Eur J Nucl Med Mol Imaging (2015) 42:79–88
DOI 10.1007/s00259-014-2862-z

ORIGINAL ARTICLE

^{177}Lu-EDTMP for palliation of pain from bone metastases in patients with prostate and breast cancer: a phase II study

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Received: 22 April 2014 / Accepted: 7 July 2014 / Published online: 29 July 2014

Abstract
Purpose The purpose of this study was to evaluate the efficacy and safety of ^{177}Lu-EDTMP for pain palliation in patients with bone metastases from castration-resistant prostate and breast cancer. The secondary objective was to compare low-dose and high-dose ^{177}Lu-EDTMP in bone pain palliation.
Methods Included in the study were 44 patients with documented breast carcinoma (12 patients; age 47±13 years) or castration-resistant prostate carcinoma (32 patients; age 66± 9 years) and skeletal metastases. Patients were randomized into two equal groups treated with ^{177}Lu-EDTMP intravenously at a dose of 1,295 MBq (group A) or 2,590 MBq (group B). Pain palliation was evaluated using a visual analogue score (VAS), analgesic score (AS) and Karnofsky performance score (KPS) up to 16 weeks. Toxicity was assessed in terms of haematological and renal parameters.
Results The overall response rate (in all 44 patients) was 86 %. Complete, partial and minimal responses were seen in 6 patients (13 %), 21 patients (48 %) and 11 patients (25 %), respectively. A favourable response was seen in 27 patients (84 %) with prostate cancer and in 11 patients (92 %) with breast cancer. There was a progressive decrease in the VAS from baseline up to 4 weeks ($p<0.05$). Also, AS decreased significantly from 1.8±0.7 to 1.2±0.9 ($p<0.0001$). There was an improvement in quality of life of the patients as reflected by an increase in mean KPS from 56±5 to 75±7 ($p<0.0001$). The overall response rate in group A was 77 % compared to 95 % in group B ($p=0.188$). There was a significant decrease in VAS and AS accompanied by an increase in KPS in both groups. Nonserious haematological toxicity (grade I/II) was observed in 15 patients (34 %) and serious toxicity (grade III/IV) occurred in 10 patients (23 %). There was no statistically significant difference in haematological toxicity between the groups.
Conclusion ^{177}Lu-EDTMP was found to be a safe and effective radiopharmaceutical for bone pain palliation in patients with metastatic prostate and breast carcinoma. There were no differences in efficacy or toxicity between patients receiving low-dose and high-dose ^{177}Lu-EDTMP.

Keywords ^{177}Lu-EDTMP · Breast and prostate carcinoma · Pain palliation · Low dose · High dose

Introduction

Bone metastases are found in nearly 60 – 80 % patients with advanced prostate or breast carcinoma [1]. The most prominent symptom of bone metastases for which patients seek medical attention is pain. Thus, the palliation of pain in patients is very important in the clinical management of advanced untreatable cancers. The management of bone pain involves a multidisciplinary approach involving systemic and nonsystemic treatments. However, many treatment options are limited in their efficacy and duration and have significant adverse effects that seriously limit the cancer patient's quality of life. Radionuclide therapy, using pharmaceuticals labelled with radionuclides, has shown good efficacy in relieving bone pain resulting from secondary skeletal metastases and in improving the patients' quality of life [2].

Hormonal therapy has also been used to alleviate bone pain in patients with breast or prostate cancer. However, bone pain can recur in hormone-treated patients because of emergence of hormone-resistant clones of cancerous cells [3]. Several radiopharmaceuticals have been used for treating painful bone metastases including ethylenediaminetetramethylene phosphonate (EDTMP) labelled with ^{32}P, $^{89}SrCl_2$ or ^{153}Sm [4–6].

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^{223}Ra, an alpha-emitting radiopharmaceutical with a potent and highly targeted cytotoxic effect on bone metastases, has been approved for the treatment of patients with castration-resistant prostate cancer and symptomatic bone metastases. Some studies have shown that bone-targeted therapy also has the potential to delay progression of osseous metastases [7–9]. Preclinical studies have outlined the prospects for ^{177}Lu-EDTMP for systemic radionuclide therapy in patients with breast or hormone-refractory prostate cancer and bone metastases [10]. The tissue penetration range of the β particles from ^{177}Lu are low ensuring less bone marrow suppression, a major advantage of this radiotherapeutic [11]. In the current phase II clinical study, we evaluated ^{177}Lu-EDTMP in patients with metastatic prostate and breast cancer. The objectives of this study were to evaluate the pain palliation effect and to compare therapeutic efficacy and toxicity profile of low-dose versus high-dose ^{177}Lu-EDTMP.

Patients and methods

Preparation of ^{177}Lu-EDTMP

EDTMP cold kit was obtained from Polatom containing 35 mg of EDTMP powder, 5.72 mg CaO, 14.1 mg NaOH. Sterile water (1 ml) was added to the kit and the contents gently shaken. $^{177}LuCl_3$ was obtained from Bhabha Atomic Research Centre (Mumbai) and was produced in a medium flux research reactor with a specific activity of 22 – 25 mCi/μg. $^{177}LuCl_3$ (50 – 150 mCi) was added to the cold kit and the reconstituted solution then incubated for 30 min at room temperature. The final preparation was filtered using a Millipore filter prior to injection.

Quality control techniques

Radiochemical purity was determined using a combination of paper chromatography and paper electrophoresis.

Paper chromatography A spot of 5 μl of the test solution was placed 1.5 cm from one end of Whatman 3 MM chromatography paper strips (12×2 cm). The paper strips were developed in ammonia/ethanol/water (1:10:20), dried, cut into 1-cm segments and the radioactivity was then measured.

Paper electrophoresis A spot of 5 μl of the complex solutions was placed on preequilibrated Whatman 3 MM (35×2 cm) chromatography paper 15 cm from the cathode. Electrophoresis was carried out for 1 h under a voltage gradient of 10 V/cm using 0.025 M phosphate buffer, pH 7.5. The strips were dried, cut into 1-cm segments and the activity was measured.

A labelling efficiency of >95 % was ensured by both techniques before intravenous injection into the patient [12].

Patients

Patients with diagnosed prostate or breast carcinoma with documented bone metastases and progressively increasing pain or pain requiring incremental doses of analgesics were included in the study. Patients suffering from multifocal pain and two or more sites of painful bone metastases corresponding to positive sites on recent ^{99m}Tc-methylene diphosphonate skeletal scintigraphy (within 4 weeks or less) were recruited. Patients with leucocyte and thrombocyte counts below 4.0×10^9/L and 100×10^9/L, respectively, or with impaired renal function (creatinine >1.5 mg/dL) were excluded from the study. None of the patients had received hemi body irradiation before ^{177}Lu-EDTMP treatment. However, local external-beam radiation and previous treatment with bisphosphonates were permitted provided the time to ^{177}Lu-EDTMP treatment was at least 4 weeks. Patients with pain caused by pathological fracture, infiltration of a nerve plexus, or peripheral nerves were excluded. All patients were informed about the potential risks and benefits of the study and written informed consent was obtained before administration of the radiopharmaceutical. The study was approved by the ethics committee of the institution.

Study design and protocol

The study was a phase II clinical trial. Patients were randomly assigned to two groups based on administered radioactivity: group A received a low dose (1,295 MBq) and group B received high dose (2,590 MBq) of ^{177}Lu-EDTMP. The radiopharmaceutical was administered slowly over a period of 1 min via an indwelling intravenous cannula followed by flushing with 10 mL of normal saline. For the assessment of toxicity, the National Cancer Institute Common Toxicity Criteria (NCI-CTC) version 3 was used [13]. The nadirs were estimated by comparison of the pretreatment levels of thrombocytes and leucocytes (baseline) with the lowest level during the follow-up period. Patients were asked to maintain a daily diary for initial 2 weeks to assess the onset of pain relief. The baseline period was defined as the week prior to the injection of ^{177}Lu-EDTMP. Patients were examined and followed up at baseline and after radiopharmaceutical administration at 1, 2, 4, 6, 8, 12 and 16 weeks on an outpatient basis. The effect of ^{177}Lu-EDTMP on pain palliation was considered to have ended when the patients reported the slightest increase in the maintenance dose of analgesic or reinitiation of the consumption of analgesic that had earlier been discontinued because of the benefits of treatment. The duration of pain-free survival was calculated accordingly.

The bone lesion score (BLS) was calculated to determine the extent of disease on the basis of the findings on skeletal scintigraphy. The entire skeleton was divided into five anatomic regions in which four regions were scored between 1 and 4 and skull lesions were scored between 1 and 3 (Table 1). A patient-rated visual analogue score (VAS) served as the basis for pain documentation [14]. On this scale, pain was rated as zero when the patient experienced no pain and ten represented intolerable pain. A multisite VAS was used that recorded the patient's pain intensity for each of several body regions (head, upper spine, lower spine, arms, legs, ribs, sternum and clavicles, and pelvis). Pain relief was assessed in terms of changes in the average baseline VAS in comparison with the average VAS at 1, 2, 4, 6, 8, 12 and 16 weeks after injection. The patients were arbitrarily divided into four categories depending upon the maximum decrease in VAS after treatment compared to the baseline VAS: complete response (CR, >70 % decrease in VAS), partial response (PR, 40 – 70 % decrease in VAS), minimal response (MR, 20 – 40 % decrease in VAS) and no response (<20 % decrease in VAS or increase in pain).

Analgesia was assessed in terms of an analgesic score (AS) on a five-point scale according to the Urological Group of the European Organization of Research and Treatment of Cancer (EORTC, protocol 30921): *0* no analgesic, *1* non-opiate analgesics occasionally, *2* non-opiate analgesics regularly, *3* opiate analgesics occasionally, *4* opiate analgesics regularly. A decrease in bone pain or AS qualified as a positive response to treatment. Quality of life was assessed using the Karnofsky performance score (KPS) [15]. Overall survival was defined as the time between the ^{177}Lu-EDTMP injection and death from any cause or the last follow-up visit or telephone contact.

Statistical tests

Descriptive statistics including the mean, median, range, standard deviation and frequencies were used to summarize the baseline demographic profile of the patients. Fisher's test was used to compare the various qualitative parameters within the groups. Continuous variables were assessed for normality of distribution using the Kolmogorov-Smirnov test. Independent *t*-tests or the Mann-Whitney test were used as and when required. The paired *t*-test was used to compare pretreatment and posttreatment quantitative variables. Survival was compared using Kaplan-Meier survival analyses, and groups were compared using log-rank tests. Repeated measures of analysis of variance were used to compare differences in VAS, AS and KPS within and between groups. Significance was assumed for p values <0.05. Statistical package used in the analyses was SPSS 19.0.0.0 (IBM USA).

Table 1 BLS in different regions of the body

Region	Score			
	1	2	3	4
Skull	0	≤2	>2	–
Spine	0	≤2	3 – 5	>5
Thorax	0	≤2	3 – 5	>5
Extremities	0	≤2	3 – 5	>5
Pelvis	0	≤10 %	10 – 25 %	>25 %

Results

From 1 December 2010 to February 2013, 49 patients were recruited. Three patients from group A and two patients from group B were excluded from the study due to lack of significant follow-up (less than 2 weeks). Thus, the final study group included 32 male patients with castration-resistant prostate cancer (age 66±9 years) and 12 female patients with metastatic breast cancer (age 47±13 years). The average Gleason score was 8±1 and, concerning the male patients, the serum prostate-specific antigen (PSA) level was 209± 421 ng/dL. The median latency duration from initial diagnosis of skeletal metastases to treatment for bone pain palliation was 15 months (range 1 – 71 months). The baseline characteristics of the patients in both groups are summarized in Table 2. Both groups were comparable with respect to all patient-related clinical and biochemical variables measured at baseline.

All patients

Overall response rate (ORR) included patients showing a CR, PR or MR. Among the 44 patients, 38 showed a response (ORR 86 %) of which 6 (13 %) were CR, 21 (48 %) were PR and 11 (25 %) were MR. Of the prostate and breast cancer patients, 27 (84 %) and 11 (92 %), respectively, showed a favourable response. There was no statistically significant difference in response rates between the prostate and breast cancer patients (p=0.893). The decreases in VAS were comparable in the patients with breast cancer and those with prostate cancer (Fig. 1). The baseline VAS in patients who had significant pain relief was 7.2±1.3 which was comparable to 6.8±1.5 in patients who did not show any response (p=0.562). No clinical/biochemical variable at baseline could be identified to distinguish responders from nonresponders (Table 3). In the patients responding to therapy, the VAS decreased from 6.8±1.5 at baseline to 3.5±1.7 during follow-up after radionuclide therapy (p<0.0001). Also, the AS decreased from 1.8±0.7 to 1.2±0.9 (p<0.0001).

Table 2 Comparison of baseline variables in the low-dose group (1,295 MBq) and high-dose group (2,590 MBq)

Variable	Group		*p* value
	A (low-dose)	B (high-dose)	
Patients, *n*	22	22	
Primary (prostate/breast), *n*	17/5	15/7	0.498
Age (years)	61±14	60±13	0.912
Bone lesion score, mean±SD	15±4	16±3	0.456
Latency time from diagnosis (months), median (range)	13.3 (1 – 71)	16.4 (2 – 57)	0.265
Analgesic score, mean±SD	1.7±0.8	1.9±0.7	0.411
Visual analogue score, mean±SD	6.5±1.6	7.0±1.3	0.216
Karnofsky performance score, mean±SD	56±5	57±5	0.542
Haemoglobin (g/dL), mean±SD	10.9±1.8	10.7±1.8	0.701
Gleason score, mean±SD[a]	8.2±0.7	8.0±1.0	0.721
Prostate-specific antigen (ng/dL), median (range)[a]	62 (1 – 2,208)	76 (1 – 554)	0.558
Radiotherapy (yes/no), *n*	8/14	8/14	1.000
Chemotherapy (yes/no), *n*	8/14	13/9	0.131
Prostatectomy (yes/no), *n*[a]	4/13	3/12	1.000
Hormonal therapy (yes/no), *n*	15/7	12/10	0.353

$p<0.05$ was considered significant

[a] Variable related to prostate cancer patients only

Maximum pain relief measured according to the VAS was observed in 10 patients (23 %) at 1 week, 16 (37 %) at 2 weeks, 15 (35 %) at 4 weeks and 2 (5 %) at 8 weeks, with no change in VAS in one patient.

The VAS at all follow-up visits measured as percentage decrease was significantly lower than the baseline score (Fig. 2). VAS at 1, 2, 4, 8, 12 and 16 weeks were significantly lower than at baseline ($p<0.0001$). There was progressive decrease in VAS from baseline to up to 4tweeks ($p<0.05$). The VAS did not change significantly between 4 and 8 weeks ($p=0.128$) and thereafter a significant increase was noted between 8 and 12 weeks ($p=0.031$) as well as between 12 and 16 weeks ($p=0.015$). There was an improvement in quality of life in the patients as reflected by an increase in mean KPS from 56±5 to 75±7 ($p<0.0001$).

Group analysis

The ORR in group A was 77 % compared to 95 % in group B; however, the difference was not statistically significant

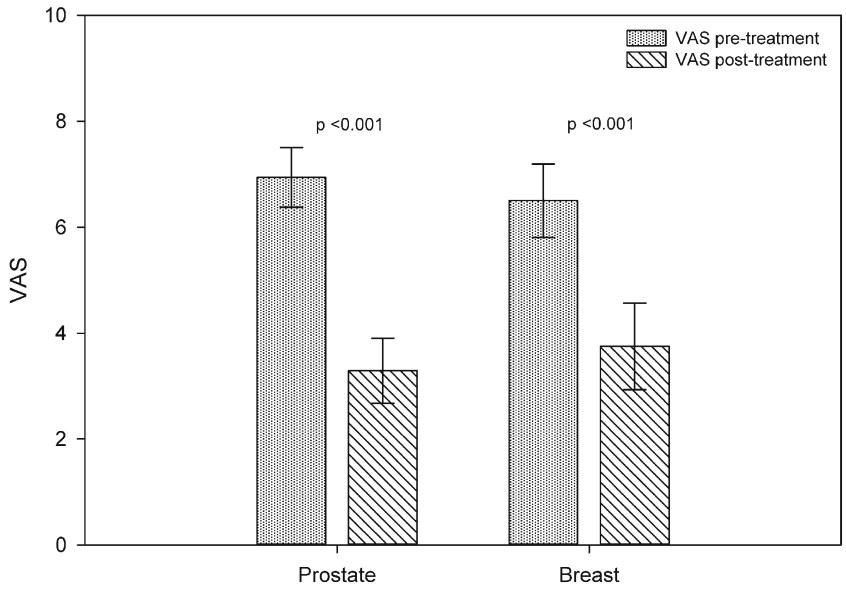

Fig. 1 The VAS in 32 prostate cancer patients decreased from 6.9±1.5 to 3.4±1.8. Similarly, the VAS in 12 breast cancer patients decreased from 6.5±1.1 to 3.7±1.3. There was a significant decrease in VAS in both prostate and breast cancer patients, but bone pain palliation was similar between prostate and breast cancer patients ($p=0.892$)

Table 3 Comparison of factors at baseline in the response and no-response groups

Variable	Group		*p* value
	Response	No response	
Patients, *n*	38	6	
Age (years)	53±13	62±13	0.072
Bone lesion score, mean±SD	17±2	15±4	0.296
Latency time from diagnosis (months), median (range)	21.5 (5.7 – 29)	14.7 (1 – 71)	0.516
Chemotherapy (yes/no), *n*	19/19	2/4	0.666
Radiotherapy (yes/no), *n*	14/24	2/4	1
Hormonal therapy (yes/no), *n*	22/16	5/1	0.38
Prostatectomy (yes/no), *n*[a]	6/21	1/4	1
Gleason score, mean±SD[a]	8±1	8±1	0.658
PSA, median (range)[a]	41 (12 – 280)	76 (1 – 2,208)	0.551

$p<0.05$ was considered significant

[a] Variable related to prostate cancer patients only

(p=0.188). Among the prostate cancer patients, 13 (76 %) in group A and 14 (93 %) in group B responded to treatment (p=0.410). Similarly, among the breast cancer patients, 4 (80 %) in group A and 7 (100 %) in group B responded to treatment (p=0.860). CR was observed in two patients (9 %) in group A and in four patients (18 %) in group B. PR was observed in ten patients (45 %) in group A and in 11 patients (50 %) in group B (Fig. 3).

The VAS decreased from 6.5±1.6 to 3.8±2.1 in group A and from 7.0±1.3 to 3.3±1.2 in group B. Also, the need for analgesics decreased similarly in both groups. The AS decreased from 1.7±0.8 to 1.1±0.9 (p=0.0003) in group A and from 1.9±0.7 to 1.3±0.9 in group B (p=0.0002). There was a significant decrease in VAS and AS in each group; however, the percentage change between the groups was comparable (Fig. 4). There was no difference in VAS at any of the follow-up visits between the two groups from baseline up to 16 weeks (Fig. 5). There was a significant improvement in mean KPS in both groups. The KPS increased from a baseline score of 56±5 to 73±9 in group A and from a baseline score of 57±5 to 76±5 in group B. The improvement in KPS between the two groups was comparable (p=0.498).

Survival analysis

The median time of onset of response was 8 days with a range between 6 and 14 days as calculated from the pain diary of the patients. The median duration of response was 3 months with

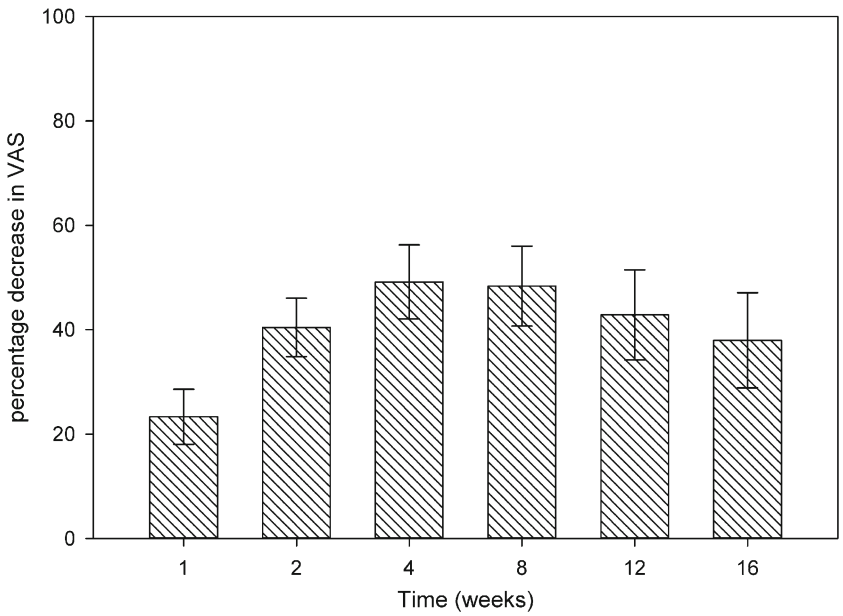

Fig. 2 Percentage decreases in VAS [calculated as ($VAS_{baseline} - VAS_{visit}$)/$VAS_{baseline}$) × 100] at follow-up visits over 16 weeks. The maximum percentage (49±22 %) decrease in VAS is seen at 4 weeks

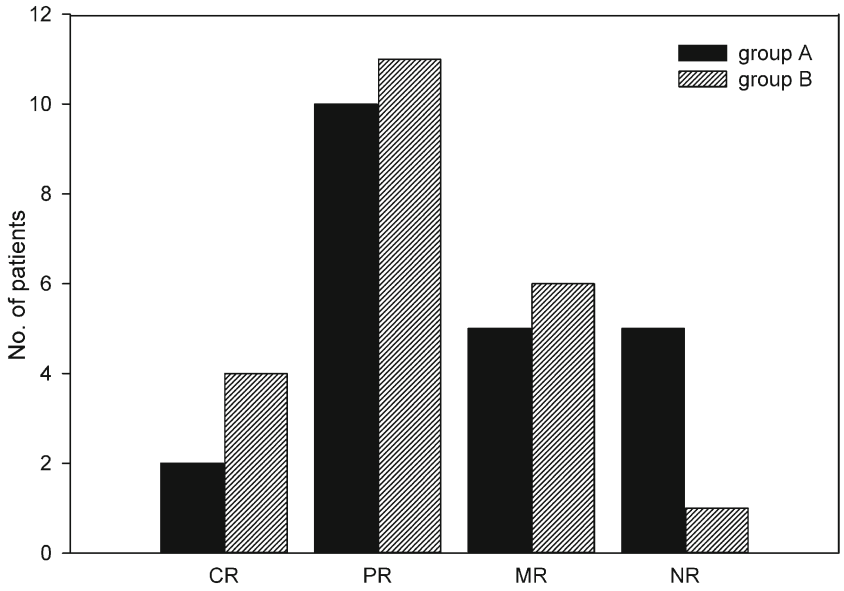

Fig. 3 Responses to pain palliation low-dose (group A) and high-dose (group B) treatment (*CR* complete response, *PR* partial response, *MR* minimal response, *NR* no response). The response rates in the low-dose and high-dose groups were similar (p=0.280)

a maximum duration of 4 months. The median pain-free survival period in the 32 prostate cancer patients was 2 months (range 15 days to 4 months) and in the 12 breast cancer patients was 3 months (range 1 to 4 months). There was no difference in pain-free survival between the prostate and breast cancer patients (p=0.196). The median duration of response in group A and group B were comparable; 2.5 months (15 days to 4 months) in group A and 3 months (1 – 4 months) in group B (Fig. 6a). The 1-year survival rate was 35 % in group A and 38 % in group B. There was no significant difference in overall survival between the groups (Fig. 6b).

Toxicity analysis

Treatment-related toxicity was evaluated in all 44 patients. Nonserious haematological toxicity (grade I/II) was seen in 15 patients (34 %) after administration of treatment. Serious toxicity (grade III/IV) was seen in 10 patients (23 %). However, 22 patients (50 %) were anaemic before treatment. At the time of recruitment, 12 patient (27 %) had haemoglobin between 9.5 and 11.0 g% and 10 patients (23 %) had haemoglobin between 8.0 and 9.5 g%. Seven patients required packed cell transfusion before treatment. Grade III/IV anaemia was seen in ten patients after treatment, of whom six had previously had II anaemia. The median haemoglobin nadir occurred at 3 weeks (range 1 to 8 weeks) and the median time to recovery was 6 weeks (range 2 to 8 weeks). Toxicity to white blood cells was nonserious with grade I and II toxicity in two and four patients, respectively. The leucocyte nadir was occurred at 4 weeks and recovered to baseline values after 8 weeks. Three patients showed grade II and one patient each showed grade I and grade III thrombocytopenia. The platelet nadir occurred at 3 weeks and recovered to baseline values after 8 weeks. There was no statistically significant difference in haematological toxicity between the groups (Table 4). None of the patients had evidence of renal toxicity, flare syndrome of pain or other side effect such as hypercalcaemia.

Discussion

Radionuclide therapy of bone metastases is a palliative treatment aimed mainly at amelioration of bone pain and prevention of disease progression that might lead to further complications. The mechanism of pain reduction using radiopharmaceuticals is not clear. Accumulation of the radionuclide in the metastases leads to irradiation of the pathological tissue with a limited effect on the surrounding normal tissues. Simultaneous shrinkage of the metastatic tumour decreases the mechanical stimulation of the periostial pain receptors [16]. However, the more likely explanation may be osteoclast inhibition due to radiation [17]. Pure alpha-emitter therapy using ^{223}Ra may be considered a better agent since significant decreases in PSA and in alkaline phosphatase levels have been reported [18, 19]. ^{177}Lu-EDTMP has selective bone accumulation, relatively low uptake in soft tissue (except the liver) and higher skeletal uptake, suggesting that it may be useful as a bone pain palliation agent for the treatment of bone metastases [20]. The low electron energy (βmax 0.497 MeV) of ^{177}Lu is another advantage, as the tissue penetration range of the β particles is low ensuring minimal bone marrow suppression, a major advantage of this radiotherapeutic application over other radionuclide therapies [11]. ^{177}Lu is not a pure β-emitter; it also emits low-energy γ rays, which also allows direct posttherapy imaging and dosimetry.

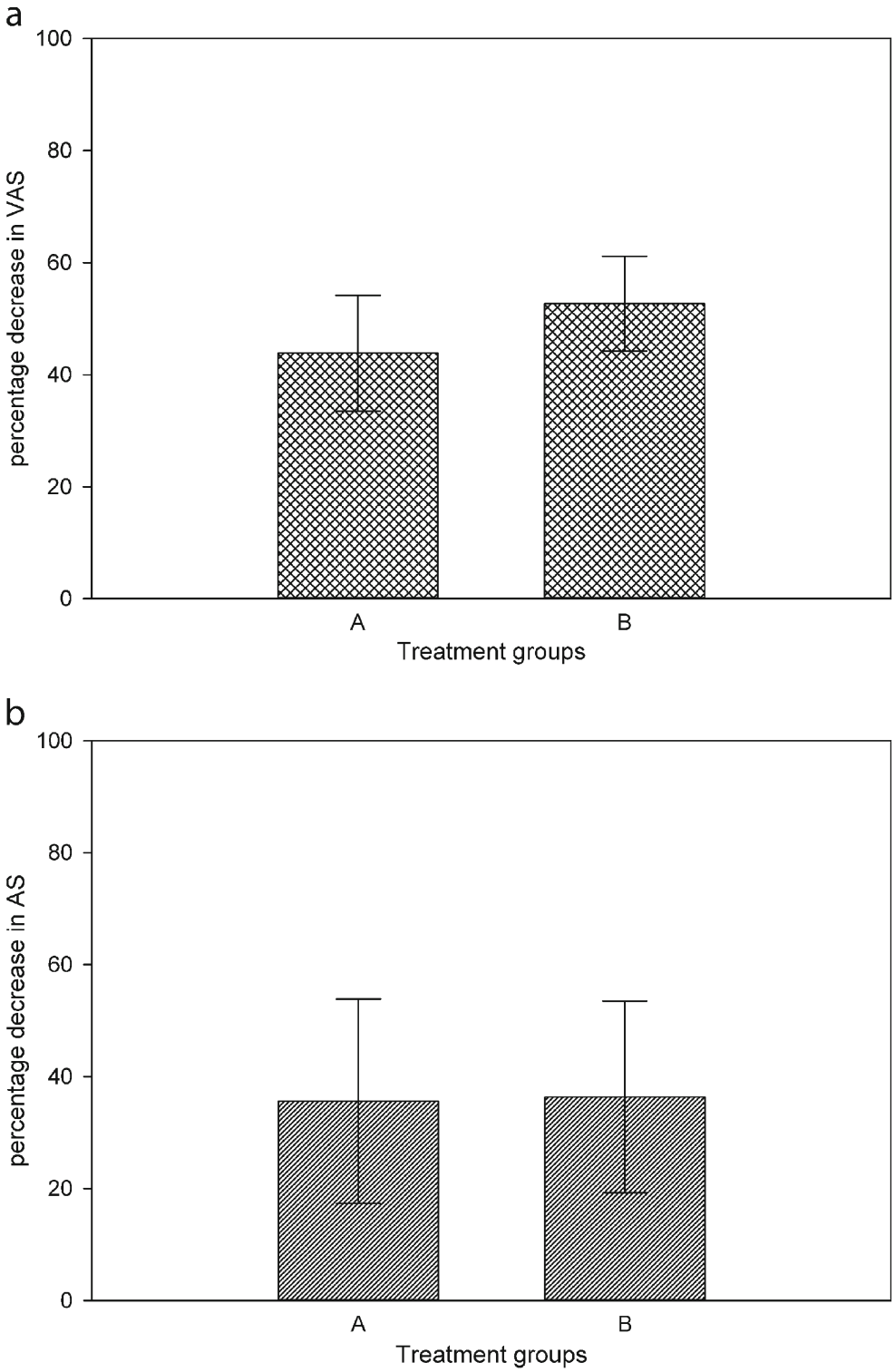

Fig. 4 Mean maximum percentage decreases in VAS and AS from baseline in groups A and B (*error bars* ±95 % CI). The decreases in the scores were comparable between the groups: **a** VAS (44±23 % and 52±19 %, respectively, p=0.201); **b** AS (36±41 % and 36±39 %, respectively, p=0.950)

In comparison with previously reported results, our results show that ^{177}Lu-EDTMP has a good palliative effect in patients with castration-resistant prostate and breast cancer and with bone disease. Pain relief has been reported in 70 to 85 % of patients after treatment with other radiopharmaceuticals such as $^{89}SrCl_2$, ^{153}Sm-EDTMP and ^{186}Re-HEDP [6, 21–24]. In this study, we found an ORR of 86 % that lasted for a median of 3.0 months. In prostate and breast cancer patients, the response rates were, respectively, 84 % and 92, values that are comparable to those in the literature that indicate a response in 70 – 90 % patients with other radiopharmaceuticals. Reported response rates in the current

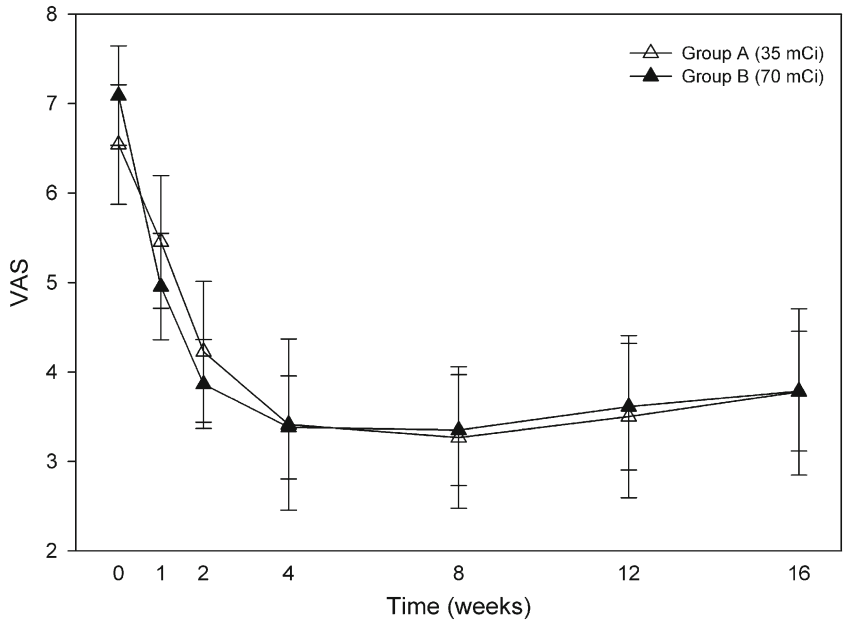

Fig. 5 VAS in group A (low dose) and group B (high dose) from the time of treatment up to 16 weeks (means±95 % CI)

literature in breast cancer patients treated with ^{153}Sm-EDTMP are 80 – 86 % [6, 25]. Pons et al. found a 92 % response rate with $^{89}SrCl_2$ in 26 breast cancer patients [23]. PSA is an established organ-specific marker for diagnosis as well as estimation of disease burden in prostate cancer patients. A survival benefit is also associated with lower PSA levels [26]. The baseline PSA level did not correlate well with response in prostate cancer patients in the current study. The average BLS in responders was 17 and in nonresponders was 15. The probability of response in our study was thus independent of the number of osteoblastic metastases as measured using BLS. Prior treatment including chemotherapy, radiotherapy or hormonal therapy received before radiopharmaceutical administration also did not appear to alter the probability of response. The low dose of ^{177}Lu-EDTMP (1,295 MBq) generated a pain palliation response rate of 77 %, which was not significantly different from 95 % achieved with a high dose (2,590 MBq).

Pain relief was noted as early as 8 days after ^{177}Lu-EDTMP administration, while the effect lasted for 2 to 4 months. Yuan et al. [27] reported a duration of pain relief of more than 3 months after ^{177}Lu-EDTMP treatment. This is similar to the findings of previous studies using radiopharmaceuticals other than ^{177}Lu-EDTMP, in which the response durations varied from 2 weeks to 9 months with the onset of response as early as 7 days to as long as 14 days [6, 21–24]. Among the

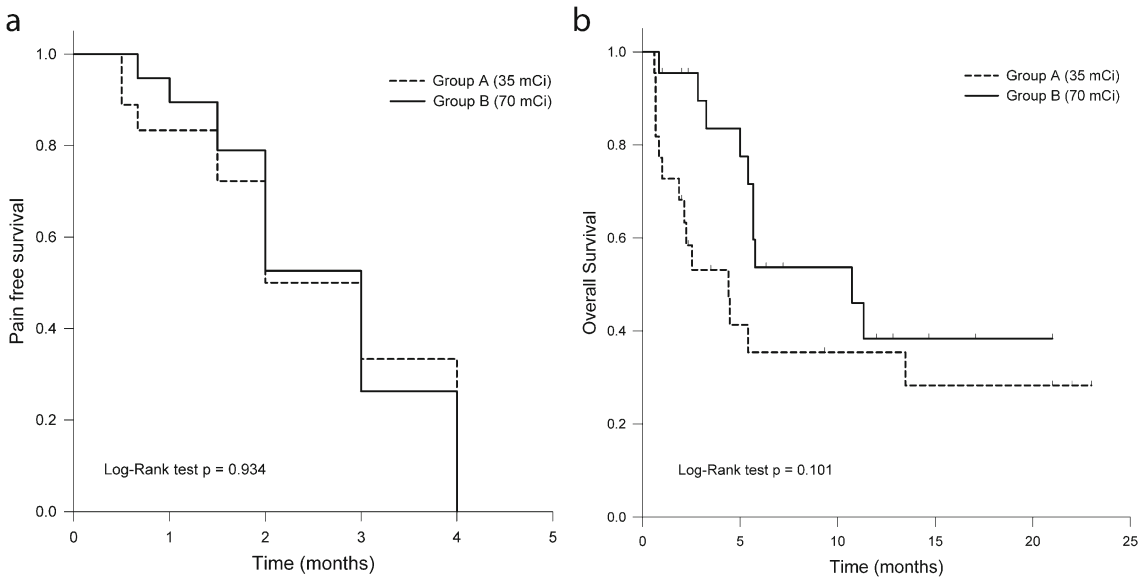

Fig. 6 Kaplan-Meier survival analyses. **a** Pain-free survival in group A (*broken line*) was comparable to that in group B (*solid line*). **b** Overall survival from the time of recruitment in group A (*broken line*) was not significantly different (log-rank test) from that in group B (*solid line*)

Table 4 National Cancer Institute Common toxicity grades after treatment with ^{177}Lu-EDTMP therapy

	All patients			Group A			Group B			*p* value
	No toxicity	Nonserious toxicity	Serious toxicity	No toxicity	Nonserious toxicity	Serious toxicity	No toxicity	Nonserious toxicity	Serious toxicity	
Anaemia	24	10	10	10	6	6	14	4	4	0.480
Thrombocytopenia	38	5	1	20	1	1	18	4	0	0.234
Leukopenia	38	6	0	20	2	0	18	4	0	0.660

$p<0.05$ was considered significant

prostate and breast cancer patients, 84 % 92 % exhibited significant bone pain palliation with a median durations of response of 2 months and 3 months, respectively. Maini et al. found a median duration of pain relief of more than 3 months with ^{153}Sm-EDTMP in 14 breast cancer patients [6]. Ahonen et al. found a similar pain-free period with $^{89}SrCl_2$ in 35 breast cancer patients [25]. The duration of pain relief was 2.5 months and 3 months in those treated with a low dose (1,295 MBq) and a high dose (2,590 MBq), respectively. Also, high-dose ^{177}Lu-EDTMP was not found to be associated with any additional survival benefit compared to the low dose. The 1-year survival rate was 35 % in patients who were treated with 1,295 MBq and 38 % in those treated with 2,590 MBq of ^{177}Lu-EDTMP. There are diverse and heterogeneous methodologies in the literature for the assessment of analgesic consumption. Palmedo et al. [21] used a medication index for assessing therapeutic efficacy. In our study, an AS based on the type of analgesia used by the patients was used to measure response to treatment. There was a significant reduction in AS from 1.8 to 1.2 2 months after ^{177}Lu-EDTMP treatment. Pain palliation in terms of reduction in AS was similar in the low-dose and high-dose groups during follow-up. The relief from bone pain was accompanied by simultaneous improvement in KPS in all patients irrespective of the type of cancer or amount of radioactivity administered.

The major dose-limiting factor with bone-seeking radiopharmaceuticals is bone marrow toxicity, which results in a reduction in peripheral blood cell counts [28]. Grade III/IV haematological toxicity was seen in 10 patients (23 %). This was probably because most patients entered the study with a low haemoglobin value attributed to prior rigorous chemotherapy regimens. Also, in prostate cancer patients, metastatic disease tends to infiltrate the bone marrow. Both these factors lead to a decreased haematopoietic reserve, which cannot always be diagnosed by simple blood count measurements. Other than the higher incidence of anaemia, 5 patients (11 %) showed thrombocytopenia and 6 patients (14 %) neutropenia during the course of follow-up. The toxicity profile was also not different between the high-dose and low-dose groups: serious haematotoxicity was seen in six patients (27 %) and four patients (18 %), respectively.

Compared with ^{177}Lu-EDTMP, radiopharmaceuticals such as ^{153}Sm-EDTMP and ^{186}Re-HEDP have a shorter half-life (1.9 days and 3.7 days, respectively) and a significantly higher maximal beta-energy (0.81 MeV and 1.07 MeV, respectively). The low electron energy (βmax 0.497 MeV) of ^{177}Lu-EDTMP is an important advantage over ^{153}Sm-EDTMP. This results in a decrease in the range of electrons from approximately 4 mm for ^{153}Sm-EDTMP to 2 mm for ^{177}Lu-EDTMP in normal osseous tissue and bone marrow. On the contrary, the longer physical half-life of ^{177}Lu (6.73 days) results in an overall longer effective half-life. Thus, ^{177}Lu-EDTMP irradiates tumour cells at a low dose rate with a relatively low dose per cell cycle, in contrast to radiopharmaceuticals such as ^{186}Re-HEDP, ^{153}Sm-EDTMP and ^{188}Re-HEDP which have a shorter effective half-life delivering radiation at a high dose rate. Also, the longer physical half-life of ^{177}Lu provides a logistic advantage in the ability to deliver the radiopharmaceutical to locations far from reactors. ^{177}Lu-EDTMP thus appears to outscore other radiopharmaceuticals theoretically in terms of physical properties and has similar biological effects. However, direct comparison with other radiopharmaceuticals is required to validate this statement.

Conclusion

This study indicates that ^{177}Lu-EDTMP is a safe and effective alternative for bone pain palliation in patients with metastatic prostate and breast carcinoma. It is a simple and well-tolerated single-session procedure that usually achieves good pain palliation and improves quality of life. Low-dose treatment would be preferable to high-dose treatment because, as well as having similar efficacy and toxicity, it is associated with lower radiation exposure to the patient and personnel as well as lower costs.

Acknowledgments We are grateful to Dr. John J. Zaknun, MD, Nuclear Medicine Section, Division of Human Health, International Atomic Energy Agency, Vienna, Austria, and Dr. Meera Venkatesh, Dr. Sudipta Chakraborty, Dr. Tapas Das, Dr. Sharmila Banerjee and Dr. M.R.A. Pillai, Radiopharmaceutical Division, Bhabha Atomic Research Centre, Mumbai, for their support in completion of the research.

Conflicts of interest None.

Funding No funding received from any organization for this study.

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