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A prospective randomized trial: A comparison of the analgesic effect and toxicity of ^{153}Sm radioisotope treatment in monotherapy and combined therapy including local external beam radiotherapy (EBRT) among metastatic castrate resistance prostate cancer (mCRPC) patients with painful bone metastases

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Bone metastases in prostate cancer constitute the most frequent cause of systemic failure in treatment, which results in numerous complications and finally leads to patient's death. Pain is one of the first and most important clinical symptoms of bone metastases and can be found among more than 80% of patients. Therefore, the most analgetic effective and simultaneously the least toxic treatment is an important point of therapeutic management in this group of patients. The aim of this prospective clinical trial was a comparison of analgetic effectiveness and toxicity of monotherapy with ^{153}Sm isotope to combined therapy (^{153}Sm + EBRT) among patients diagnosed with multiple painful bone metastases due to CRPC (mCRPC).

177 patients with mCRPC were included into the prospective randomised clinical trial in which 89 patients were assigned to the ^{153}Sm isotope monotherapy, while 88 patients were assigned to the combined therapy including ^{153}Sm isotope therapy and EBRT. All patients were diagnosed (bone scan and X-ray or/and CT or/and MRI) with painful bone metastases (bone pain intensity >= 6 according to VAS classification). The following additional inclusion criteria were established: histologically confirmed adenocarcinoma of prostate, multifocal bone metastases, no prior chemotherapy or palliative radiotherapy to bone. All patients signed informed consent.

The combination of the isotope therapy with EBRT was more effective analgetic treatment than isotope therapy alone. The highest pain decline was noticed in the first weeks after treatment termination. In the whole group, a total or partial analgesic effect was observed among 154 (87%) patients while among 23 (13%) patients there was a lack of analgesic effect or even pain intensification.

The results of this clinical trial demonstrated that for patients with multiple mCRPC it is recommended to combine the ^{153}Sm isotope therapy with local EBRT because of a greater analgetic effect. It is important to note that combined therapy did not intensify the toxicity of treatment.

Key words: prostate cancer, bone metastases, isotope therapy, radiotherapy, mCRPC

Prostate cancer belongs to the most frequently diagnosed malignant tumors among males in the United States and Europe [1, 2]. Unfortunately, despite the recent improvement in results of treatment, we are still faced with a significant number of patients with biochemical progression, and subsequent distant metastases. Prostate cancer distant metastases are first diagnosed in the bone, with more than 80% of all patients in the metastatic stage of disease [3, 4]. The characteristic feature of prostate cancer bone metastases is their multifocal nature with related pain, which is one of the first symptoms of metastases reported by patients. Pain affects the quality of life, and often does not respond to standard available pharmacological pain therapeutic options [5]. Thus, relief of pain remains the primary goal of therapy. Current treatment options for painful bone lesions include systemic therapy (hormonal therapy, radioisotopes, chemotherapy, and bone modifying agents such as bisphosphonates and denosumab) and local treatment: external beam radiotherapy (EBRT) and orthopedic surgery [6,

7]. Still the controversial issue is a simultaneous combination of the radioisotope therapy with EBRT [8-10]. Therefore, the aim of this prospective randomized clinical trial was to compare of analgesic effectiveness and toxicity of ^{153}Sm isotope in monotherapy with combined therapy (^{153}Sm isotope plus local EBRT) and/or bisphosphonate treatment among mCRPC patients with multiple painful metastases to the bone.

Patients and methods

Study patients. 177 men with ages between 48 years and 85 years old with histologically confirmed prostate cancer and radiographic evidence of at least three bone metastases with bone pain intensity ≥ 6 according to VAS (Visual Analogue Scale) classification were eligible for participation in this prospective randomized clinical study carried out between August 2008 and September 2010. All patients documented failure of hormonal therapy (CRPC), indicated by rising prostate-specific antigen (PSA) levels in 3 measurements at 2 weeks intervals and setting of castrate serum testosterone levels by chemical (<50 ng/dL) or surgical castration (<20 ng/dL) and antiandrogen manipulations. Other inclusion criteria were the minimal hematological reserve (erythrocytes, leukocytes, hemoglobin, blood platelets), and function of liver, and kidney, and in addition, an albumin-adjusted serum calcium between 2.0 mmol/L (8.0 mg/dL) and 2.9 mmol/L. All patients had minimal Karnofsky performance status (KPS) over 60. The key exclusion criteria for the study included prior EBRT to bone or bone surgery due to metastases, or chemotherapy, and life expectancy <3 months. All patients eligible to the study signed informed consent. The average age of patients qualified for the study was 69 years (range: 48 and 85 years). Among 163 (92%) patients the initial histological grade of malignancy was ≥ 7 according to the Gleason classification, while among the remaining 14 (8%) patients it was 6. 122 patients (69%) suffered from pain localized in ≤ 3 places, while the other 55 patients (31%) were diagnosed with the so-called "multiple pain", which was defined by patients as affecting practically all body parts with some dominate area. The average PSA level measured at the time of inclusion to the trial was 24 ng/mL (range: 10 ng/mL to 890 ng/mL). Pain intensity was measured among all patients by a 10-degree numerical and analogue VAS scale, while the patients' general condition was measured with the KPS activity scale. The comparison of a scintigraphy image and the results of at least two image examinations (X-ray and/or CT and/or MRI) allowed for the classification of bone metastases as either osteoblastic or mixed. The distribution of the most important prognostic factors in investigated groups is presented in Table 1. For each patient, the dose of ^{153}Sm isotope (Quadramet product made by CIS Biointernational B.P. 3291192 GIF-SUR-YVETTE Cedex, France) was calculated by means of the 37 MBq/ 1 body mass kg formula. The allowed bisphosphonate in this clinical study was pamidronate (90 mg iv for 4 weeks) between the 3rd and 7th days after the application of ^{153}Sm, and then after every 28 days, in both arms. Due to reimbursement reasons in Poland zoledronic acid was not administered among the investigated patients, instead, solely pamidronate was only used. For patients treated with EBRT the irradiation field was limited to the area of the highest pain intensity as indicated in the clinical examination (the highest pain location referred by patients and revealed by the palpation painful area, and bone involvement in the CT/MRI image). EBRT was performed from 3 to 14 days after the isotope administration according to one of the following fractionation schedule: among 79 (90%) patients 8 Gy in one fraction was used, among 6 (7%) patients 5 fractions of 4 Gy, and among 3 (3%) patients ten fractions of 3 Gy. The mean area of irradiation field was 59 cm^2 (range: 45cm^2 to 95 cm^2). Follow-up after the isotope therapy was conducted in the following way: the first visit was scheduled between 14 and 15 days, the second visit between 28 and 35 days, and the third visit between 77 and 84 days.

The intensification of adverse effects and the intensity of myelotoxicity were classified according to the National Cancer Institute Common Toxicity Scale (NCI CTC) version 3.0. If the pain was alleviated after the isotope treatment or combined treatment there was an attempt at reducing the amount of analgesics. Statistical data analysis of the study results was performed in the Department of Computer Science and Statistics at Poznan Medical University.

Results

The most analgetic effect for prostate cancer patients with multiple painful bone metastases was achieved by combining the isotope therapy with EBRT in comparison with isotope monotherapy ($p < 0.001$). In the whole group of patients (both arms), a positive effect of treatment (complete and partial relief of pain) was found among 154 (87%) out of 177 patients, while a dissatisfactory effect (no improvement or the intensification of pain) was found among only 23 (13%), patients (Table 2). In both investigated arms there was a statistically significant decrease in comparison at the baseline of pain severity dur-

Table 1. Basic characteristics of patients in study at baseline treated for painful multiple bone metastases (mCRPC).

Variable	Arm I– (n = 89) (isotope mono-therapy)	Arm II (n = 88) (isotope + EBRT)	P value
Age (mean)	68 (±8)	69 (±7)	ns
Baseline pain intensity	7 (±1.3)	7.3 (±1.4)	ns
BSI	67 (±27)	62 (±29)	ns
KPS	58 (±8)	56 (±8)	ns
Gleason< 7	7	7	ns
Gleason >7	82	81	ns
Osteoblastic metastasis	57	54	ns
Osteoblastic –osteolytic (mixed) metastasis	32	34	ns

ing the first ($p < 0.001$), the second ($p < 0.001$), and the third ($p < 0.001$) follow-up visits. Moreover, there was a statistically significant pain severity decrease in both treated arms between the first and the second follow-ups ($p < 0.05$), however, a significant further pain decrease was not found between the second and the third follow-up visits ($p > 0.05$). In the group treated with isotope plus EBRT, among 20 (23%) patients a complete withdrawal of analgetic treatment was possible. All patients were monitored during the 3-month period by pain and medication diaries.

Treatment toxicity. The analysis of toxicity demonstrated no statistically significant differences between investigated arms in decrease of hemoglobin concentration, the number of erythrocytes, thrombocytes, blood platelets, and neutrophils. There was a necessity to perform a single erythrocyte mass transfusion during follow-up among 12 patients (6 in two groups) between 5 and 7 weeks after the initiation of the isotope therapy. In the study, in both arms, it was defined as grade 3 of toxicity according to ctc v. 3.0 classification (6 patients) and grade 2 of toxicity (6 patients). Thrombocyte concentrate transfusion was necessary among 3 patients (1 patient from the isotope alone arm and 2 patients from the combined therapy arm) between 5 and 12 weeks after treatment initiation. In the remaining group of patients there was an idiopathic improvement of morphotic blood elements between 6 and 12 weeks of observation and other pharmacological intervention was unnecessary.

In the examined groups among as few as 8 (4%) patients (4 patients in each arm) there was a short pain intensification (flare syndrome), which was temporally and probably causally related to radiopharmaceutical administration and/or EBRT. It was observed between 2 and 5 days after the therapy and required a short period steroid therapy. During the follow-up visit , 3 cases of mild asymptomatic hypercalcemia in both arms were observed, where the calcium level did not exceed the 10.7 mg/dL level. Calcium level decrease was attained by means of intensified hydration and diuresis and the use of bisphosphonates. The above symptoms were observed only in the group of patients with mixed metastases. The treatment with bisphosphonates was probably associated with mild hypocalcaemia (above 7.2 mg/dL.), which was observed among 61 patients (34%) during the first examination, while only 5 patients were diagnosed with clinical symptoms such as paresthesia and painful muscular construction. In the same group of patients administered with bisphosphonates between 7 and 10 days after administration there were 5 cases of significant creatinine level increase (>0.5 mg/dL) in blood serum. Treatment continuation with simultaneous fluid balance and correction of total dose of bisphosphonates were applied and we did not observed further increases in toxicity. The patients administered the first time intravenous infusion of bisphosphonates reported other adverse effects, which were temporary body temperature increase – 23/95 (24%), joint and muscular pain – 20/95 (21%), and nausea – 11/95 (11.5%). The observation did not reveal any pathological fractures or spinal cord compression.

Table 2. The effect of analgesic treatment in investigated groups of patients with mCRPC.

Arm	Complete response VAS ≤ 2	Partial response VAS 3 – 5	Dissatisfactory effect VAS ≥ 6
I	38 (42.5%)	38 (42.5%)	13 (15%)
II	55 (62.5%)	23 (26%)	10 (11.5%)

Table 3. The evaluation of toxicity according to NCI CTC v.3.0 in investigated groups of patients with mCRPC.

Variable	Arm I– (n = 89) Isotope monotherapy	Arm II (n = 88) Isotope + EBRT
Hemoglobin		
grade 2	11 (13%)	17 (19%)
grade 3	2 (2.3%)	4 (4.5%)
grade 4	-	-
Leukocytes		
grade 2	15 (17%)	22 (25%)
grade 3	2 (2.3%)	3 (3.3%)
grade 4	-	-
Neutrocytes		
grade 2	13 (15%)	18 (20%)
grade 3	3 (3.5%)	6 (6.8%)
grade 4	-	-
Thrombocytes		
grade 2	8 (9%)	12 (13%)
grade 3	3 (3.5%)	4 (4.5%)
grade 4	-	-

NCI CTC: National Cancer Institute Common Toxicity Criteria

Discussion

In this study we reported the clinical outcome after administration of Samarium-153 (^{153}Sm), an emitter of beta-particles that concentrates in the areas of enhanced osteoblastic activity, in comparison to other possible combinations with local EBRT limited to the area of the most painful bone metastases for mCRPC patients. Our results confirmed that in patients with multiple bone metastases with leading painful site it is recommended to combine the ^{153}Sm isotope therapy with local EBRT because of a greater analgesic effect, which does not intensify the toxicity of this combined treatment. However, radionuclide therapy with ^{153}Sm alone is a feasible treatment opportunity among patients with mCRPC and extensive painful bone metastases. We cannot exclude some bias due to the inclusion of patients with visceral metastatic stage of disease, which, for example, after short period of follow-up, resulted in switching to palliative chemotherapy. However, a notable reduction of pain intensity was observed at the end of the study where patients were still available for follow-up. The proportion of patients obtaining a 50% reduction or more

of baseline pain defined as partial response after therapy was 70% in 77 – 84 days. The overall results from our study are analogous to data presented in other randomized controlled trials and in large observational studies [8, 9, 11, 12]. There were not clear differences in clinical efficacy among available radionuclides, which induce clinical relevant pain relief and complete pain relief in range from 50% to 95% and from 20% to 30% of patients, respectively.

The follow-up for all patients from our study was short because of the high rate of patients switched to palliative chemotherapy. Therefore, it was not possible to analyze the duration of pain relief and toxicity beyond this short follow-up because other methods of therapy were introduced. An interesting fact was that the myelotoxicity limited to the introduction of postisotope therapy alone or combined therapy was clinically unimportant. In trials conducted for patients with less advanced metastatic disease, the duration of pain relief is usually in a range of 1 month to 6 months [3]. What is interesting is that relief of bone pain in our study was associated with a change in KPS score. However, the patients in general showed rapidly deteriorating disease with increase of PSA level during the follow-up period. Thus, it seems difficult to demonstrate improvement in performance score and biochemical response in such a group of patients. In other studies with less advanced disease, pain relief of ^{153}Sm therapy has been shown to improve general performance status evaluated by KPS [13]. Radionuclides are not restricted for the relief of opioid resistant pain only. Several trials have shown favorable long-term efficacy and tolerability profile among patients with no need of opioids, or among patients not suffering from pain on such drugs [14]. Despite the fact that bisphosphonates may influence bone metabolism, bone uptake of ^{153}Sm or clinical efficacy of radionuclides have shown not to be affected by a concomitant therapy with bisphosphonates [14]. In our study, patients were treated only with the pamidronate bisphosphonate, which was due to financial problems with reimbursement for other bone modifying agents such as zoledronic acid.

One of the most important issues in palliative treatment, is the hematological toxicity, which in our study was mild, acceptable and fully reversible with the use of replacement therapies without stem cell growth factor support. The hematological toxicity showed nadir between weeks 4 and 6 with 2 episodes of reversible grade 3 thrombocytopenia observed within the expected time window of radionuclide toxicity. The time course of bone marrow impairment, excellent tolerability to ^{153}Sm therapies, and the lack of effects of replacement therapies supported this conclusion. ^{153}Sm has a wide therapeutic scale and dose-finding studies have shown that doses up to 111 MBq/kg are safe, but associated with an increased number of episodes of reversible hematological events [15]. What is interesting that in our study EBRT in dose range from 8 Gy to 20 Gy didn't influenced the level of hematological toxicities.

Randomized controlled trials have shown that radioisotopes have induced pain relief in a non significantly different way than EBRT [16, 17]. The impact of radionuclides on survival rate is controversial. A significantly reduced survival rate was reported with ^{89}Sr versus local field radiotherapy for bone pain in metastatic prostate cancer in a European randomized, multi-center trial [18]. This data is in direct contrast to data from other similar trial where no difference in survival rate was observed among patients who received ^{89}Sr and palliative radiotherapy [19].

Patients with mCRPC should initially be referred to palliative chemotherapy and further treatment manipulation (abiraterone), which has a documented, significant effect on survival rate and also improvement in quality of life and pain relief [20]. However, in Poland during the time when this study was conducted, chemotherapy as a palliative method of treatment was not very popular and radionuclide therapy obtained regulatory approval for pain relief only. Recently, chemotherapy has been much more popular but concurrent systemic administration of chemotherapy with isotope therapy has so far been regarded contraindicated. However, combined use of radionuclides and chemotherapy may act synergistically and improve pain palliation [21]. Several reports have demonstrated improvement in pain relief, reduced development of new painful sites, improved progression-free survival, and the overall survival in mCRPC prostate cancer [17, 18]. The combination of radioisotopes and chemotherapy, including docetaxel is currently being pursued in clinical trials.

In the USA 21% to 40% of oncologists used radionuclides alone or in combination with EBRT, respectively, among patients with prostate cancer [20]. We conclude that radionuclide therapy with local EBRT should be considered an option among palliative modalities in mCRPC patients with multiple painful bone metastases.

The key issue in our study is the power additional painkiller effect and the toxicity effect of EBRT, which was combined with isotope therapy. The analgesic mechanism of radiotherapy has not been completely recognized. There is a dual effect observed after the administration of radiotherapy: on the one hand there is a significant decrease in the production of inflammatory mediators, hence the anti-inflammatory effect (which is deemed to be responsible for the initial analgesic effect), and on the other hand the destruction of malignant cells, hence the cytotoxic effect (deemed responsible for the subsequent analgesic effect) [22]. Despite the fact that a range of prospective clinical studies combining the isotope therapy and cytostatic agents are currently being carried out, the recommendations regarding the isotope therapy advise against the combination of isotope therapy with chemotherapy or radiotherapy. Another problem is the possible combination of isotope therapy with wide field EBRT affecting one half of the body (hemibody irradiation). A simple calculation of doses implies that simultaneous hemibody irradiation with a dose of 6 Gy (upper part of the body) and 8 Gy (lower part of the body) and 17 Gy as the amount absorbed by the skeleton during systemic radioisotope therapy (red bone marrow – 4Gy) may lead to very probable severe complications of combined therapy. Nevertheless, as proven by our own research, us-

ing the small field technique does not seem to significantly increase the risk of adverse effects. At the same time, an increased analgetic effect has been noticed in the group of patients treated with simultaneous radiotherapy (a parallel to the results of a TRANSCANADA study with the application of ^{89}Sr). Despite the fact that the level of mielotoxicity was higher in the group with combined therapy, the differences between the groups (apart from the hemoglobin concentration) were not statistically significant. There was only a weak correlation between the total amount of dose administered (especially when the therapy covered two smaller, or one big field) and the decrease in the amount of erythrocytes and the hemoglobin concentration. The fact that no patient had previously been administered with cytostatics was probably a factor favorable to a better tolerance of combination therapy. Still, the analysis of the number of patients with adverse effects (according to the NCI CTC scale) requires caution during qualification for treatment and necessitates close supervision of patients after the administration of treatment schedule when combining the application of radioisotope and radiotherapy with large fields, and among patients after chemotherapy.

Conclusion

The ^{153}Sm isotope therapy is an effective and safe method of treating multifocal and painful prostate cancer bone metastases, and when it is combined with small field local radiotherapy, its analgetic efficacy increases. It is important that the analgetic result of combined therapy is not related to the increased treatment toxicity.

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