Rhenium-186-labeled Hydroxyethylidene Diphosphonate Dosimetry and Dosing Guidelines for the Palliation of Skeletal Metastases from Androgen-independent Prostate Cancer

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ABSTRACT

Rhenium-186 (tin)-labeled hydroxyethylidene diphosphonate (186Re-labeled HEDP) was evaluated in 27 men with progressive androgen-independent prostate cancer and bone metastases. Administered activities ranged from 1251 to 4336 MBq (33.8–117.2 mCi). The primary objectives were to assess tumor targeting, normal organ dosimetry, and safety. Antitumor effects were assessed by posttherapy changes in prostate-specific antigen and, when present, palliation of pain. Whole-body kinetics, blood and kidney clearance, skeletal dose, marrow dose, and urinary excretion of the isotope were assessed. Targeting of skeletal disease was observed over the period of quantification (4–168 h). Radiation doses to whole body, bladder, and kidney were well tolerated. The dose-limiting toxicity was myelosuppression (grade III) at 296 MBq (80mCi). Probe clearance (whole body) and urinary excretion measurements were highly correlated.

Of the six patients treated at the highest dosage schedules (three at 1510 MBq/m² and three at 1665 MBq/m²), three showed a posttherapy decline in prostate-specific antigen of 50% or more. The declines were not sustained. The determination of total activity retained at 24 h, as well as an estimate of marrow dose, correlated with the amount of myelosuppression observed. These results suggest that a single 24-h measurement of retained activity would allow individualized dosing and an improved therapeutic index relative to fixed dosing schema. Repetitive dosing is required to increase palliation.

INTRODUCTION

Bone is the most frequent and potentially debilitating site of prostate cancer spread. When present at diagnosis, palliation can be achieved with androgen ablation, but this rarely results in the elimination of disease. With the proliferation of an androgen-independent tumor, bone metastases can result in pain, spinal cord compromise with the attendant loss of function, and compromise of hematopoietic reserve (1, 2). At this point, the goal is palliation because no single approach has been shown to prolong life. For a patient with painful lesions that can be encompassed by a single or wide-field portal, external beam radiation provides the most effective and durable pain relief. Unfortunately, the diffuse nature of the disease limits the long-term utility of the approach, because other areas often become symptomatic soon after the first area has been treated. The need for effective systematic palliation is obvious.

Systemic options can be divided into those that are directed at the tumor cells themselves, e.g., hormonal agents or chemotherapy, and those that are directed at the surrounding stromal element, e.g., bisphosphonates. In most cases, primary oncolytic therapy is preferred because durable palliation is generally not obtained unless some degree of tumor cell kill is affected. However, even in the case where a chemotherapy regimen is successful, pain palliation may not be achieved for several weeks (3). Furthermore, the lack of a survival benefit observed in two randomized comparisons, where the combination of mitoxantrone plus a corticosteroid was shown to be superior to a corticosteroid (4) and the combination of suramin plus hydrocortisone was shown to be superior to hydrocortisone (5), shows how the effects on tumor and effects on pain are often dissociated. It also highlights the need for more effective therapies directed to the tumor.

Bone-seeking radiopharmaceuticals use a carrier molecule to deliver radiation to abnormal areas of the skeleton. They have the advantage of treating all areas simultaneously, and depending on the isotopic label, can be used for imaging or for treatment. A number are in clinical use including [32P]orthophosphate, [32P]polyphosphate, 89Yt-labeled EDTA, and 89Sr. With 32P, marrow suppression was the limiting toxicity with variable pain attenuation. 89Sr-labeled lactate or chloride is less toxic to the marrow but has no penetrating gamma or X-ray emission for imaging and quantification purposes, other than the bremsstrahlung from the high energy β emission. It has limited antitumor effects, and myelosuppression, in particular thrombocytopenia, may persist for up to 12 weeks after a single
1308 186Re-labeled HEDP Dosimetry

injection. 186Re-labeled HEDP4 and 153Sm-labeled EDTMP are radioactive metal diphosphonates (6–10) in which bone local-
ization is provided by the diphoshonate moiety, whereas the radioactive label simultaneously emits gamma energies for im-
aging and β energies for therapy. The β energy emitted limits therapeutic radiation exposure from a range of 200 µm to 2 mm
(11), whereas the half-life of 3.8 days permits easy shipping and handling. In Phase I investigations, an excellent correlation
between 186Re and technetium-99m scans was observed, along
with significant palliative effects.

The clinical manifestations of prostatic cancer and in particu-
lar the spread to osseous sites make the determination of treat-
ment efficacy difficult (2). Standard Phase II response cri-
teria, which require objective and reproducible measures of regression, do not apply. The ability to measure changes in PSA
on a serial basis provides a reproducible end point to assess treat-
ment effects (2). In this scheme, treatments that do not
produce consistent declines in PSA are not evaluated further. Of
equal importance is the determination of the quality of a pa-
tient’s survival.

On the basis of preliminary data showing significant pal-
lialion of painful bony lesions using an administered activity of
1295 MBq (35 mCi), a Phase I study using an escalating dose
schedule was investigated in patients with hormone-independent
prostatic cancer (12–14). Correlations with measured biochem-
ical parameters were performed.

PATIENTS AND METHODS

Patient Population. Patients with histologically con-
firmed androgen-independent prostate cancer and skeletal me-
tastases were considered. All had documented castrate levels of
testosterone. Entry required a minimum of four bone metastases,
at least one of which was symptomatic and demonstrable on a
standard bone scan and/or radiograph, that had not been treated
with external beam radiation therapy. Patients who were pain
free were eligible only if they required narcotic analgesics to
achieve a pain-free status. Entry required a WBC >4,000 cells/
mm3, platelet count >100,000 cells/mm3, and serum creatinine
<1.5 mg/dl. Patients were excluded if they had received external
beam radiation therapy within 3 weeks prior to entry, had sym-
ptomatic spinal cord compromise documented by prestudy myelog-
raphy or magnetic resonance imaging, or if they had participated
in a clinical trial of another investigational drug within 30 days.

Patients with American Heart Association class IV heart disease
or with a life expectancy of <12 weeks were likewise excluded.
There was no limit on the amount or the number of sites that had
received radiation therapy. Similarly, there were no restrictions
on the basis of prior chemotherapy, provided the patient had
recovered from the myelosuppressive effects of the previous
treatment. Myelosuppression was graded using the commonly
accepted National Cancer Institute Common Toxicity Criteria
(15).

The pretreatment evaluation included a complete history
and physical examination with particular attention to the

4 The abbreviations used are: HEDP, (tin) hydroxyethylidene diphos-
phonate; PSA, prostate-specific antigen; ROI, region of interest.
associated with the handling of therapeutic quantities, including patient and personnel exposure. The estimated gamma ray exposure factor is 0.007 R-m²/Ci-h. Patients could theoretically be treated on an outpatient basis, even at the highest dose levels. The half-life (16) of 90.64 h is convenient in terms of shipment of kits for labeling and does not present an appreciable radiation waste disposal problem. To maintain hydration status, patients were instructed to drink two glasses of water prior to injection of the isotope and to consume at least 4 glasses of water each day for the week following treatment. Hospitalization was not required for treatment.

**Imaging and Sampling Methods.** Whole-body scans and multiple conjugate spot views were performed with a dual-headed gamma camera (Genesys Model 2143 3000-1B; ADAC
Table 1 Whole-body clearance parameters determined from urine excretion (UE) and whole-body (WB) crystal measurements

The short-term and long-term clearance times are denoted by $T_1$ and $T_2$, respectively. The short-term and long-term amplitudes, which are the percentages of activity retained at time zero, are denoted by $A_1$ and $A_2$. Parameters are those of Eq. A.

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Corporation, Milpitas, CA) at 4, 24, 48, 72, and 168 h after injection (see Fig. 2 for a sample whole-body image set.) The camera was interfaced to a dedicated work station where ROIs were drawn and counts versus time were generated for further fitting and analysis (Pegasys work station; ADAC Corp.). Three 5-min sessions consisting of anterior and posterior posterior views were taken at the level of the head, thorax, and pelvis (Fig. 3). A transmission scan was taken on the seventh day using a $^{57}$Co sheet source; the principal gamma energy imaged was 122 keV. This was used to correct the static spot views for attenuation.

Tumor:normal tissue ratios were determined by taking the ratio of the average counts per pixel over the tumor to the average counts per pixel over the normal femur. The femur was selected as the normal bone because of the ease of quantification and the fact that it tended to be uninvolved in the majority of patients.

**Pharmacokinetics.** Serial blood samples were taken at 0.5, 1, 2, 4, 12, 24, 48, and 72 h after infusion to assess blood clearance. Blood data were counted, and %-dose/l was calculated, plotted, and fit with a dual exponential (four parameters) consisting of short-term and long-term exponential clearance times and amplitudes determined using a graphical analysis package (BLD). The basic equation fit to the blood and whole-body data consisted of two exponentials:

$$\text{dose}(t) = A_1 e^{-0.693 T_1 t} + A_2 e^{-0.693 T_2 t}$$

where $A_1$ is amplitude of the short-term component (% - dose/l), $T_{1/2}$ is biological half-life of the short-term component (h); $A_2$ is amplitude of long-term component (% - dose/l), and $T_{2/1}$ is biological half-life of the long-term component (h).

Sample results are shown in Fig. 4 for patient 12, and the whole-body clearance parameters measured for all patients using the urine excretion and the WB data are presented in Table 1.

**Whole-Body Clearance Determinations: Two Methods.** Patients were counted seated in front of a 12.7-cm NaI (TI) crystal detector equipped with a heavy side shield at a distance of 4.3 m with posterior and anterior counts taken for 2 min at each position. This method has the advantage that one is counting versus a calibration source of $^{186}$Re, and shifts in detector sensitivity are compensated for. Counts were taken at the same time blood samples were drawn. Sample whole-body clearance data are shown in Fig. 4 and are depicted as WB-1.

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**Fig. 4** Sample data set (patient 12) determined from ROI analysis and graphical fitting of spot view data. a, blood clearance data; b, plasma clearance data; c, whole-body clearance determined from urine excretion; d, whole-body (WB) clearance measured with a crystal detector; e, renal clearance; f, pubic bone tumor clearance; g, normal femoral bone clearance; h, spinal (T10) tumor clearance.
The cumulative renal excretion of $^{186}$Re-labeled HEDP was determined by collecting urine at intervals of 3–12 h over a time period of ~72 h after infusion of the isotope. Sample data from patient 12 is depicted in Fig. 4d showing activity retained in the whole body determined by subtracting the excreted activity from the total administered activity. Dual exponentials were fit to the clearance data using the same graphical analysis methods as described above. Data from the patient series is shown in Tables 1–3, with the exception of patients 1–3 and 17, who were excluded due to loss of urine during the collection period.

Conjugate View Method of Quantification. The method of conjugate views was used to estimate organ and tumor activity (17–19). With this method the activity, $A$ (MBq), in a particular region can be estimated with:

$$A = \frac{[Ca^*CPd^{-\mu s/2}]}{1/E} * (\mu s/2)$$

where $Ca$ is the count rate in the anterior view (cpm), $CP$ is the count rate in the posterior view (cpm), $d$ is the patient thickness (cm), $E$ is the camera calibration factor (cpm/MBq; from standard in FOV), $s$ is the thickness of the region containing the activity (cm), and $\mu$ is the attenuation coefficient of the region containing the activity (cm$^{-1}$).

The last term involving $\mu s/\sinh(\mu s/2)$ simplifies for regions of the size under consideration, and Eq. B becomes:

$$A = \frac{[Ca^*CPd^{-\mu s/2}]}{1/E}$$

The use of the $^{57}$Co sheet source for the transmission correction was validated in a series of measurements involving an anthropomorphic phantom with a number of $^{180}$Re sources (20) in different anatomical locations.

Dosimetric Methodology. This study is similar to others (12–14) in the methodology used:

(a) For MIRD dosimetry (21), this model permits the calculation of the radiation dose to a so-called “standard man” with a tabulated set of organ masses and geometry. The model separates the physics from the biology by use of a so-called S-factor that contains the characteristics of the nuclide and has units of cGy per MBq-h (rad/mCi). This is multiplied by a biological term that is measured for each patient, the so-called cumulated activity (units of MBq-h) based on the measurements of activity contained in an organ over time (refer to Fig. 4, d–h). The cumulated activity for an organ is the area under a particular curve. The product of the two yields the radiation dose to the target organ of interest (see Table 3).

(b) The organs targeted by $^{180}$Re-labeled HEDP (referring to the scans in Figs. 2 and 3) included the skeleton (consisting of cortical bone and cancellous bone), the whole body, and the kidneys. These are considered as target organs in the MIRD methodology described above and also act as the source of activity when calculating the radiation dose to the marrow, which is the critical or dose-limiting organ.

(c) The International Commission on Radiological Protection assumption (22) of a 50%/50% distribution of the total skeletal activity between cortical and cancellous bone.

(d) The so-called fixed model assumes that a constant fraction (22%) of the whole-body activity (23) is initially in the skeleton. The remainder of the body activity is assumed to be the total body activity minus the activity in the kidneys and skeleton.

(e) The variable model where the activity in the skeleton is assumed to be the total body activity minus the kidney and blood activity. The remainder of the body term is taken to be the activity in the blood.

(f) The use of S-factors for $^{180}$Re-labeled from MIRDose II (24) for dose calculations and verifications.

Marrow dose estimates were calculated using both approaches [(d) and (e)] and tabulated in Table 2. Whole-body probe data were considered more reliable than urine excretion, which were subject to incomplete collection as well as to the uncertainty in assigning collection times. A complete set of whole body probe data from 27 patients were acquired and used to calculate whole-body retentions from which the marrow dose estimates were derived using the two models described above.

RESULTS

Tumor Targeting, Whole Body, and Renal Doses. Table 3 shows the ratios of tumor:normal bone and the exponential clearance times determined from the fits to clearance data described above. In cases where the ratio approached 1, the ratio of the effective clearance times is almost 2.1. The average ratio is 3.9 ± 2.4. The average clearance time from tumor is 62 ± 12.7 h versus 45.8 ± 16.7 h for normal bone. Whole-body doses ranged from 0.003 to 0.018 cGy/MBq (0.11–0.65 rad/mCi) using the whole-body probe data. This is similar to the dosimetry obtained from the urine-based measurements of whole-body clearances. These doses ranged from 0.003 to 0.67 cGy/MBq (0.22–0.67 rad/mCi) with no significant difference in the average values. The urinary excretion values are slightly higher, which could be attributed to inadequate collection. The renal doses are tabulated ranging from 0.06 to 0.67 cGy/MBq (2.29–24.74 rad/mCi), with an average of 0.15 cGy/MBq (5.61 rad/mCi). These doses were well tolerated by all 27 patients.

Only transitory drops in PSA were observed with higher doses of $^{180}$Re-labeled HEDP (25) suggesting limited effects on tumor proliferation per se (Table 4). Thresholds for grade II toxicity were 2960 MBq (80 mCi), with a corresponding estimated marrow dose of 125 cGy (fixed) and 447 cGy (variable). This is the maximum tolerable dose at the grade II level. The probability of grade II or greater myelosupression increased in relation to the measured radioactivity retained at 24 h. It was also proportional to the marrow dose estimate using both the fixed and variable model.

A grade III toxicity (neutropenia) occurred in one of the six patients treated at 110 mCi in whom the 24-h retention was 2624 MBq (71 mCi). The estimated marrow dose was 426 cGy using the fixed model and 1595 cGy using the variable model in this one patient.

There was substantial targeting of bone metastases (Table 3) with average tumor/nontumor = 3.9 ± 2.4; Teff tumor = 62.1 ± 13 h; Teff normal bone = 45.8 ± 17 h.

Clearance dynamics are such that a 24-h, whole-body retention measurement of activity retained is sufficient to estimate the radiation risk to the marrow.
Antitumor Effects. PSA declined, and blood count ranges are shown in Table 4, which shows the nadir for both WBC and platelet counts. Note that a PSA decline of >50% was observed only at the higher activity levels (2960 MBq; 80 mCi) and that these declines were not sustained.

DISCUSSION

In this study, patients were administered levels of $^{186}$Re ranging from 555 MBq/m² to 1665 MBq/m² (15–45 mCi/m²) in single doses with at least three patients at each level in steps of 555 MBq/m² (15 mCi/m²). The radiation dosages to the target organs at risk for radiation side effects were calculated including the marrow, whole body, and kidneys. The marrow was confirmed as the critical dose sensitive organ; thrombocytopenia was the major toxic effect. A number of basic dosimetry studies have been carried out with $^{186}$Re-labeled HEDP (12–14, 26, 27). This study differs from those in that the objectives included determining the largest tolerable single dose of $^{186}$Re-labeled HEDP, the hematological consequences, and the resultant overall antitumor effect as measured by the posttherapy change in PSA (25). Pain relief was an additional objective in this Phase I study but was not systematically evaluated.

The comparative radiobiological effects of an internal emitter such as $^{186}$Re and external beam therapy are a matter of considerable current research interest. Actual experimental evidence is minimal, but it has been estimated by studying the comparative radiation effect of the internal emitter $^{131}$I and external beam treatment upon the thyroid gland (28). These estimates suggest that the effect of the internal emitter is about one-third that of a given external beam treatment on a cGy for cGy basis. If this is a true relative biological effectiveness (RBE), then a dose of 2400 cGy from the $^{186}$Re-labeled HEDP compound was the minimum required to administer the equivalent of 800 cGy given externally, a dose of external beam irradiation that has been shown to provide rapid palliation of painful bone metastases (2). However, as was the case in this study, a single 800 cGy fraction does not produce durable palliation (29). Maxon’s dosimetry estimates for radiation delivery to the skeleton in humans were based on sequential imaging scans using selected ROIs for tumor involvement and normal bone. Two models for isotope distribution in the lesion were used: the first, assuming a distribution on the surface in the outer 1 mm of a lesion; and the second, a uniform distribution throughout a lesion. Density measurements were provided by a computed tomography scan through the ROI. In a summary of the Phase I dosimetry experience, tumor doses ranged from 1,000 to 14,000 cGy (median, 2369 cGy), with a median marrow dose of 100 cGy after a single 35-mCi injection (26). Organs such as the liver, spleen, colon, stomach, and gonads were 0.2 cGy/mCi, whereas the bladder averaged a dose of 54 cGy (27). These data show that therapeutic tumor doses can be delivered. Tumor targeting was also confirmed with tumor:normal count ratios and clearance times.

### Table 2

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a P, platelet; N, neutrophil.
Estimates of Marrow Toxicity. The present study attempts to provide a method to optimize dosing of the isotope based on the relationship between retained radioactivity at 24 h and the degree of myelosuppression observed. It is based on the “scout dose” concept and a series of measurements using conjugate view imaging, whole-body clearances, and urine excretion. It is adaptable to variations in patient retention than a single prescription and has the potential to improve the therapeutic index, reducing marrow dose in the case of high retention and improving delivery to tumor in the case of low retention. A difficulty with this approach is that grade II toxicity was observed in one patient at 125 cGy to the marrow (fixed model dose), a relatively low level radiation dose. This possibly reflects the previous history of patients treated in that they had already undergone either chemotherapy or external beam (radiotherapy) or both (see Table 2). Although this represents a typical mix of patients for whom bone-seeking radioisotope therapy is considered, it shows that other patient factors can contribute to the myelosuppression observed. This would include whether the patient had received prior chemotherapy, the amount and extent of prior external beam radiation, and the extent of marrow replacement by tumor. Four of the five (80%) of the patients in whom grade II or greater myelosuppression was observed had received external beam radiation (three cases) or both radiation and chemotherapy (one case). The highest whole-body retention observed was associated with the development of grade III myelosuppression in a patient who had received no radiation or chemotherapy. It should also be noted that in a study by Maxon (26), some untreated controls experienced a grade I toxicity that was considered part of their disease course.

Modification of Treatment Protocols. Given that the primary objective of bone-seeking radioisotopes is to palliate pain, and that this can be achieved with repetitive administration of 129.5 MBq (35 mCi) each (26), it would seem prudent to perform a thorough dosimetric study with the initial dose on an outpatient basis. The critical measurement with the marrow dosimetry models used (fixed and variable) is that of whole-body retention. The use of urine excretion and/or whole-body crystal techniques can be performed consistently. These measurements would serve to identify those patients at the extrema in terms of cGy/MBq (rad/mCi) to the marrow (i.e., those patients beyond the dashed line in Fig. 5) and provide the basis for optimizing further administrations in terms of timing and amount.

Patients should be carefully monitored for myelosuppression (30). Those with high retentions or a potentially high cGy/MBq dose to marrow may require an individualized course of therapy. This modified course could involve fewer administrations, possibly at a lower dose, spread out over longer intervals (31).

Present strategies for pain palliation often involve the administration of multiple doses, typically 111–130 MBq (30–35 mCi) each, given at intervals of 8–10 weeks between thera-
pies. The first therapy presents itself as an opportunity for a 24-h dosimetric study sufficient to identify those patients with high retention characteristics. It could also be compared with the $^{99m}$Tc-labeled HEDP scan to confirm targeting. This can be performed adequately on an outpatient basis. Other strategies to minimize radiation dose include hydration prior to administration for the reduction of bladder wall dose (32), which is geometry dependent, and a careful monitoring of platelet and WBC levels. Other possible precautions involve a marrow biopsy or noninvasive estimate of marrow cellularity using magnetic resonance imaging/nuclear magnetic resonance parametric imaging (33). The latter would provide a baseline estimate of marrow cellularity (25% of the active marrow can be imaged and quantified in a single imaging session) and reveal any damage from previous radiation or chemotherapy.

**Extension to Other Bone-seeking Compounds.** Given that a scout dose of from 111 to 130 MBq (30–35 mCi) could be given with minimal public exposure, the patient considered for treatment could be imaged and/or counted over a period of 72 h as an outpatient, after which time the percentage-whole body retention at 24 h would be determined. Alternative dosing schemes would involve fractionation of the maximum tolerable dose to optimize pain relief over the course of the disease with dosimetry performed over the course of the first administration.

An underlying problem in a number of comprehensive studies involving other bone-seeking agents for pain palliation are the calculated doses to the marrow, exceeding in many cases 1000 cGy/MBq. These ordinarily toxic marrow doses reflect the shortcomings of the dosimetry models used (34) and present a confounding situation to the clinician intent on treating to the maximum tolerable dose with a single administration or who may approach this limit through multiple therapies.

This study established: (a) a maximum tolerable threshold of 125 cGy (fixed)—447 cGy (variable) to the marrow, at which point low-grade toxicity (grade II) was observed; and (b) that a single measurement of whole-body activity retained at 24 h predicts for significant myelosuppression, i.e., of the 20 patients who retained <1110 MBq (30 mCi), 2 (10%) showed grade II or greater myelosuppression, whereas 4 of 7 (60%) patients who retained greater than 30 MBq showed grade II or greater myelosuppression. Furthermore, the substantial variation in marrow sensitivity and radiation dose estimates to the marrow [0.03–0.39 cGy/MBq (or 1–14 cGy/mCi)] suggests that for patients in whom multiple administrations are considered, a dosimetry study performed over the course can be used to optimize dosing for the individual patient. Whether this approach will ultimately improve the therapeutic index of the compound requires prospective validation.

The wide range of the observed thresholds for marrow toxicity make predicting a safe fixed dose difficult. If patients are treated with a fixed dose of 1110–1295 MBq (30–35 mCi × 4 for instance), a careful dosimetry after the first course of therapy seems warranted and could be used for minimizing future complications. The dosimetry could be performed on an outpatient basis and the patient monitored for toxicity (blood changes and marrow damage) over time. Renal toxicity does not appear to be a problem at any of the dose levels studied. The patient group represents a typical mix of those treated previously, some with external beam therapy and others with chemotherapy and some with both. The ability to tolerate additional marrow damage could account for the variable sensitivity.

The clinical results to date show that $^{186}$Re-labeled HEDP, $^{153}$Sm-labeled EDTMP, and $^{89}$Sr can provide palliation of pain. On close examination, however, the proportion of patients showing pain relief is higher than the proportion showing antitumor activity. The dissociation of pain relief and antitumor activity may be a result of an inhibitory effect of the isotope on the release of local mediators such as prostaglandins or growth factors (35) or to a direct toxic effect on bone osteoclasts. A similar dissociation has been observed with low-dose corticosteroids, cold diphosphonates, and the bone resorption inhibitor gallium nitrate (36). An alternative hypothesis is that there may be sufficient tumor cell kill at the site of deposition of the isotope to produce pain palliation without affecting measured PSA values. Ultimately, randomized comparisons will be required to exclude a placebo effect. These results show the importance of a careful evaluation of the end point of the therapeutic intervention in patients with prostatic cancer.

The results from dosimetry studies show a wide range of uptake in selected lesions. This suggests that pretreatment dosimetry estimates may be used to select an appropriate administered activity for an individual patient. Ideally, an administered dose would be selected to achieve a targeted radiation dose to either the marrow or to the tumor. Those tumors with intense uptake can be treated with the aim to long-term palliation, minimizing the risk to the bone marrow. Furthermore, experimental studies in dogs have shown that once the cortex is eroded, the ability of the isotope to distribute through the lesion is reduced, making significant palliation unlikely. Indeed, these compounds have no effect on spinal cord

### Table 4 $^{186}$Re-labeled HEDP dosimetry: PSA declines and blood count changes over the course of therapy as a function of escalating administered activity

<table>
<thead>
<tr>
<th>Activity (MBq)</th>
<th>No. of patients</th>
<th>WBC median (range)</th>
<th>NADIR (range)</th>
<th>PLAT median (range)</th>
<th>NADIR (range)</th>
<th>&gt;50% PSA decline</th>
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<tr>
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<td>162</td>
<td>84–215</td>
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<td>136</td>
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<tr>
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<td>3.4–9</td>
<td>94</td>
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<td>3515 (95)</td>
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Median values are shown for WBCs and platelets (PLAT) in units of $10^3$ cells/mm$^3$. The first therapy presents itself as an opportunity for a 24-h dosimetric study sufficient to identify those patients with high retention characteristics. It could also be compared with the $^{99m}$Tc-labeled HEDP scan to confirm targeting. This can be performed adequately on an outpatient basis. Other strategies to minimize radiation dose include hydration prior to administration for the reduction of bladder wall dose.
lesions (7), and the presence of epidural compromise is a contra-indication to treatment. In addition, if one considers the short range of the β energies of the isotope in bone (0.5 mm) or soft tissue (1 mm), the probability of a dense sclerotic lesion receiving a significant radiation dose would appear small. This further suggests that one application of the isotope might be to consolidate the response in bone to primary hormonal therapy.

Our conclusions are that:

(a) Only transitory drops in PSA were observed with higher doses of $^{186}$Re-labeled HEDP, which shows that alternate dosing strategies are needed to improve the therapeutic index of the compound;

(b) Thresholds for grade II toxicity were 2960 MBq (80 mCi) with a corresponding marrow dose of 125 cGy (fixed) and
447 cGy (variable) is the maximum tolerable single dose at the grade II level. The probability of toxicity as well as severity increased with the amount of activity retained at 24 h. It was also proportional to the marrow dose estimate using both the fixed and variable models.

(c) A grade III toxicity (neutropenia) occurred in one of the six patients treated at the highest dose level (24-h retention was 2624 MBq [71mCi]). Estimated marrow dose was 426 cGy (fixed) and 1595 cGy (variable) in this one patient.

(d) There was substantial targeting of bone metastases (see Table 3) with average tumor/nonumor = 3.9 ± 2.4; Tefl tumor = 62.1 ± 13 h; and Tefl normal bone = 45.8 ± 17 h; however, the net radiation dose delivered to the tumor was subtherapeutic, consistent with the low proportion of patients who showed durable declines in PSA. The results further suggest that multiple administrations are needed to increase cell kill.

(e) Clearance dynamics are such that a 24-h whole-body retention measurement of activity retained is sufficient to estimate the radiation risk to the marrow.

(f) Caution should be exercised with pretreated patients, particularly with prior radiotherapy.

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irradiation is more effective than local field irradiation alone in the
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