours, extending bladder care reduces the radiation absorbed dose further (19). Two of our patients (6%) showed signs of urinary bladder toxicity, and both had contributing factors such as prior radiotherapy and urinary infection, reflecting the importance of aggressive bladder care. In 7 patients (54%) of the 40 Gy/200 mg

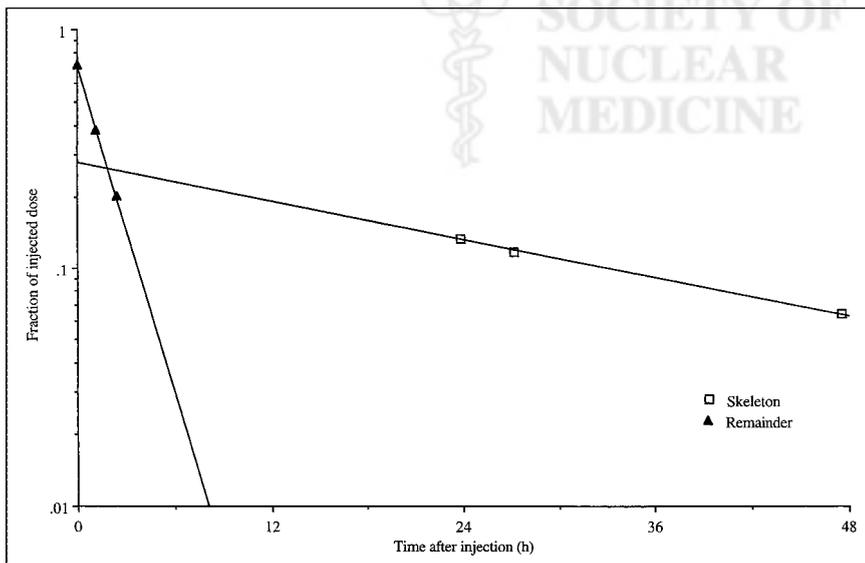


FIGURE 5. ^{166}Ho -DOTMP whole-body patient residence curves derived from whole-body counts obtained using NaI probe.

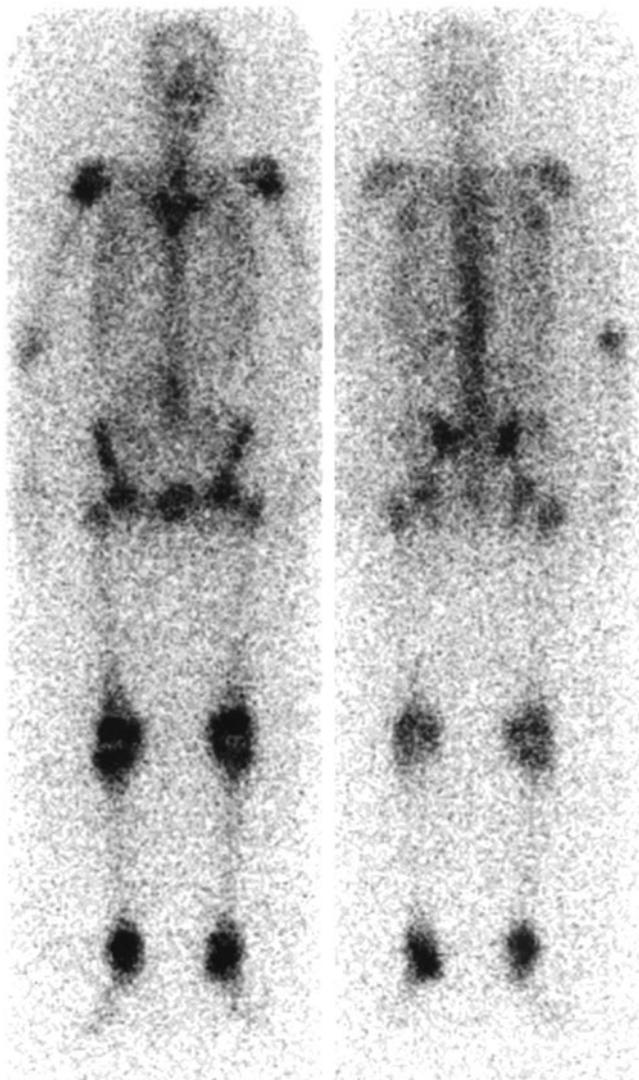


FIGURE 6. ^{166}Ho -DOTMP whole-body gamma camera images (anterior [left] and posterior [right]) obtained at 19 h after test dose.

melphalan group (13 patients), renal dysfunction developed. Although radiation exposure to the kidney likely contributed to this toxicity, its true incidence and its relationship to radiation could not be assessed because of other factors that contribute to renal dysfunction in this patient population, including myeloma kidney, subsequent therapy with bisphosphonates, other nephrotoxic agents, disease progres-

TABLE 1

^{166}Ho -DOTMP: Radiation Absorbed Dose to Organs

Target organ	Mean (Gy/37 MBq [rad/mCi])	SD (Gy [rad])
Bone marrow	0.0200 (2.14)	0.0070 (0.73)
Urinary bladder	0.0200 (2.07)	0.0008 (0.08)
Bone surface	0.0300 (3.04)	0.0100 (1.08)
Kidneys	0.0005 (0.05)	0.0020 (0.17)
Whole body	0.0020 (0.24)	0.0008 (0.08)

TABLE 2

^{166}Ho -DOTMP: Estimated Radiation Absorbed Dose to Organs

Marrow dose level (Gy)	Mean dose to bone surface (Gy)	Mean dose to urinary bladder* (Gy)	Mean dose to kidneys (Gy)
20	31.6	23.8	0.95
30	45.3	32.5	0.81
40	59.1	47.6	1.10
All patients	50.9	39.4	0.97

*Estimated dose to mucosa of noncatheterized bladder.

sion, and other unrelated causes. To address this problem, lower dosages and further detailed renal dosimetry will be evaluated in planned future studies on a cohort of additional patients.

Despite the good correlation between skeletal uptake after trace-dose pharmacokinetic studies and therapy doses in patients, significant interpatient differences in skeletal uptake of the agent require that radiation absorbed dose be estimated before treatment for each patient (15,20). The wide range of initial skeletal uptake (16%–53%) seen in our patients underscores the importance of estimating individual patient doses.

Skeletal dose calculation was based on the assumption that the second part of the biexponential curve is solely due to skeletal retention. Whole-body images obtained at 3 h and afterward showed a good qualitative correlation with this assumption. Radioactivity retained in the body was essentially limited to the skeleton, along with the expected minimal activity in the urinary tract and the near-complete disappearance of blood-pool activity as seen on these images. This was also the experience in other studies (18).

The serum concentration of ^{166}Ho -DOTMP fell rapidly, with an average half-life of elimination of 2.4 h, and urinary excretion reciprocated this pattern. The average activity in the blood at 4 h was 5.25% of the injected dose, whereas the average cumulative urinary excretion in 4 h was 61% of the injected dose. The dose to other nonskeletal organs or sites

TABLE 3

^{166}Ho -DOTMP: Radiation Exposure at Escalating Marrow Dose Levels

Marrow dose level (Gy)	% Skeletal uptake at time zero		Mean administered amount (GBq [mCi])	Mean radiation exposure (mSv [mR]/h*)
	Mean	Range		
20	31.8	21.0–40.0	42.8 (1,158)	0.11 (10.8)
30	35.3	23.4–53.6	61.1 (1,652)	0.17 (17.3)
40	28.5	15.3–50.0	84.4 (2,280)	0.18 (18.4)

*Measured at 1 m.

was significantly low, largely because of rapid blood disappearance and lack of organ or tissue uptake of the agent.

The MIRD schema (21), used in our study to estimate radiation absorbed dose, assumes a uniform distribution of radioactivity in the organs. Although it is possible for bone-seeking radionuclides to have significant inhomogeneous skeletal uptake in the presence of osteoblastic skeletal metastases such as those from prostate cancer, images obtained of this patient group show a low likelihood that, with the diffuse osteolytic process in multiple myeloma, focal overdosage will be a significant factor. Whole-body scans obtained after administration of the treatment dose showed mild heterogeneity in bone uptake consistent with the appearance of multiple myeloma on a typical bone scan.

The generally low skeletal uptake seen in our patients (average extrapolated uptake at time zero, 31.6%) is in keeping with the poor skeletal function resulting from the diffuse osteolytic process of multiple myeloma. Eighteen patients (56%) had less than 30% uptake at time zero (Table 4). Normal skeletal retention at 24 h for commonly used bone-seeking radionuclides has been reported to be approximately 50% (22,23). Despite the generally low skeletal uptake seen in our study, myeloablation was achieved in our patient population. Although these patients also received myeloablative doses of melphalan, ¹⁶⁶Ho-DOTMP as a single agent was found to result in myeloablation in doses as low as 22 Gy to the bone marrow (16). Bone marrow recovery after treatment was uneventful and within the expected period (mean, 14 d), indicating that even with a combination of potentially myeloablative agents, full recovery is possible.

The low levels of radiation exposure from treated patients (average, 0.17 mSv [16.9 mR]/h at 1 m) is explained by the predominant β-emission and low-energy γ-radiation of ¹⁶⁶Ho (81 keV at 6.6%). Higher-energy γ-radiation (1.3 MeV at 0.9%) does not appear to contribute significantly to radiation exposure. Eleven patients (34%) had exposure of less than 0.2 mSv (20 mR)/h at 1 m (Table 5). The cutoff dose of 0.07 mSv (7 mR)/h for patient discharge was chosen to reflect a conservative practice for radiation safety in the general population.

TABLE 4
¹⁶⁶Ho-DOTMP: Skeletal Uptake at Time Zero (Extrapolated)

% Uptake at time zero	No. of patients
<19	6
20–29	12
30–39	8
40–49	3
>50	3
Total	32

TABLE 5
¹⁶⁶Ho-DOTMP: Radiation Exposure Rate Immediately After Therapy

Exposure rate at 1 m (mSv [mR]/h)	No. of patients
<0.10 (10)	3
0.10–0.19 (10–19)	18
0.20–0.29 (20–29)	6
>0.30 (30)	5
Total	32

CONCLUSION

Our study indicated that ¹⁶⁶Ho-DOTMP, with a short half-life and rapid excretion by the kidneys, can be used in the myelopreparative treatment of multiple myeloma. Low radiation exposure levels from treated patients will be advantageous for radiation safety. Significant early uptake and retention in the skeleton, rapid clearance from the blood, and essentially no soft-tissue retention should result in minimal systemic toxicity. Vigorous and systematic bladder management after therapy is important to prevent significant radiation-induced damage to the bladder mucosa. Findings from this study suggested that single large myeloablative doses of ¹⁶⁶Ho-DOTMP can be safely administered to myeloma patients, although more stringent approaches are needed for the evaluation of radiation absorbed dose in kidneys. The physical characteristics, ease of administration, biodistribution characteristics, and radiation safety advantages of ¹⁶⁶Ho-DOTMP make feasible its use in myelopreparatory regimens for multiple myeloma.

ACKNOWLEDGMENTS

The authors thank Drs. Richard Ghalie and Hazel Brietz of the NeoRx Corp. for their useful critical review of the manuscript and Kathy Lillaby, RN, for her assistance with the database.

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