Original Article

Clinical utility of ^{188}Rhenium-hydroxyethylidene-1,1-diphosphonate as a bone pain palliative in multiple malignancies

ABSTRACT

^{188}Rhenium-hydroxyethylidene-1,1-diphosphonate (^{188}Re-HEDP) is a clinically established radiopharmaceutical for bone pain palliation of patients with metastatic bone cancer. Herein, the effectiveness of ^{188}Re-HEDP for the palliation of painful bone metastases was investigated in an uncontrolled initial trial in 48 patients with different types of advanced cancers. A group of 48 patients with painful bone metastases of lung, prostate, breast, renal, and bladder cancer was treated with 2.96–4.44 GBq of ^{188}Re-HEDP. The overall response rate in this group of patients was 89.5%, and their mean visual analog scale score showed a reduction from 9.1 to 5.3 ($P < 0.003$) after 1 week posttherapy. The patients did not report serious adverse effects either during intravenous administration or within 24 h postadministration of ^{188}Re-HEDP. Flare reaction was observed in 54.2% of patients between day 1 and day 3. There was no correlation between flare reaction and response to therapy ($P < 0.05$). Although bone marrow suppression was observed in patients receiving higher doses of ^{188}Re-HEDP, it did not result in any significant clinical problems. The present study confirmed the clinical utility and cost-effectiveness of ^{188}Re-HEDP for palliation of painful bone metastases from various types of cancer in developing countries.

Keywords: Bone metastasis, hydroxyethylidene-1,1-diphosphonate, pain palliation, radionuclide therapy, rhenium-188

INTRODUCTION

Skeleton is the most common site for metastases in patients suffering from cancer of breast, prostate, lung, thyroid, and kidney. The lifetime risk of bone metastases has been estimated to be ~70% in patients with cancer of breast and prostate,[1,2] and for lung cancer patients, the lifetime risk is about 30%–40%.[3] Patients with disseminated skeletal metastases often experience severe and refractory pain with their condition being complicated by fractures that impair quality of life.[4] Factors contributing to bone pain have not been completely understood; however, various theories have been put forward to explain the pathophysiology of bone pain.[5,6] In more than 50% of patients with multiple skeletal metastases, chemotherapy is ineffective in controlling the bone pain. Although external beam radiation therapy has been proved effective for pain palliation in 75% of the patients with osseous oligometastases, the extent of therapy is limited by the radiation burden to the whole body.[7] In addition, while treating one site for pain relief, areas outside the radiation field may become symptomatic.

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Another effective approach for relieving bone pain in patients with multifocal skeletal metastases is the systemic administration of radiopharmaceuticals.[4,8-13] Various bone-seeking beta-emitting radiopharmaceuticals such as ^{32}P as sodium orthophosphate,[14] ^{89}Sr-chloride,[15-22] ^{153}Sm-ethylenediamine tetramethylenephosphonic acid (EDTMP),[17,23-29] ^{186}Re-HEDP,[19,22,29-38] and ^{188}Re-HEDP have been clinically evaluated earlier.[29,39-48] ^{177}Lu-EDTMP is another bone pain-palliating agent which has established its clinically utility.[49] A recent review by Guerra Liberal *et al*. on therapeutic radiopharmaceuticals had provided a perspective beyond ^{89}Sr and ^{153}Sm for bone pain palliation.[17]

Among the radioisotopes suitable for bone pain palliation, ^{188}Re enjoys a special status since it is available from a commercial ^{188}W/^{188}Re generator, which can be housed in a hospital radiopharmacy. Availability of ^{188}Re from a generator allows in-house preparation of ^{188}Re-HEDP, on a need basis, like many other ^{99m}Tc-radiopharmaceuticals. In this context, it could be noted that procurement reactor produced radioisotope-based bone pain-palliating agents often involves logistical issues and may not be available on demand.

Compared to ^{153}Sm-EDTMP, reports on clinical investigations with ^{188}Re-HEDP are rather limited.[29,40,41,44,45,47,48] Available clinical studies, however, clearly indicate the therapeutic efficacy of ^{188}Re-HEDP for palliation of bone pain. Clinical studies show ~40% of the administered ^{188}Re-HEDP activity clearing through renal route within 8 h postadministration. Quick clearance of radiotracer from nontarget organs helps in significant reduction of radiation dose to the whole body.[41] ^{188}Re decay (half-life - 16.9 h) involves beta-emission with a maximum energy of 2.1 MeV. The beta decay is associated with a gamma emission with energy 155 keV (15% abundance), which permits visualization of radiotracer distribution within the body during therapy. Recently, we have developed a lyophilized kit for the preparation of ^{188}Re-HEDP.[42] The present study reports the clinical efficacy of ^{188}Re-HEDP for palliation of bone pain in patients with different types of malignancies.

MATERIALS AND METHODS

Sodium perrhenate ($Na^{188}ReO_4$) was freshly eluted from ^{188}W/^{188}Re generator procured from ITG, Germany. Ammonium perrhenate and anhydrous sodium acetate were purchased from M/s. Sigma Aldrich, USA. A 1 mM solution of ammonium perrhenate was prepared by dissolving ammonium perrhenate (26.8 mg) in water for injection (10 mL). Lyophilized HEDP kits were received as a gift from Bhabha Atomic Research Centre, India. Quality control of ^{188}Re-HEDP preparation was carried out using instant thin-layer chromatography-silica gel (ITLC-SG) paper procured from M/s. Varian, USA.

All patients enrolled for the present study were histologically proven cases of carcinoma and were diagnosed with extensive skeletal metastases by ^{99m}Tc-methylene diphosphonate (MDP) whole-body scans. All patients reported consistent multifocal bone pain, which could not be controlled by opioid analgesics. The eligibility criteria for patients to receive ^{188}Re-HEDP therapy involved adequate bone marrow function, which includes hemoglobin level of >13 g/dL, total leukocyte counts $>3.5 \times 10^9$/L, and platelet counts $>100 \times 10^9$/L. In addition, all the patients had baseline mean pain score >6 on visual analog scale (VAS)[50] and performance status based on the Karnofsky score above 40.[51] Life expectancy of the patients was estimated to be at least 3 months. Patients who had received chemotherapy, radiotherapy, or external beam radiotherapy within 4 weeks before administration of ^{188}Re-HEDP were excluded from the study. Patients exhibiting pathological bone fractures or spinal cord compression, patients younger than 18 years, and pregnant female patients were excluded from the study.

Complying with the Declaration of Helsinki, all patients were informed about the procedure as well as possible adverse effects of ^{188}Re-HEDP therapy, and written consent was obtained before therapy. Necessary regulatory approvals from the local ethics committee and institutional review board were obtained before the commencement of this study.

Preparation of ^{188}rhenium-hydroxyethylidene-1,1-diphosphonate

^{188}Re-HEDP was prepared following a procedure reported elsewhere.[42] Freeze-dried HEDP kit was allowed to attain room temperature. About 100 µL of 1 mM ammonium perrhenate solution (~1 µmol) was mixed with 1 mL of freshly eluted $Na^{188}ReO_4$ from a ^{188}W/^{188}Re generator and transferred into the HEDP kit vial. The contents were thoroughly mixedm and the vial was heated at 100°C for 15 min. After cooling the vial to room temperature, 0.5 mL of sterile 1M sodium acetate solution was added to bring the preparation to physiological pH.

Radiochemical purity determination

Radiochemical purity (RCP) of ^{188}Re-HEDP complex was determined by ITLC-SG, following a reported procedure using two solvent systems, viz., acetone and physiological saline.[42] About 4 µL of the test solution was placed on two independent ITLC-SG strips. One strip was developed in acetone while the other was developed in physiological saline. In acetone, ^{188}Re-HEDP complex and reduced rhenium (ReO_2)

remained at the point of spotting while perrhenate moved to the solvent front. In saline, both ^{188}Re-HEDP and perrhenate moved to the solvent front while ReO_2 remained at the point of spotting. The strips were dried and analyzed on a TLC scanner. From the peak area measurements, RCP of ^{188}Re-HEDP complex was calculated.

^{188}Rhenium-hydroxyethylidene-1,1-diphosphonate administration and imaging protocol

Patients were intravenously administered a dose of 2960–4440 MBq of ^{188}Re-HEDP in 50 mL of saline over a period of 10 min. Subsequently, the patients were restricted to an isolation room for 2–4 h under constant observation. All patients were given oral or intravenous hydration (500 mL) before and after the infusion of radiotracer. Urinary incontinence was managed by bladder catheterization before administration of the radiotracer. Whole-body images were acquired on a dual head gamma camera (Symbia T-200, Siemens, Germany) at 2 h and 24 h posttherapy. The image acquired immediately after the administration of ^{188}Re-HEDP was used to confirm the expected biological distribution, whereas the 24 h image showed metastatic bone lesions in the body.

Efficacy and safety assessments

Relief to the patient from bone pain was evaluated at baseline and at 4, 8, and 12 weeks posttherapy. Overall pain score was calculated by averaging the pain score of all painful sites in each patient using VAS. A score of zero indicates the absence of bone pain, while a score of 10 indicates steady and severe bone pain.

Usage of analgesics was indicated by a score obtained by multiplying the score representing a given type of medication by the frequency of medication. Data on analgesic use and quality of life were collected at the baseline (pretherapy) and at 4 weeks posttherapy. The scores for different type of analgesics used and their frequency of usage are summarized in Table 1.

Table 1: Scores indicating types of analgesic and frequency of usage

	Score
Type of analgesic	
No analgesic	0
Nonsteroidal anti-inflammatory drugs	1
Strong narcotics	2
Frequency	
No analgesic	0
One tablet a day	1
Two tablets a day	2
Three tablets a day	3
>3 tablets a day	4

Mobility score and Karnofsky performance score were used as indicators for the patient's quality of life. Mobility score of zero indicated pain-free mobility, a score of one indicates mobility with some pain, a score of two indicated mobility with moderate pain, a score of three indicated mobility with severe pain, while a score of four indicated complete immobility of the patient.

Vital body parameters (blood pressure, pulse, weight, etc.) and a complete blood count with erythrocyte, leukocyte, and platelet counts were performed at baseline and 2, 3, 4, 6, and 8 weeks posttherapy. Common Terminology Criteria for Adverse Events, version 4.0, was followed while grading the toxic effects of therapy.

Data analysis

SPSS Version 20 from IBM was used to calculate mean and standard deviation (SD). For each patient, the baseline data were compared with posttherapy data using paired sample "*t*" method. Values are presented with 95% confidence interval and *P* value for each comparison was determined. Value of $P < 0.05$ was necessary to consider the observation statistically significant.

RESULTS

^{188}Rhenium-hydroxyethylidene-1,1-diphosphonate preparation and quality control

^{188}Re-HEDP was prepared using freeze-dried HEDP kits as per the procedure mentioned in the previous section. Following this procedure, ^{188}Re-HEDP could be consistently prepared with >95% RCP.

Imaging studies

After administration of ^{188}Re-HEDP, images were acquired at 4 h and 24 h postinjection (p.i.). As expected, high bone to background ratio as well as tumor to normal bone ratio was observed. Figure 1 shows the ^{188}Re-HEDP scan and ^{99m}Tc-MDP scan of a patient 4 h postadministration of the respective radiopharmaceutical. As expected, one-to-one concordance between the two scans was observed. Four-hour images generally show higher background and both the kidneys are visible. However, quality of the images significantly improved 24 h postinjection. Figure 2 shows a typical image obtained 24 h postadministration of ^{188}Re-HEDP complex.

Patient characteristics

Patients included in the present study had different types of cancers in advanced stages with widespread, painful, and skeletal metastases, as indicated in Table 2. A significant population of these patients had received radiotherapy and/or systemic hormonal therapy or chemotherapy earlier. In

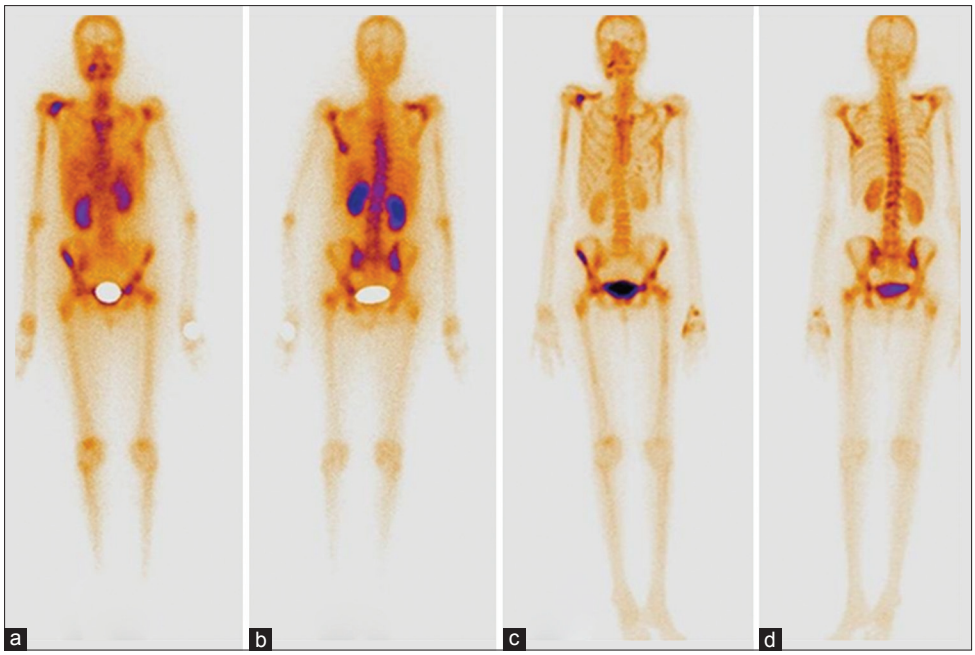

Figure 1: Whole-body anterior (a) and posterior images (b) acquired 4 h after intravenous administration of 86 mCi of ^{188}rhenium-hydroxyethylidene-1,1-diphosphonate. Whole-body anterior (c) and posterior images (d) of the same patient 4 h after intravenous administration of 10 mCi of ^{99m}Tc-methylene diphosphonate

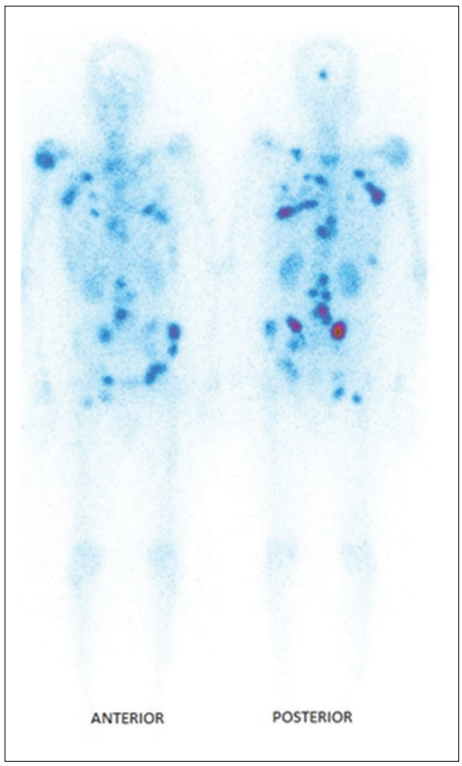

Figure 2: Typical distribution of ^{188}rhenium-hydroxyethylidene-1,1-diphosphonate complex 24 h postadministration

most of these patients, opioids failed to control bone pain. It is pertinent to note that six patients had undergone prior radionuclide therapy. Duration of patient follow-up was up to 12 weeks posttherapy.

Table 2: Patient characteristics

	Cancer type					
	Bladder	Breast	Lung	Prostate	Renal	Sarcoma
Male	0	0	4	11	4	1
Female	2	25	1	0	0	0
Group total	2	25	5	11	4	1

Pain and performance assessment

Irrespective of cancer types, the variation in pain and in mobility scores of the patients is summarized in Table 3. Individual pain scores of the patients showed significant decrease over a period of 12 weeks post ^{188}Re-HEDP therapy. Mean (SD) pain score for the study group was 8.31 (1.0) (range 7.1–9.4, $n = 48$) at baseline, which reduced to 5.90 (0.8) (range 4.1–7, $n = 48$) at week 4 and 3.60 (0.4) (3.0–4.6, $n = 48$) by week 8. At 12 weeks posttherapy, the score markedly reduced to 1.80 (0.4) (range 1.2–2.2, $n = 10$), suggesting a significant decrease in pain posttherapy. The difference between the mean pain score at week 4, 8, and 12 to the mean pain score at baseline was found to be statistically significant with $P < 0.001$. All patients who were on analgesics before therapy either reduced the dose or completely discontinued analgesics 4 weeks posttherapy.

Pain palliation was accompanied by improvement in the mobility score as well as Karnofsky performance score [Table 3] of the patient. Mean (SD) mobility score for the study group was 2.8 (0.61) (range 2–4, $n = 48$) at baseline, which markedly decreased to 1.50 (0.5) (range 1–2, $n = 48$) 4 weeks

Table 3: Improvement in pain and mobility of patients after therapy

	Mean (SD)			
	Baseline	4 weeks	8 weeks	12 weeks
VAS score	8.31 (1.0) (n=48)	5.90 (0.8) (n=48)	3.60 (0.4) (n=48)	1.80 (0.4) (n=10)
Mobility score	2.80 (0.6) (n=48)	1.50 (0.5) (n=48)	-	-
Karnofsky score	43.0 (5.6) (n=48)	59.0 (5.6) (n=48)	-	-
Analgesic score	5.30 (3.7) (n=48)	3.60 (4.1) (n=48)	-	-

SD: Standard deviation; VAS: Visual analog scale

posttherapy (>40% reduction of the baseline score). Similarly, the Karnofsky performance score of the study group, which was 43.0 (5.6) (range 40–60, n = 48) at the baseline, showed a significant increase to 59.0 (5.6) (range 50–80, n = 48) after 4 weeks posttherapy. This corresponds to >60% increase from the baseline value ($P < 0.001$).

Safety assessment

The main factor limiting the therapeutic dose of ^{188}Re-HEDP (2960–4440 MBq) is bone marrow suppression, which resulted in the reduction of peripheral blood counts. However, no significant change was observed in the hemoglobin counts. Decrease in platelet and leukocyte counts began 3 weeks posttherapy with a nadir at 5 weeks and showed a quick recovery by 8–9 weeks posttherapy. Twelve patients (25%) developed Grade-I platelet toxicity, eight patients showed Grade-II toxicity (16.7%), six patients showed Grade-III platelet toxicity, and three patients developed Grade-IV platelet toxicity. Nine patients (18%) developed Grade-I leukocyte toxicity while four patients (9%) developed Grade-II toxicity. Four patients showed Grade-III toxicity (9%) while three patients developed Grade-IV toxicity. No other clinically significant adverse reactions were observed. Although significant bone marrow suppression was detected in patients receiving higher doses of ^{188}Re-HEDP, clinical intervention was needed only in six patients who required a packed cell or blood product transfusion. All the six patients were administered with erythropoietin or PEG-GCSF or megakaryocyte-stimulating factors to enable them to recover their normal counts. Of the nine patients who showed Grade-III or Grade-IV platelet toxicity, majority had a baseline platelet count below 200,000/mL. Others had widespread bone metastases, a super-scan pattern, on the whole-body bone scan or have received radionuclide therapies or chemotherapy earlier.

The distribution of ^{188}Re-HEDP in the body observed at 4 h p.i. correlated well with the pretreatment ^{99m}Tc-MDP scan. Onset of pain relief was observed around 4–5 days posttherapy, and pain-free period lasted for at least 7 weeks in 75% of the patients (37 patients). A complete response was observed in 15 (30%) patients, a partial response in 26 patients (54%), and a minimal response in three (6%) patients. No response was seen in four patients (8.3%). Duration of pain relief was <4 weeks in two patients (4%), 4–8 weeks in 36 patients (75%) and >8 weeks in 6 (12.5%) patients. The mean duration of pain relief was 5.4 (4.18) weeks (range, 3–12 weeks, n = 48) for the study group.

The analgesic score revealed a similar trend and a significant reduction in the mean analgesic score was seen after treatment ($P < 0.002$). The mean analgesic score was 5.30 (3.7) before treatment and 3.60 (4.1) at the end of the 2 weeks ($P < 0.0001$).

Twenty-six patients (54.2%) experienced a flare response within 2–4 days postadministration of ^{188}Re-HEDP and it lasted for 3–5 days. There was no significant correlation between the flare reaction and pain response ($P > 0.01$). However, there was a significant association between flare response and dosage as well as presence of super-scan pattern of metastases ($r = 0.43$, $P < 0.05$).

DISCUSSION

Several radiopharmaceuticals such as ^{32}P-orthophosphate, $^{89}SrCl_2$, ^{153}Sm-EDTMP, ^{177}Lu-EDTMP, and ^{186}Re-HEDP are clinically proven bone pain-palliating agent. Among these, ^{32}P and ^{89}Sr are known to cause severe bone marrow toxicity.[29] In addition, the two radioisotopes being pure β-emitters, simultaneous scintigraphy during therapy is not possible. High cost and limited availability of ^{89}Sr are the other drawbacks that prevented its widespread clinical use.[52] The other three bone pain-palliating agents based on reactor-produced radioisotopes ^{153}Sm, ^{177}Lu, and ^{186}Re, which cause mild-to-moderate bone marrow toxicity, are, however, not "off-the-shelf" radiopharmaceuticals in any nuclear medicine centers. In this context, ^{188}Re-HEDP enjoys a special status since it is the only radiopharmaceutical for bone pain palliation, which could be prepared on a need-to-use basis in a hospital radiopharmacy having access to ^{188}W/^{188}Re generator. In addition, ^{188}Re-HEDP therapy could be made available at a reasonable cost to ensure that this treatment modality becomes more accessible for majority of patients.

Limited literature on clinical studies with ^{188}Re-HEDP for bone pain palliation has reported 70%–80% response[29,40,41] to ^{188}Re-HEDP therapy. In another group of 32 patients with bone metastases from different types of cancers, analgesic intake could be reduced in 82% of patients after ^{188}Re-HEDP therapy.[53]

In addition, about 70% of the patients reported significant improvement in quality of life, while 22% reported a minor improvement.[53] With a dose of 1100 MBq of ^{188}Re-HEDP, a response rate of 80% was obtained in a cohort of 61 patients with various primary tumors.[43] In a study reported by Liepe *et al*., using a dose of 2700–3459 MBq of ^{188}Re-HEDP, pain relief was demonstrated in 76% of patients, of which 20% patients were pain-free without additional dose of analgesics. In addition, a significant increase in Karnofsky performance scale (11% increase from baseline value) was observed within 12 weeks posttherapy.[41] In contrast, dose-escalation study in a small number of patients ($n = 6$) using 3300 MBq of ^{188}Re-HEDP showed a decline in response rate.[40] Lam *et al*.[44] reported a phase-I safety and toxicity study using a combination of ^{188}Re-HEDP and capecitabine in hormone-refractory prostate cancer patients with bone metastases. The study demonstrated that capecitabine (2500 mg/m^2/day) may safely be used in combination with ^{188}Re-HEDP (37 mg/kg). These studies are excellent examples showing the benefits of combined therapeutic strategies. Palmedo *et al*.[45] observed that in patients with advanced progressive hormone-refractory prostate carcinoma, instead of a single dose of ^{188}Re-HEDP, multiple sessions of ^{188}Re-HEDP therapy improved pain palliation as well as overall survival of the patients.

In our study, 90% of the patients experienced relief from bone pain. Observed variation in therapeutic response between different clinical studies could be related to some heterogeneous factors, such as patient selection criteria, lower than optimal dose administration, tumor type, response criteria, and the method of administration. Comparable results for the efficacy and duration of pain relief using higher doses of ^{188}Re-HEDP have been reported in the previous studies. In a dose-escalation study, a small number of metastatic cancer patients showed a better response rate with high therapeutic dose.[46] For ^{188}Re-HEDP, a standard dose of 1100 MBq is recommended as safe even in heavily pretreated patients.[43] However, some clinical data support the use of higher doses of ^{188}Re-HEDP, which is more likely to reduce tumor markers, ablate micrometastasis, and possibly, even eliminate the bone lesions.[41] In addition, when extensive skeletal involvement is present, the calculated absorbed dose to specific metastatic deposits has been shown to be significantly reduced.[16] This finding could possibly explain why a better response is observed in when patients were administered higher doses of ^{188}Re-HEDP. On the other hand, lower doses may be enough to get a good response in patients with few metastatic lesions.[11,18,19,31]

Due to high-energy beta of ^{188}Re, bone marrow toxicity is a possible adverse effect of ^{188}Re-HEDP therapy. In these patients, thrombocytopenia is the dose-limiting factor, whereas leukopenia is not significant.[11] Dose-escalation studies have indicated that 3300 MBq (~89 mCi) is the maximum ^{188}Re-HEDP dose tolerated in prostate cancer patients with lower levels of platelet counts.[40] Patients with adequate platelet counts, however, tolerate up to 4400 MBq (~119 mCi) of ^{188}Re-HEDP. In fact, bone marrow suppression and the subsequent adverse effects could be affected by various factors other than the dose administered. Suggested factors include the patient's overall condition, metastatic load, pretreatment blood cell count, and previous therapies,[32,33] if any. Our study showed that decline in blood cell count does not depend solely on the dose administered and that baseline blood count determination is important while selecting the best mode of treatment. Thus, we could safely administer higher doses in patients with sufficient blood cell counts. Blood toxicities associated with this modality clearly indicate the necessity of monitoring the patients before and after receiving radionuclide therapy, particularly patients with widespread skeletal metastases. A flare reaction is another adverse effect of bone-seeking therapeutic radionuclides and is probably related to transient inflammatory reactions that modify intratumoral pressures. Flare reactions can be managed by analgesics or steroid agents.[20]

An incidence of flare reaction of 10%–30% has been reported with ^{186}Re-HEDP and up to 50% with ^{188}Re. In our study, flare reactions occurred in more than half of patients and could be due to the patients' awareness of the probable short-term worsening of bone pain, higher administered dose, or greater fluctuations in the level of pain. The present study suggests that the flare response is not predictive of pain palliation, which contradicts the reports on the predictive power of flare reactions for treatment response.[34,38] Furthermore, bone scintigraphy and alkaline phosphatase level of responders and nonresponders in this study were not significantly different, which is another controversial issue in the literature.

Although several studies have demonstrated that administering therapy, when the patient is in better clinical condition, may significantly improve the response rate, this understanding has not been translated into clinical practice to unleash the full potential of radionuclide therapy. This underutilization could be due to specialists' inadequate knowledge and misconceptions about the adverse effects of this mode of therapy or due to restricted availability and cost of bone pain-palliating radionuclides.

CONCLUSION

^{188}Re-HEDP is an effective, clinically useful, radiopharmaceutical for bone pain palliation. Possible side effects of this therapy

can be significantly minimized upon careful selection of patients and administered dose. Although several studies have demonstrated that administering therapy, when the patient is in better clinical condition, may significantly improve the response rate,[18,19,31] this understanding has not been translated into a clinical practice to unleash the full potential of radionuclide therapy. This underutilization could be due to specialists' inadequate knowledge and misconceptions about the adverse effects of this mode of therapy or due to restricted availability and cost of bone pain-palliating radionuclides. Clinical studies, like the present study, could help popularize and simultaneously alleviate misconceptions on the adverse effects of this mode of therapy, especially in India. In this context, development of a freeze-dried HEDP kit has been an appropriate step in right direction.

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Conflicts of interest

There are no conflicts of interest.

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