# Evaluation of Thrombocytopenia in Patients Treated with Rhenium-186-HEDP: Guidelines for Individual Dosage Recommendations

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A potential limitation of rhenium-186-1,1-hydroxyethylidene diphosphonate ($^{186}$Re-HEDP) therapy in patients with painful bone metastases is thrombocytopenia. Given the palliative character of this therapy, it is essential to be able to predict the degree of thrombocytopenia before therapy. **Methods:** Thus far, 39 prostatic cancer patients with multiple painful bone metastases were treated. Twenty-one patients underwent the therapy twice, resulting in 60 therapies. From the pre-therapy $^{99m}$Tc-HDP scintigram, the bone scan index (BSI) was determined as an index of the extent of bone involvement. **Results:** The administered activity ranged from 1104 to 3479 MBq $^{186}$Re-HEDP. The platelet count was lowest 4 wk following therapy. From this value and the pretreatment level, the percentage decrease in the platelet count was determined (47% ± 19%, range 14%–89%). The BSI ranged from 8 to 93. Regression analysis showed a functional relation ($R = 0.78$; $p < 0.001$) of the percentage of platelet decrease with BSI and administered activity normalized to standard body surface area. **Conclusion:** Using this relation, it is possible to predict thrombocytopenia by pretreatment bone scintigraphy and to adjust the dosage to each patient to avoid unacceptable toxicity.

**Key Words:** painful bone metastases; rhenium-186-HEDP; thrombocytopenia; bone scan index

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Patients with prostate cancer will develop bone metastases in nearly 70% of all cases (*1*). Bone metastases are a major cause of serious morbidity, resulting in pain, hypercalcemia, loss of function following pathological fractures and neurological symptoms from nerve compression.

Bone pain, confined to single sites, usually responds favorably to local external beam radiotherapy (*2*). Treatment planning differs in cases of widespread bone metastases, where hemibody (half-body) or whole-body irradiation appears to be more appropriate. However, all tissues in the irradiated area receive a similar radiation dose, which may cause considerable side effects, mainly presenting as bone marrow suppression, gastrointestinal symptoms and radiation pneumonitis (*3,4*).

The application of bone-seeking radiopharmaceuticals is a promising substitute for hemibody or whole-body radiotherapy. Several authors described the favorable effect of strontium-89-chloride ($^{89}$Sr) in patients with metastatic prostate cancer (*5–7*). Robinson et al. reported an increasing number and quality of responses with increasing dosages of $^{89}$Sr (*7*), but other investigators have not been able to demonstrate a dose-response relationship (*8*). Toxicity is limited to temporary myelosuppression, of which the most sensitive indicator is the peripheral platelet count (*8*). Unfortunately, $^{89}$Sr has a relatively long physical half-life (50 days) and does not emit gamma rays suitable for post-therapy quantitative imaging. Similar to the toxicity of $^{89}$Sr, Turner et al. (*9*) described thrombocytopenia as the dosage limiting toxicity of samarium-153-ethylenediaminotetramethylenephosphonic acid ($^{153}$Sm-EDTMP). Rhenium-186-1,1-hydroxyethylidene diphosphonate ($^{186}$Re-HEDP) has recently been developed for the palliative treatment of metastatic bone pain (*10*). Initial results have shown that $^{186}$Re-HEDP is able to reduce pain in about 80% of patients (*11–13*). Rhenium-186 has a relatively short physical half-life ($T_{1/2}$ = 89.3 hr) with a beta emission suitable for therapy ($E_{max}$ = 1.07 MeV) combined with a gamma emission suitable for external imaging ($E_\gamma$ = 137 keV) with an external photon yield of 9%. Radionuclides with short physical half-lives present the possibility of multidosage therapy, which may be more effective in palliation of bone pain (*14*). Furthermore, the short physical half-life reduces the problems of radioactive waste handling and storage (*15*).

Because $^{186}$Re-HEDP delivers a substantial dose to the bone marrow, bone marrow toxicity will be the dosage limiting factor. In most patients treated with bone-seeking radiopharmaceuticals, bone marrow toxicity is confined to thrombocytopenia, while leucopenia plays only a minor role (*8*). Moreover, these patients often show an increased

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bleeding tendency caused by additional use of nonsteroidal anti-inflammatory drugs, and by tumor infiltration of the bladder in prostate cancer patients. Therefore it is important to be able to predict the risk of thrombocytopenia prior to administration. Due to the inhomogeneous distribution of the radioactivity within the skeleton of patients with bone metastases, this has been found difficult to do based on bone marrow absorbed dose calculations.

As part of ongoing studies with $^{186}$Re-HEDP, we evaluated the degree of thrombocytopenia and correlated it to the administered activity and the extent of bone metastasis expressed by the bone scan index (BSI) which, as we have shown earlier, determines the fraction of administered activity taken up by the skeleton (*16*). On the basis of these findings we developed a model to predict the risk of thrombocytopenia that may be used to individualize dosage recommendations.

## MATERIALS AND METHODS

### Patients

The patients included in this report took part in two separate studies. Twenty patients with histologically confirmed prostatic cancer (mean age: 69 yr, range: 55–80 yr) entered a study with $^{186}$Re-HEDP dosage escalation, nine of whom received two administrations. Nineteen patients with prostatic cancer (mean age: 71 yr, range: 59–81 yr) entered a study with a fixed administered activity of 1295 MBq of $^{186}$Re-HEDP, twelve of whom received two administrations. In total, 60 treatments (39 first and 21 second injections) were given in the two studies.

All patients were suffering from metastatic bone pain and failed prior hormonal therapy. No patients received prior chemotherapy. They all had scintigraphic and radiological evidence of at least four bone metastases. Each patient had adequate hematological function with a leukocyte count $>4.0 \times 10^9$/liter, and a platelet count $>150 \times 10^9$/liter. Some patients who entered the fixed dosage protocol received prior local external beam radiotherapy at limited parts of the skeleton.

The study was approved by the hospital review board and all patients gave written informed consent.

### Preparation of $^{186}$Re-HEDP

Enriched $^{185}$Re was irradiated at the Reactor of the University of Missouri, St. Louis, MO to produce $^{186}$Re. The $^{186}$Re-HEDP complex was prepared by reconstitution of a lyophilized mixture of $Na_2H_2$-HEDP (10 mg), $SnCl_2.2H_2O$ (3.85 mg) and gentisic acid (3 mg) with 1 ml of a radioactive solution of $Na^{186}ReO_4$ (2000–2800 MBq per 0.005–0.1 mg Re) in saline. The $^{186}$Re-HEDP complex was formed by reduction of the Re(VII) with the stannous ion and brief heating (10 min at 98–100°C). The pH of the resulting solution was adjusted to 5–6 by adding 1 ml of sodium acetate solution (39 mg of sodium acetate trihydrate/ml). Besides this kit formulation which had to be reconstituted, a ready-to-use liquid formulation with the same components and concentrations as in the kit was used. Both formulations have an identical pharmacokinetic behavior (*17*). Radiochemical purity of the $^{186}$Re-HEDP complex was checked by chromatography using Whatman 3MM paper. Free perrhenate and reduced hydrolyzed rhenium ($^{186}ReO_2$) were determined in two separate systems using acetone and 0.01 *M* $Na_2H_2$-HEDP in 0.9% (w/v) saline as the solvent, respectively. The radiochemical purity of $^{186}$Re-HEDP prior to injection proved to be consistently over 97%.

All components originated from Mallinckrodt Medical Inc. (St. Louis, MO) and were manufactured according to GMP procedures.

### Study Design

The trial design of the dosage escalation study involved sequential groups of three patients treated with 1295, 1850, 2405, 2960 and 3515 MBq of $^{186}$Re-HEDP, respectively. Following evaluation of each group of three patients, escalation of administered activity was implemented in increments of 555 MBq. If any one patient in a group experienced unacceptable toxicity, defined as grade 3 or 4 toxicity at any point, or grade 2 toxicity which did not resolve by 8 wk following injection, three more patients were injected at the same level. When none of the three additional patients experienced unacceptable toxicity, the administered activity was escalated. In the fixed dosage protocol, patients received 1295 MBq of $^{186}$Re-HEDP. In both protocols, treatment could be repeated at 8-wk intervals if pain recurred (same administered activity as the initial dosage). Patients were hospitalized in an isolated room in the nuclear medicine ward for 24 hr. Rhenium-186-HEDP was administered as a bolus injection via a running intravenous saline drip.

### Toxicity

For toxicity assessment, the 1988 National Cancer Institute Common Toxicity Criteria were used (*18*). The maximal decrease of platelet count during the 8-wk follow-up period was expressed as a percentage of the pretreatment level (week 0). Body surface area (BSA) was calculated according to Boer (*19*): $BSA\ (m^2) = 0.2025 * BW^{0.425} * H^{0.725}$ in which BW is body weight (in kg) and H is height (in m).

The influence of external beam radiotherapy on platelet toxicity was measured in two subgroups of patients who all received 1295 MBq of $^{186}$Re-HEDP: 10 patients with and 11 patients without prior external beam radiotherapy.

### Bone Scan Index

Two weeks prior to therapy, a diagnostic whole-body scintigram was performed using $^{99m}$Tc-hydroxymethylene diphosphonate (HDP) (Mallinckrodt Medical, Petten, The Netherlands). From these scintigrams, the BSI was determined in order to provide an index of the extent of metastatic disease as described by Blake et al. (*20*).

In brief, by this method the skeleton is divided into four anatomical regions: (1) spine and skull; (2) pelvis; (3) shoulder girdle and ribs; and (4) extremities.

Each region is scored visually on a scale of 0 to 10 for the apparent proportion of skeleton involved. Scores for each region are summed, and the sum renormalized to a scale of 0 to 100 as an index for the extent of skeletal involvement. BSI values were calculated independently by two nuclear medicine physicians.

### Statistical Analysis

Data were analyzed using the SYSTAT 5.0 program (SYSTAT, Inc., Evanston, IL). Multiple regression analysis was applied to the group of first injections (n = 39) to calculate the functional relation of the measured percentage of platelet decrease (%DEC) with BSI and administered activity normalized to standard body surface area (ADN). For validation of this relation, the "one leave out" method was used (*21*). Thus, we predicted the %DEC for each individual patient from an equation derived from the data of the remaining 38 patients.

**TABLE 1**
Patient Survey

| Patient no. | BSI | Dosage (MBq) | Dosage per 1.73 $m^2$ body surface area (MBq) | Platelet decline calculated (%) | Platelet decline measured (%) | Toxicity grade |
|---|---|---|---|---|---|---|
| 03P330 | 20 | 1252 | 1117 | 34 | 33 | 0 |
| 04P330 | 65 | 1104 | 986 | 35 | 54 | 0 |
| 05P330 | 63 | 1834 | 1541 | 46 | 61 | 0 |
| 07P330 | 43 | 1865 | 1798 | 51 | 69 | 1 |
| 08P330 | 60 | 1835 | 1833 | 52 | 41 | 0 |
| 09P330 | 35 | 1830 | 1601 | 47 | 51 | 1 |
| 10P330 | 40 | 1814 | 1826 | 52 | 47 | 1 |
| 11P330 | 20 | 2353 | 1825 | 48 | 34 | 1 |
| 12P330 | 28 | 2339 | 2034 | 53 | 64 | 1 |
| 14P330 | 53 | 2373 | 2336 | 60 | 64 | 1 |
| 15P330 | 23 | 2914 | 2716 | 64 | 68 | 1 |
| 16P330 | 43 | 2911 | 2324 | 64 | 46 | 1 |
| 17P330 | 60 | 2928 | 2500 | 62 | 62 | 1 |
| 01P341 | 20 | 1252 | 1114 | 35 | 29 | 1 |
| 02P341 | 90 | 1316 | 1175 | 28 | 21 | 0 |
| 03P341 | 40 | 1310 | 1120 | 42 | 22 | 1 |
| 04P341 | 68 | 1163 | 1027 | 34 | 28 | 0 |
| 05P341 | 48 | 1249 | 1172 | 39 | 44 | 1 |
| 06P341 | 65 | 1300 | 1126 | 37 | 33 | 0 |
| 07P341 | 45 | 1261 | 987 | 38 | 32 | 1 |
| 08P341 | 75 | 1299 | 1069 | 31 | 28 | 1 |
| 09P341 | 70 | 1228 | 1074 | 34 | 30 | 1 |
| 11P341 | 10 | 1285 | 1231 | 37 | 14 | 1 |
| 12P341 | 93 | 1240 | 1293 | 26 | 21 | 0 |
| 14P341 | 43 | 1300 | 1323 | 44 | 34 | 0 |
| 18P330 | 13 | 2880 | 2720 | 59 | 71 | 1 |
| 19P330 | 8 | 2895 | 2253 | 47 | 56 | 1 |
| 20P330 | 13 | 2891 | 2537 | 56 | 61 | 1 |
| 22P330 | 43 | 3428 | 3525 | 85 | 89 | 3 |
| 24P330 | 73 | 3479 | 3067 | 77 | 56 | 0 |
| 25P330 | 48 | 3456 | 3007 | 72 | 88 | 3 |
| 27P330 | 48 | 3453 | 3173 | 81 | 63 | 1 |
| 15P341 | 88 | 1264 | 1143 | 17 | 55 | 1 |
| 16P341 | 40 | 1295 | 1164 | 39 | 72 | 1 |
| 17P341 | 45 | 1270 | 1202 | 40 | 44 | 1 |
| 18P341 | 30 | 1266 | 1094 | 37 | 35 | 1 |
| 19P341 | 50 | 1266 | 1161 | 40 | 39 | 1 |
| 20P341 | 73 | 1263 | 1124 | 33 | 26 | 1 |
| 22P341 | 30 | 1281 | 1182 | 40 | 48 | 1 |

The paired t-test was used to compare %DEC between the first and second injections (n = 21). The independent t-test was used to test the influence of external beam radiotherapy ($p < 0.05$ was considered to be statistically significant).

## RESULTS

Characteristics of each first treatment course are summarized in Table 1. In most patients, the nadir of platelet count occurred at Week 4 (Fig. 1). After the first dosage, grade 1 toxicity (75–150 × $10^9$ platelets/liter) was observed 27 times. Two patients showed grade 3 toxicity (25–50 × $10^9$ platelets/liter). The other courses showed no thrombocytopenia below 150 × $10^9$/liter. The mean percentage of decrease in platelet count after the first injection was 47% ± 19%. The BSI ranged from 8 to 93 (mean: 54 ± 23). The reproducibility of its calculation between two independent observers was good (R = 0.96).

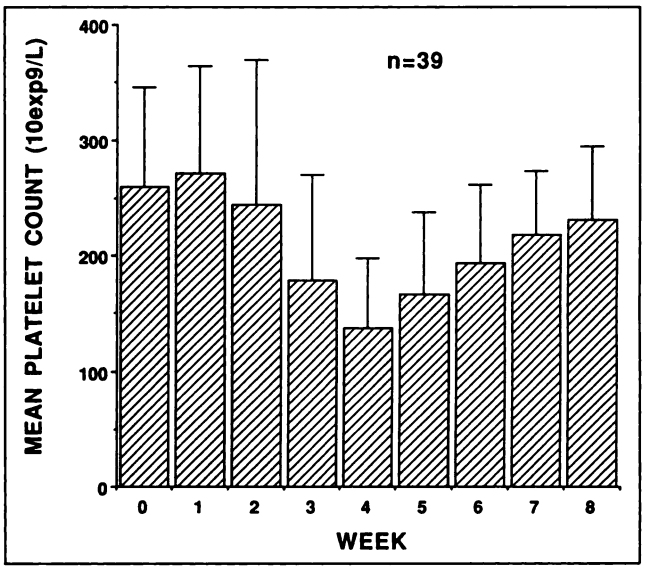


**FIGURE 1.** Mean platelet count with standard deviation following $^{188}$Re-HEDP administration.

Regression analysis showed a functional relation (R = 0.78; $p < 0.001$) of percentage of platelet decrease (%DEC) with BSI and administered activity (MBq) normalized to standard body surface area of 1.73 $m^2$ (ADN), expressed by the following formula:

$$\%DEC = 0.018 \times ADN + 0.714 \times BSI - 0.008 \times BSI^2 + 2.994.$$

Figure 2 shows a graphic representation of this relationship. The plot levels off for BSI values >50, indicating that the influence of the BSI on platelet decrease diminishes above this value.

Application of the "one leave out" method revealed that the residuals as calculated from predicted minus measured values proved to be normally distributed, homoscedastic and without systematic pattern.

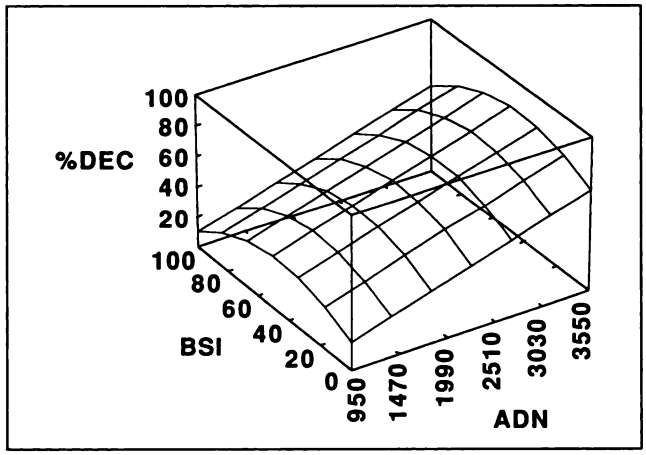


**FIGURE 2.** Graphic representation of the relationship between BSI, ADN and %DEC.

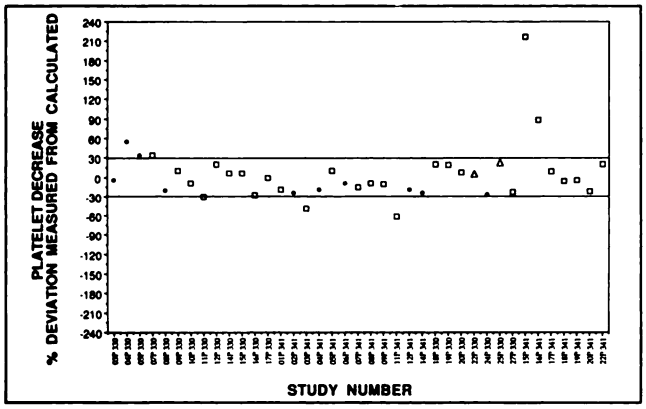


**FIGURE 3.** Calculated and actual % of platelet decrease expressed as a percentage of the calculated value: 100*(%DEC measured − %DEC calculated/%DEC calculated). Calculation was done according to the "one leave out" method for each patient. Symbols between solid lines represent the patients in which the actually observed percentage decrease deviated 30% or less from the predicted value. Toxicity grade was 0 (●), 1 (□) or 3 (△).

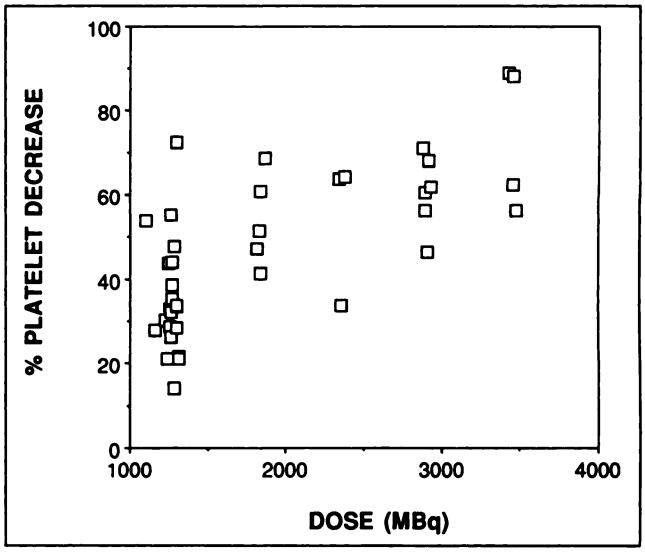


**FIGURE 4.** Influence of administered activity of $^{186}$Re-HEDP on platelet decrease relative to baseline level.

In Figure 3 the clinical relevance is illustrated by plotting the relative residuals for each patient. In only 5 of 39 treatments was there a discrepancy greater than +30% between measured and calculated percentage decreases in the platelet count while the majority of patients showed a discrepancy less than +30%. Therefore, a patient presenting with a lower bound baseline level of 150 × $10^9$ platelets/liter who is calculated to drop 50% in platelet count, may actually show a drop of up to 65% leading maximally to a grade 2 toxicity.

One should realize that the percentage decrease in platelet count is specified by %DEC = (1 − nadir of platelet count/baseline platelet count) * 100. Thus, for each patient a maximum %DEC can be introduced which is set by the patient's baseline count and a lowest acceptable platelet count, e.g., 75 × $10^9$/liter. Subsequently, a maximum tolerable dosage can then be calculated for each individual patient by simply rearranging the formula:

$$\text{Dosage (MBq)} = \frac{\text{BSA} * [(1 - 75/\text{baseline count}) * 100 - 0.714 * \text{BSI} + 0.008 * \text{BSI}^2 - 2.994}{0.018 * 1.73},$$

in which BSA is the patient's body surface area.

The influence of administered activity of $^{186}$Re-HEDP on the decrease of platelet count relative to baseline level is demonstrated in Figure 4 showing that dosage alone does not adequately predict %DEC.

Patients who received prior external beam radiotherapy to the skeleton did not show a more severe drop in platelet count than patients who were not previously irradiated (mean platelet decrease was 33% ± 16% versus 38% ± 11%, respectively, p = 0.46).

The platelet decrease after the second injection (n = 21) was 49% ± 19% compared to 41% ± 16% after the first treatment in these patients. Although these values are not significantly different (p = 0.057), there seems to be a tendency for a slightly higher platelet decrease after repeated treatment. Therefore, with some reservation, the formula can also be used for second treatments.

## DISCUSSION

Side effects of the therapeutical use of bone-seeking radiopharmaceuticals in patients with multiple bone metastases are mainly limited to hematologic toxicity. Thrombocytopenia will be dosage limiting in these patients.

Following whole-body exposure by external radiation, thrombocytopenia develops slowly over a period of approximately 30 days after doses of 200–400 cGy. After doses of 600–1000 cGy, which effectively stop new platelet production, the decrease in platelet count reflects the life span of the platelet, and platelet count levels below 20 × $10^9$/liter develop in approximately 9 days (*22*). Maxon et al. (*10*) estimated that an administered activity of 1295 MBq of $^{186}$Re-HEDP will deliver average radiation doses of about 75 cGy to the red marrow, thus the bone marrow absorbed dose will be in the order of 200 cGy in patients receiving dosages up to 3515 MBq of $^{186}$Re-HEDP.

In our study, thrombocytopenia has been the predominant hematologic toxicity. All patients showed a decrease in platelet count compared to pretreatment levels. The decrease was limited to grade 1 toxicity in all but two patients (grade 3) and did not lead to apparent bruising. The nadir of total platelet count occurred 4 wk after injection. Prior local external beam radiotherapy to metastatic lesions did not influence the platelet suppression. This is in agreement with the $^{89}$Sr data of McEwan et al. (*23*) who found that extensive prior external beam radiotherapy is not associated with greater platelet suppression than local field radiotherapy.

The administered activity by itself does not determine the grade of toxicity. The condition of the patient, ex-

pressed by pretreatment platelet count and metastatic load (BSI), is an important additional factor. Previously, we described a close correlation between the BSI and the fraction of the administered dose taken up by the skeleton (*16*). Therefore, it is not surprising that the degree of platelet decrease does not only depend on the administered dose, but also on the BSI.

A good correlation was found between ADN (administered activity normalized to standard body surface area), BSI and the percentage of platelet decrease. It must be stressed that this formula only holds for the range of BSI as mentioned above.

Most skeletal metastases are primarily bone marrow metastases, showing a pattern similar to the distribution of bone marrow (*24*). Thus, about 90% of the bone metastases are localized within the distribution of the hematopoetic active marrow (*25*). This implies that patients with extensive metastatic disease will have an impaired bone marrow function. This will lead to the so-called peripheral marrow expansion. Appelbaum et al. observed recovering marrow in the midshaft of long bones (nontrabecular bone) despite administration of high doses of $^{153}$Sm-EDTMP to beagles (*26*). Autoradiography revealed that most of the isotope was deposited in trabecular bone, but that the midshaft regions of long bones were spared. As a result, peripheral blood counts recovered by Day 28, while marrow biopsy from the humeral head remained aplastic. This is a possible explanation for the curving of the plot in patients with a high BSI (Fig. 2). This means that the role of the BSI in thrombocytopenia is less important in the higher range. Patients with a high BSI have extensive disease, causing impaired function of the trabecular bone, which can lead to an abundant hematopoiesis in the marrow space in the midshaft of the long bones and extramedullary hematopoiesis, resulting in a less severe decrease of platelet count.

Calculation of the bone marrow absorbed dose from radionuclides deposited on bone surfaces is a difficult problem due to the complex geometry of the soft tissue and bone intermixture (*27*). This problem is very prominent in patients with bone metastases, where the normal bone marrow distribution is disturbed by the metastases. Therefore, it would be convenient to be able to predict toxicity prior to therapy by a simple method. With the formula using the BSI as an index of metastatic bone involvement and the ADN, it is possible to estimate the decrease of platelets by pre-therapy bone scintigraphy. Moreover, through this formula a maximum tolerable dosage can be estimated for each individual patient to establish the optimal dosage schedule so that unacceptable toxicity can be avoided. Further studies are needed to confirm the clinical utility of this formula, especially in multiple dosage schedules. Prospective studies are currently underway.

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## REFERENCES

1. Paulson DF. The impact of current staging procedures in assessing disease extent of prostatic adenocarcinoma. *J Urol* 1979;121:300–302.
2. Hendrickson FR, Shehata WM, Kirchner AB. Radiation therapy for osseous metastasis. *Int J Radiat Oncol Biol Phys* 1976;1:275–278.
3. Gilbert HA, Kagan AR, Nussbaum H, et al. Evaluation of radiation therapy for bone metastases: pain relief and quality of life. *Am J Roentgenol* 1977; 129:1095–1096.
4. Fitzpatrick PJ, Rider WD. Half body radiotherapy. *Int J Radiat Oncol Biol Phys* 1976;1:197–207.
5. Lewington VJ, McEwan AJ, Ackery DM, et al. A prospective, randomized double-blind crossover study to examine the efficacy of strontium in palliation in patients with advanced prostate cancer metastatic to bone. *Eur J Cancer* 1991;27:954–958.
6. Laing AH, Ackery DM, Bayly RJ, et al. Strontium-89 chloride for pain palliation in prostatic skeletal malignancy. *Br J Radiol* 1991;64:816–822.
7. Robinson RG, Spicer JA, Preston DF, et al. Treatment of metastatic bone pain with strontium-89. *Nucl Med Biol* 1987;14:219–222.
8. Lewington VJ. Targeted radionuclide therapy for bone metastases. *Eur J Nucl Med* 1993;20:66–74.
9. Turner JH, Claringbold PG, Hetherington EL, et al. A phase 1 study of samarium-153-ethylenediaminetetramethylene phosphonate therapy for disseminated skeletal metastases. *J Clin Oncol* 1989;7:1926–1931.
10. Maxon HR, Deutsch EA, Thomas SR, et al. Rhenium-186(Sn)HEDP for treatment of multiple metastatic foci in bone: human biodistribution and dosimetric studies. *Radiology* 1988;166:501–507.
11. Maxon HR, Schroder LE, Thomas SR, et al. Rhenium-186(Sn)HEDP for treatment of painful osseous metastases: initial clinical experience in 20 patients with hormone-resistant prostate cancer. *Radiology* 1990;176:155–159.
12. de Klerk JMH, Zonnenberg BA, van Rijk PP, et al. Treatment of metastatic bone pain in patients with breast or prostate cancer with Re-186-HEDP. Preliminary results [Abstract]. *Eur J Nucl Med* 1991;18:528.
13. Maxon HR, Schroder LE, Hertzberg VS, et al. Rhenium-186(Sn)HEDP for treatment of painful osseous metastases: results of a double-blind crossover comparison with placebo. *J Nucl Med* 1991;32:1877–1881.
14. Kasi LP, Fossella FV, Podoloff, et al. Multidose $^{153}$Sm-EDTMP for pain palliation in metastatic bone disease [Abstract]. *J Nucl Med* 1992;33:992–993.
15. Ketring AR. Samarium-153-EDTMP and $^{186}$Re-HEDP as bone therapeutic radiopharmaceuticals. *Nucl Med Biol* 1987;14:223–232.
16. de Klerk JMH, van Dijk A, van het Schip AD, et al. Pharmacokinetics of rhenium-186-HEDP after administration of rhenium-186-HEDP to patients with bone metastases. *J Nucl Med* 1992;33:646–651.
17. van het Schip AD, de Klerk JMH, van Dijk A, et al. Pharmacokinetics of Re-186-HEDP: comparison of two formulations in patients with bone metastases [Abstract]. *Eur J Nucl Med* 1993;20:876.
18. Cancer Therapy Evaluation Program, Division of Cancer Treatments. *Common toxicity criteria: guidelines for reporting adverse drug reactions.* Bethesda, MD: National Cancer Institute; 1988.
19. Boer P. Estimated lean body mass as index for normalization of body fluid volumes in man. *Am J Physiol* 1984;247:F632–F636.
20. Blake GM, Zivanovic MA, McEwan AJ, Ackery DM. Stronium-89 therapy: strontium kinetics in disseminated carcinoma of the prostate. *Eur J Nucl Med* 1986;12:447–454.
21. Draper NR, Smith H. Multiple regression and mathematical model building. In: Draper NR, Smith H, eds. *Applied regression analysis*, second edition. New York: John Wiley and Sons; 1981:412–422.
22. Donnall Thomas E, Cronkite EP. Radiation injury. In: Isselbacher KJ, Adams RD, Braunwald E, et al, eds. *Harrison's principles of internal medicine*, ninth edition. Tokyo: McGraw-Hill Kogakusha, Ltd.; 1980:941–945.
23. McEwan AJB, Porter AT, Venner PM, Amyotte G. An evaluation of the safety and efficacy of treatment with strontium-89 in patients who have

previously received wide field radiotherapy. *Antibody Immunoconj Radiopharm* 1990;3:91–98.
24. Scher HI, Yagoda A. Bone metastases: pathogenesis, treatment and rationale for use of resorption inhibitors. *Am J Med* 1987;82 (suppl 2A):6–28.
25. McKillop JH. Bone scanning in metastatic disease. In: Fogelman I, ed. *Bone scanning in clinical practice*. Berlin: Springer;1987:41.
26. Appelbaum FR, Sandmaier B, Brown PA, et al. Myelosuppression and mechanism of recovery following administration of samarium-153-EDTMP. *Antibody Immunoconj Radiopharm* 1988;1:263–270.
27. Johnson J, Langhorst SM, Loyalka K, et al. Calculation of radiation dose at a bone-to-marrow interface using Monte Carlo modeling techniques (EGS4). *J Nucl Med* 1992;33:623–628.