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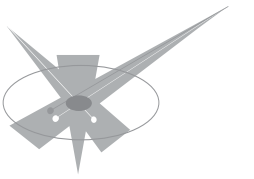

Original Paper

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Efficacy of samarium 153 and strontium 89 treatment for bone metastases in prostate cancer patients: monotherapy vs. treatment combined with external beam radiotherapy. Preliminary report

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A Study Design
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E Manuscript Preparation
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Summary

Background Approximately 60–80% of metastatic prostate cancer patients suffer from pain caused by bone metastases. Bone metastases have a negative impact on patient performance status.

Aim The aim of study was to compare the efficacy of treatment with strontium 89 or samarium 153 in monotherapy vs. radioisotope treatment combined with external beam radiotherapy (EBRT) in prostate cancer patients with bone metastases.

Materials/Methods We retrospectively analyzed one hundred (n=100) metastatic prostate cancer patients aged between 53 and 84 years, who we divided into four treatment groups: 30 pts received Sr-89 monotherapy; 30 patients received Sm-153 monotherapy; 20 pts received Sr-89 combined with EBRT; and 20 pts received Sm-153 combined with EBRT. Follow-up was 4 months. All patients prior to therapy had their bone metastases confirmed by bone scan examination. Pathologic fractures were excluded and the nature of metastases (osteoblastic/mixed) was evaluated with X-ray films and/or CT and/or MRI. Sr-89 therapy consisted of a standard dose of 150MBq, while Sm-153 was administered proportionally to body weight (37MBq/kg). In combined treatment groups EBRT was given to the dominant metastatic site with 8Gy in one fraction or 20Gy in five daily fractions. Treatment efficacy was determined by change in pain intensity evaluated according to visual analogue scale (VAS), changes in Karnofsky performance status (KPS) and in the use of analgesics.

Results Complete pain relief (VAS<3) was observed in 33% and 40% of patients in Sr-89 and Sm-153 monotherapy groups and in 50% and 60% of patients treated with Sr-89 and Sm-153 therapy combined with EBRT, respectively. Unsatisfactory response to treatment (VAS>5) was noted in 20% of patients in both monotherapy groups and in 10% and 15% of patients in Sm-153 and Sr-89 combined with EBRT, respectively. Decrease in pain intensity and in the use of analgesics as well as improvement in performance status were statistically significant for combined therapy vs. monotherapy ($p<0.05$). Treatment was well tolerated, with 3 patients suffering from severe pancytopenia and 22 patients with mild leucopenia and/or thrombocytopenia.

Conclusions Radioisotope therapy with Sr-89 or Sm-153 combined with external beam radiotherapy in comparison with radioisotope monotherapy improves efficacy of treatment. Treatment toxicity is low.

Key words **prostate cancer • bone metastases • radioisotope therapy • radiotherapy**

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Background

Approximately 60–80% of metastatic prostate cancer patients suffer from pain caused by bone metastases. The most common sites of bone metastases in prostate cancer are vertebral column, ribs, pelvic bones and cranium [1,2]. The decision of which therapeutic option to use in the treatment of bone metastases (surgery, external beam radiotherapy (EBRT), radioisotopes or bisphosphonates) depends on the stage of disease, anatomical site and type of bone remodelling. After years of studies it has been postulated that bone metastases originating from different primary organs differ significantly in their influence on function of osteoclasts and osteoblasts. Neoplastic cells may directly or indirectly (e.g. by stimulation of the immunological system) stimulate via chemical mediators (PTH-rP, IL-6, TNF, TGF) osteoclasts or osteoblasts or only modify their activity [3,4]. Such pathologically enhanced activity of osteoclasts results in intensification of osteolytic processes accompanied by tendency to hypercalcaemia. On the other hand, increased stimulation of osteoblasts results in overproduction of bone matrix and hypercalcification. However, in the majority of patients both above-mentioned processes take place without a distinct imbalance between them – such metastases are classified as mixed [2,4]. Bone metastases are best imaged and diagnosed with a bone scan, which beside its confirmatory diagnostic value also gives information on the level of dissemination of the disease and localization of lesions (it is possible to visualize lesions as small as 1.5–2mm in diameter). Examination with X-ray film remains a valuable supplement to diagnosis obtained solely by bone scan – it can provide data which are not possible to obtain from a bone scan, such as presence of pathologic fracture or differentiation between osteolytic and osteosclerotic lesions. However, the sensitivity of X-ray examination to detect bone metastases is about four to even five times lower than that of a bone scan. Computed tomography (CT) and magnetic resonance imaging (MRI) are mainly reserved for cases in which the results of bone scan and X-ray examinations are indecisive and the result of the examination determines the type of therapy to be administered. Recently also positron emission tomography (PET) is being incorporated into more and more cases of diagnosis of bone metastases in patients with prostate cancer [1–4].

Patients who are qualified for radioisotope therapy typically have multiple osteoblastic lesions; however, partial responses are also reported in the subgroup of patients with small osteolytic lesions (large and advanced osteolytic metastases usually do not respond to radioisotope therapy) [5–7].

Aim of Study

The aim of the study was to compare the efficacy of treatment with strontium 89 or samarium 153 in monotherapy vs. radioisotope treatment combined with external beam radiotherapy (EBRT) in prostate cancer patients with bone metastases.

Materials and Methods

We retrospectively analyzed one hundred (n=100) metastatic prostate cancer patients aged between 53 and 84 years. All patients prior to therapy had their bone metastases confirmed by bone scan examination. Pathologic fractures were excluded and the nature of metastases (osteoblastic/mixed)

Table 1. Efficacy of pain treatment.

Response	Treatment			
	Sr-89	Sm-153	Sr-89 + EBRT	Sm-153 + EBRT
Complete	33% (10)	40% (12)	50% (10)	60% (12)
Partial	47% (14)	40% (12)	35% (7)	30% (6)
Unsatisfactory	20% (6)	20% (6)	15% (3)	10% (2)

was evaluated with X-ray films and/or CT and/or MR; 75 patients had typical osteoblastic metastases and 25 patients had mixed type of metastases. The most common locations of metastases were as follows: the lumbo-sacral part of the vertebral column was affected in 70% of patients, pelvic bones in 60%, and ribs in 50% of patients. The majority of patients suffered from generalized pain from multiple (more than 3) pain sites. Almost all patients were treated before entering the study with bisphosphonates and analgesics with disappointing results. Patients were divided into four treatment groups: 30 pts received Sr-89 monotherapy; 30 patients received Sm-153 monotherapy; 20 pts received Sr-89 combined with EBRT; and 20 pts received Sm-153 combined with EBRT. Strontium 89 therapy consisted of a standard dose of 150MBq, while Samarium 153 was administered proportionally to body weight (37MBq/kg). In combined treatment groups EBRT was given to the dominant metastatic pain site (mostly in the vertebral column and pelvic bones) with 8Gy in one fraction or 20Gy in five daily fractions. External beam radiotherapy was typically administered 2 to 4 weeks after radioisotope treatment. Treatment efficacy was determined by change in pain intensity evaluated according to the visual analogue scale (VAS), changes in Karnofsky performance status (KPS) and in the use of analgesics. The VAS scale is a 10-point scale where 0 stands for no pain and 10 means terrible, unbearable pain. Karnofsky performance status scale has 100 points, where death is represented by 0 points and fully active well-being is equal to 100 points. As complete therapeutic effect in pain treatment we assumed decrease in VAS scale below 3 points; partial effect was between 3 and 5 points; and unsatisfactory effect was defined as lack of VAS scale decrease below 6 points.

In statistical analysis of data with normal Gaussian distribution the evaluation of agreement was performed with Shapiro-Wilk test, while testing for difference was done with Student's t-test or variance analysis with repeated measurements with Bonferoni's test. For data with non-Gaussian distribution testing for differences was performed with Mann-Whitney and Freedman test and for multiple comparisons with Dunn test. Correlations were tested with Pearson's correlation coefficient for data with normal distribution and with Spearman's correlation coefficient in other cases. Hypotheses were tested at the level of significance α=0.05.

Results

Prior to therapy median pain intensity recorded with VAS scale was 7 (very strong pain), ranging from 6 to 10, while performance status evaluated with Karnofsky scale varied between 40 and 80 with median score of 50. These numbers were similar across subgroups of patients treated with Sr-89 and Sm-153 respectively. Differences were not statistically significant ($p>0.05$). Gradual decrease in pain intensity was observed typically as early as at 8–14 days after radioisotope therapy. After 2 months VAS score for the whole group had decreased in a statistically significant fashion ($p<0.05$) and median score of VAS was 3 (low intensity periodical pain) with a range of 0 to 8.

A detailed description of pain treatment is given in Table 1.

Statistical analysis did not show statistically significant differences between efficacy of monotherapy with Sr-89 and Sm-153 ($p>0.05$); however, a trend has emerged toward higher efficacy of samarium in comparison with strontium in patients with mixed type of metastases. It has been proved that combined therapy consisting of radioisotope and external beam radiotherapy statistically significantly increased efficacy of treatment ($p<0.05$). For all groups a significant improvement was noted in terms of activity according to the Karnofsky scale – the score increased from 50 to 80; observed differences were statistically significant ($p<0.05$). The amount of analgesics

Table 2. Efficacy of treatment – changes of VAS, KPS and use of analgesics (median value and range of scores).

Treatment option	Change in pain intensity; VAS scale (0–10)	Change in performance status; KPS (0–100)	Decrease in the use of analgesics
Sr-89	**–3** range (–8 to +2)	**+20** (–20 to +40)	**40%**
Sm-153	**–3** (–7 to +1)	**+30** (–20 to +40)	**45%**
Sr-89 + EBRT	**–5** (–7 to +2)	**+30** (–20 to +40)	**55%**
Sm-153 + EBRT	**–5** (–8 to +2)	**+30** (–20 to +40)	**60%**

used decreased by a mean value of 50% compared to the number of analgesics used prior to treatment with radioisotope and EBRT. Efficacy of treatment in terms of changes of VAS, KPS and use of analgesics is shown in Table 2.

After 16 weeks analgesic response remained satisfactory in 80% of patients. In terms of adverse effects of therapy there were 3 cases of severe pancytopenia reported (2 cases after Sr-89 and 1 case in the Sm-153 group) and 22 cases of significant, albeit short-term and not necessitating any further treatment, decrease in leukocyte and platelets count (11 after Sr-89 and 11 after Sm-153). Overall, myelotoxicity was more frequently observed in the combined therapy groups (30% vs.22%), but there were no significant differences in clinical course of treatment related to that difference. Hypercalcaemia was noted in 5 patients, and was successfully treated with bisphosphonate therapy.

Studies on correlation of treatment efficacy and levels of PSA did not show statistical significance; however, there was a trend toward lower efficacy of treatment in patients with elevated levels of alkaline phosphatase.

Discussion

Radioisotope treatment of bone metastases remains a palliative approach, with the main aim of treatment being alleviation of pain and prevention of progression of metastatic lesions and pathologic fractures. Loco-regional external beam radiotherapy is undoubtedly a more efficient method of pain treatment than radioisotope therapy. However, in the case of multiple lesions it is impractical or even impossible to cover all pain sites with treatment and in such cases radioisotopes remain the treatment of choice [7–9]. As previously mentioned, the optimal patients referred for radioisotope therapy are those with multiple, osteoblastic or mixed type metastases to bones, under condition that radioisotope will be selectively accumulated in the lesion. Accumulation of radioisotope results in selective irradiation of metastatically transformed bone with minimal risk of toxicity to surrounding normal tissues. Killing even only a fraction of neoplastic cells in a metastatic lesion in bone results in a decrease in release of inflammatory and pain mediators and at the same time by lowering the mass of metastasis diminishes mechanical irritation of pain receptors [5,6,10]. When analyzing the results of treatment with radioisotopes, attention must be paid to the significant differences in their characteristics. The mechanism of uptake of studied radioisotopes varies distinctly, which may have important consequences in terms of overall efficacy of treatment. Strontium 89 is a calcium analogue and as such will be taken up and incorporated into collagen fibres in all sites of enhanced bone transformation, which is typical for osteoblastic metastases to bones. Thanks to the long biological half-life of Sr-89 of 50.5 days, doses may be proportionally low, because for such a long period after incorporation into the osteoblastic lesion the radioisotope will exert its therapeutic action. Samarium 153 is administered as a chelated tetraphosphonian compound (lexidronian), which implies its high specificity and selectiveness of accumulation in places of bone transformation (affinity to hydroxyapatyte) induced by presence of neoplastic cells. Half-life of Sm-153 is 1.9 days, which determines the necessity to administer high activeness (dose); however, on the other hand it makes such treatment similar in fashion to the classic EBRT approach (high dose in short overall

treatment time). With a high dose administered the efficacy of the therapy will be sufficient even if the radioisotope binds to hydroxyapatyte for only a short time [2,6,11,12]. The mechanisms of action of samarium and strontium described in previous paragraphs explain the similar efficacy of both radioisotopes in cases of osteoblastic bone metastases (in monotherapy reported efficacy of 75–80%) [6,11–15]. In the case of samarium treatment, solid osteoblastic lesions with high proportion of hydroxyapatyte sufficiently bind this compound, while in the case of strontium it is the high activity of osteoblasts that enables such a large amount of radioisotope to be incorporated into pathologically transformed bone matrix. In treatment of mixed metastases, efficacy of treatment decreases proportionally to increase of osteolytic component and size of lesion. In such patients the treatment of choice should be Sm-153. The reason for this recommendation lies in the large disproportion of activity of osteoclasts and osteoblasts within ostolytic lesions – the possibility of fast incorporation and longer "sheltering" for strontium in the metastatic lesion is then small – which will result in relatively low accumulated dose of irradiation and obviously less effective pain treatment. Slightly higher efficacy of samarium in this setting results from less specific mechanism of binding to hydroxyapatyte – a high dose even if bound more "loosely" and for a short time will inevitably give at least a partial therapeutic effect. Our observations suggest slightly higher and often delayed myelotoxicity for Sr-89, especially in the younger subset of patients. However, what is widely confirmed in literature data, the percentage of early haematological complications is similar for both radioisotopes, accounting for approximately 25% of cases. The risk of such complications increases proportionally to not only every administered dose of radioisotope but also is a result of prior or concurrent treatment with other anticancer modalities such as radiotherapy, chemotherapy, hormonotherapy or symptomatic pain treatment, etc. [5,6,16,17]. Analgesic effect of Sm-153 in our study as well as in literature data appears a little earlier than after Sr-89 treatment, but according to many authors is also shorter and therefore requires more frequently repeated treatment [5,6,11,12]. Combining radioisotope therapy with pharmacotherapy with bisphosphonates requires detailed knowledge on mechanisms of action of both treatments. Sr-89 as a calcium analogue competes with ionized calcium circulating in blood to be taken up within the bone. Therefore concurrent treatment with calcium may lower the efficacy of this radioisotope. As for bisphosphonates, no interaction has been reported with Sr-89 treatment when administered concurrently (different points of uptake in the bone). Moreover, administering bisphosphonates immediately after injection of radioisotopes practically precludes the risk of hypercalcaemia, which is quite common after Sr-89 therapy, with incidence reported to be 15%. The analgesic effect of such treatment may be even doubled. It is a similar situation for Sm-153 therapy, although in that case it is indicated to withhold therapy with bisphosphonates at least 2 to 4 weeks prior to planned radioisotope treatment (possibility of competitive antagonism of uptake between tetraphosphonate Sm-153 composite and bisphosphonate). Administering bisphosphonate on the third day after radioisotope therapy not only does not decrease the efficacy of treatment but also inhibits the development of hypercalcaemia and may enhance the analgesic effect [18]. Similarly, positive results may be obtained with combining radioisotope therapy with external beam radiotherapy or chemotherapy. Unfortunately, each of these combinations is related to an increase in probability of side effects (6,7,9,12,17). It can be concluded that efficacy of radioisotope treatment is not only dependent on type of cancer and dose and type of radioisotope used, but is a combination of some other factors such as number, size, location and type of bone metastases, presence of fractures, presence of neuropathic pain as well as scheme of therapy (monotherapy or polytherapy) [6,14,19,20].

Conclusions

1. Combining Sr-89 and Sm-153 radioisotope therapy with local radiotherapy significantly increases efficacy of treatment, decreases use of analgesics and risk of pathologic fractures and statistically significantly increases the quality of life.

2. Serious complications after radioisotope therapy (also when combined with radiotherapy) are rather infrequent and in most cases result from improper referral for such treatment.

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