Radionuclide Treatment in Metastasized Prostate Cancer

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1. Introduction

The majority of patients with metastasized prostate cancer experiences painful osseous metastases during the course of the disease [1]. Androgen ablation results in pain reduction in most patients with painful metastases. In hormone refractory prostate cancer (HRPC) painful osseous metastases is one of the most prevalent clinical problems [2]. Local radiotherapy, chemotherapy, and bisphosphonates were shown to provide some pain relief [1]. Bone seeking intravenous radionuclide treatment is an effective other modality in these patients. Radionuclide treatment was initially introduced in 1942 using Strontium-89 (Sr89) [3].

Reported pain response rates to radionuclides vary widely from 36% to 92% [4–7] probably depending on assessment method and population characteristics. Oosterhof et al. (2003) [7] showed that patients with a smaller decrease in hemoglobin concentration after radionuclide treatment had a better pain response. Others found better responses in patients with less extensive osseous involvement [4,8–10].

Whether the relatively long half-life of 50.5 days for Sr89 and toxicity of bone marrow suppression account for the reported reduction in survival when compared to external beam radiotherapy [7] is unknown but it may favor the use of radionuclides with shorter half-lives such as Rhenium-186 (Re186, half-life 3.8 days), Re188 (17 hours), and Samarium-153 (Sm153, 2 days) [11]. Although Re186 was shown to be superior to placebo in a randomized trial [12], only minimal differences with respect to efficacy and toxicity of Re186 versus Sr89 was shown and most non-randomized studies in breast and prostate...
cancer suggest similar efficacy for Sr89 and Re186 [5,8,13]. Whereas toxicity may be reduced in patients treated with radionuclides with a shorter half-life, such as Re186, and recovery from myelosuppression may be shorter, Sr89 seems to provide somewhat longer duration of efficacy. Sporadically, 117mSn (low-energy conversion electrons) and 223Ra (alpha-emitter) are used in bone metastases but experience in prostate cancer management is limited [14,15].

The percentage of prostate cancer patients presenting with osseous metastases at initial diagnosis decreased significantly over recent years. Moreover, due to earlier diagnosis, many patients have HRPC even before the clinical manifestation of osseous metastases. This often implies that chemotherapeutic agents will be applied earlier in disease, in some cases even in the absence of metastasized disease. Although bisphosphonates seem to delay skeletal related events and reduce the need for chemotherapeutic agents, they are less effective in management of acute osseous pain. For these reasons, radionuclide treatment may be valuable in patients with osseous metastases from hormone and chemotherapy refractory prostate cancer in later phases of disease.

Here the most widely used radionuclides for treatment of painful osseous metastases from prostate cancer are reviewed.

2. History of radionuclide treatment for osseous metastases

Early studies using radionuclides for painful osseous metastases comprise Phosphor-32 (P32) [16,17], and Strontium-89 (Sr89) [18,19]. Both substances have a natural tendency to bind to bone. Over 80% of the total body phosphate is present in bone, bound as inorganic phosphate to hydroxyapatite. Radiophosphorus, administered intravenously as P32-sodium orthophosphate for skeletal targeting, was used extensively in the 1970s to treat metastatic hormone refractory prostate cancer (HRPC) [20]. More recent data suggest equal efficacy after oral administration [21]. The main disadvantage of P32 therapy is dose-limiting myelosuppression with reversible pancytopenia with nadir values at 5–6 weeks after administration. In comparison to Sr89 the higher myelotoxicity of P32 rendered Sr89 the radionuclide of choice for painful osseous metastases [22]. P32 is nowadays rarely used in the US or Europe but its relatively low costs and oral availability make it a potential alternative to Sr89.

Compared with hemi-body radiation the use of radionuclides such as Sr89 provide pain relief from multiple bone lesions with less toxicity like bowel and pulmonary complaints often observed after hemi-body radiotherapy. More recently used radionuclides such as Rhenium-186, Rhenium-188, and Samarium-153 all lack the natural tendency to bind bone. Hence, chelation with a bisphosphonate is required to target these radionuclides to areas of osteoclastic/osteoblastic activity (Table 1).

### 3. Strontium-89 (Sr89)

Strontium is named after the UK-village it was first discovered in in 1790. Strontium is close to calcium

<table>
<thead>
<tr>
<th>Radionuclides</th>
<th>N</th>
<th>Tumor</th>
<th>Study design</th>
<th>Result</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sr89 vs Sm153</td>
<td>N = 57</td>
<td>Prostate</td>
<td>Non-randomized, retrospective</td>
<td>No difference in pain response rate and toxicity</td>
<td>[49]</td>
</tr>
<tr>
<td>Sr89 vs 32P</td>
<td>N = 31</td>
<td>Various tumors</td>
<td>Non-randomized</td>
<td>No difference in pain response rate and response duration. Higher drop in platelet count for P32 but not clinical relevance</td>
<td>[21]</td>
</tr>
<tr>
<td>Sr89 vs Re186</td>
<td>N = 44</td>
<td>Various tumors</td>
<td>Non-randomized</td>
<td>No difference in pain response or toxicity. Re188 best improvement in QoL. Earlier pain response in Re186, similar duration of response, earlier recovery from hematological toxicity in Re186 (6w versus 12w)</td>
<td>[13]</td>
</tr>
<tr>
<td>Sr89 vs Re186</td>
<td>N = 50</td>
<td>Breast</td>
<td>Randomized</td>
<td>Bone uptake and soft-tissue clearance higher for Sm153</td>
<td>[91]</td>
</tr>
<tr>
<td>Sm153 vs Re186</td>
<td>N = 29 (prostate, N = 22)</td>
<td>Various tumors</td>
<td>Non-randomized</td>
<td>No differences in pain response, Karnofsky performance score, and bone marrow toxicity</td>
<td>[11]</td>
</tr>
<tr>
<td>Sm153-EDTMP vs Re188-HEDP</td>
<td>N = 46</td>
<td>Breast, Prostate</td>
<td>Non-randomized</td>
<td>No difference in response rate or toxicity</td>
<td>[35]</td>
</tr>
<tr>
<td>Re186 vs Sr89</td>
<td>N = 60</td>
<td>Prostate</td>
<td>Non-randomized, retrospective (selection on metastases extent)</td>
<td>No difference in pain response rate and toxicity</td>
<td>[35]</td>
</tr>
</tbody>
</table>
in the periodic table of elements and has the same metabolic handling. Strontium-89 has a natural affinity for metabolically active bone. The cause of the higher affinity of Sr^89 is debated. Since Sr^89 is close to calcium in the periodic table and bone metabolism and turn-over is higher in osseous metastases from prostate cancer it can be postulated that more readily uptake of calcium and Sr^89 in these areas accounts for the higher affinity observed. Strontium-89 is a beta-emitter with a physical half-life of 50.5 days. The partial range in tissue is approximately 7 mm. Sr^89 was shown to have a higher affinity for tumor containing bone than normal bone and half-life in normal bone (14 days) is considerably shorter than in tumor containing bone (50 days). Excretion is renal and thus glomerular filtration rate should be considered prior to administration. A double-blind randomized trial showed higher efficacy for Sr^89 compared to the Sr^86 and Sr^88 radionuclides [24]. The role of dosing Sr^89 is less clear. Dose-finding studies did not find an association between pain relief and dose [19,25]. Retrospective analyses, however, suggested that higher doses of Sr^89 resulted in improved pain relief [26]. In general, 130–200 MBq is used to treat osseous metastases in prostate cancer.

3.1. Sr^89 and pain response

A placebo-controlled randomized study using the low dose of 75 MBq i.v. Sr^89 could not confirm an improvement in pain response superior to placebo [27] whereas a higher dose of Sr^89 (150 MBq) was associated with a risk reduction of pain relief of 0.32 [24]. Initial studies using intravenous Sr^89 showed efficacy for pain relief as high as 80%. Complete pain response rates vary widely among studies and have been reported in 8–77% of cases whereas a reduction in pain was reported by 18–50% of patients treated with Sr^89 for an overall response rate varying from 33 to 82% [24,25,28–34]. A pain flare occurs in 15% of patients within one week after infusion [26]. The duration of response varies between 14 days and up to 15 months with a median of around 60 days [7,35,36]. The problematic assessment of pain response and documentation of analgetics use hamper comparison between studies and probably explains the wide variation in reported pain responses.

Although Sr^89 is assumed to exert pain relief through a reduction in growth of bone metastases, serological PSA and alkaline phosphatase responses have only been observed in a minority of patients [35,36]. In 37% of patients Turner et al. [37] observed a more than 50% reduction in serum PSA whereas Oosterhof et al. (2003) [7] found biochemical responses in 13% of patients. Others, however, did not observe a noticeable response when Sr^89 was applied to treat painful osseous metastases in HRPC [35,38].

An important medical condition in patients with HRPC is the development of acute spinal cord compression (SCC) resulting in lower body paralysis. Signs of SCC are a contraindication for radionuclide treatment. The possible flare up after radionuclide treatment and the higher efficacy of local treatment such as external radiotherapy and surgery make latter 2 options first choice. In a retrospective analysis Soerdjbalie et al. (2002) [39] found a reduced incidence of SCC during follow-up in patients treated with Sr^89 but not in patients treated with the biphosphonate olpadronate.

3.2. Sr^89 toxicity

The most frequently observed toxicities are associated with the bone marrow suppression associated with Sr^89 use: a reduction in white-blood cell count and thrombocyte count between 11–65% in more than half the patients. Blood cell counts do return to normal within 8 weeks and rarely cause grade 3 or 4 toxicity when Sr^89 is applied to patients with normal hematological parameters. The influence of Sr^89 on serum hemoglobin concentration seems to be limited and did not exceed the reduction in serum hemoglobin observed in patients treated with external beam radiotherapy [7]. No difference in hematological toxicity between external beam radiotherapy and Sr^89 was observed in a randomized trial [7]. The reduced survival of patients treated with Sr^89 compared with external beam radiotherapy observed in this recent EORTC trial remained unexplained but placebo controlled randomized studies with Sr^89 could not confirm an unfavorable effect of Sr^89 on overall survival [24,27]. Similarly, other radionuclides were not associated with decreased survival [24,27,40].

3.3. Sr^89 response prediction

Several patient characteristics could predict a favorable response to Sr^89. A normal serum hemoglobin prior to treatment is associated with a higher pain response rate [10,35]. Oosterhof et al. (2003) [7] found that patients who had a response to treatment showed a lesser decrease in median hemoglobin level after 4 and 8 weeks than those who did not respond to treatment. This finding applied to both radionuclide and external beam radiotherapy. Beer et al. (2004) found an association between
anemia, response to androgen ablation and survival in patients with metastasized prostate cancer even after correcting for extent of disease [41]. They suggested that anemia may lead to increased intratumoral hypoxia rendering tumor cells more resistant to therapeutic interventions such as radiation [42]. Moreover, possible etiological factors of anemia such as cytokines (IL6, IL8) are often elevated in prostate cancer patients [43] and may play a role in response to pain stimuli in these patients as well [44]. Hence, the factors leading to anemia may increase pain perception and decrease sensitivity to radiation through hypoxia thus resulting in a decreased pain response.

Other predictors of a poor pain response were low performance status, higher serum PSA, more extensive osseous metastases [7,8], and poor PSA response [45]. These findings make clear that efficacy of Sr89 increases when applied in earlier phases of disease where the patient has a better performance, and less extensive disease and pain.

Repeated doses of Sr89 were shown to result in similar pain response rates when compared to initial treatment efficacy rates [9,28,35]. Due to myelotoxicity it is generally advisable to repeat dosing at intervals of at least 6 weeks.

3.4. Comparison of Sr89 and external beam radiotherapy

External beam radiotherapy is an effective means of treating pain of osseous metastases in prostate cancer. Several studies compared the efficacy of external beam radiotherapy and Sr89. Oosterhof et al. (2003) [7] compared Sr89 (150 MBq) and local field external beam radiotherapy in a randomized fashion. Patients treated with Sr89 showed a 34.7% pain response rate whereas external beam radiotherapy resulted in pain reduction in 33.3% of patients. One third of the study population had only one painful metastatic site. The authors concluded that the higher costs associated with radionuclide treatment favor external beam radiotherapy. In comparison to hemi-body radiotherapy Sr89 treatment showed similar response rates with fewer new active sites during follow up suggesting that a preventive effect was present after Sr89 treatment [46,47]. Adjuvant high-dose Sr89 (400 MBq) to external beam radiotherapy did result in a reduced number of new sites but not in less pain in the initial painful site [48]. This additive effect to external beam radiotherapy, however, was not confirmed for the normal Sr89 dose (150 MBq) [40].

Data suggests that a combination of external beam radiotherapy and Sr89 was of limited value for pain control (Table 2).

3.5. Comparison of Sr89 with other radionuclides and chemotherapy

Comparison of Sr89 in osteoblastic metastases with other radionuclides such as 32P [21], Rhenium-186 [5,13,35], and Samarium153 [49] showed comparable efficacy for pain control. Most studies, however, were non-randomized. In one randomized study of patients with osseous metastasized breast cancer the hematological parameters returned quicker to baseline after treatment with Re186 compared to Sr89 [5]. Hence, radionuclides based on Samarium and Rhenium with shorter half-lives compared to Sr89 may be preferable over Sr89 especially when repetitive or chemotherapy-combined approaches are considered.

In a recent report Nilsson et al. (2005) [50] used a double-blind randomized study-design to compare the palliative efficacy of a combination chemotherapy protocol (FEM, 5-FU, epirubicin, mitomycin-C) and Sr89. Both arms in the study showed comparable reduction in pain score during the entire 12 weeks of the study. Treatment related toxicity, however, was higher in the FEM arm where the number of hospitalizations due to treatment toxicity was twice as high as in the Sr89 arm.

4. Rhenium-186 (Re186)

Rhenium is a group VII metal. Irradiation of enriched Rhenium-185 produces the radionuclide Rhenium-186 (Re186). Re186 decays with the emission of a beta particle (Emax 1.07 Mev) and (9%) gamma ray

<table>
<thead>
<tr>
<th>Study design</th>
<th>Radiotherapy</th>
<th>Pain reduction</th>
<th>Median survival</th>
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<td>n</td>
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<tr>
<td>Dearnaley et al.</td>
<td>78</td>
<td>matched control</td>
<td>hemibody</td>
</tr>
<tr>
<td>Oosterhof et al.</td>
<td>203</td>
<td>randomized</td>
<td>hemibody/local</td>
</tr>
<tr>
<td>Quitly et al.</td>
<td>284</td>
<td>randomized</td>
<td>local</td>
</tr>
</tbody>
</table>

Table 2 – Comparison of radionuclides and external beam radiotherapy (EBRT = external beam radiotherapy, Sr89 = Strontium-89)
(137 keV) which renders it suitable for imaging (Fig. 1) with a physical half-life of 3.8 days. Re-186 bound with the bisphosphonate hydroxyethylidene diphosphonate (HEDP) was first described for treatment of painful bone metastases in the late 1970’s [51,52]. The complexed Re186 binds to hydroxyapatite crystals by forming hydroxide bridges in a hydrolysis reaction. Re186-HEDP is cleared from the plasma with a half-life of 41 hours and the majority is secreted within 24 hours with the urine. It has been used for the palliation of bone pain in several studies with response rates ranging from 30 to 80% with mean duration of response of 7–9 weeks [53,54]. In a rat animal model, Re186-HEDP delayed clinical symptoms from vertebral metastases such as leg paralysis and urinary retention in the bladder [55]. The maximum tolerated dose for Re186-HEDP is 2960 MBq [56,57] and no dose response was noted in the dose range of 1295–2960 MBq [58]. Typically, pain response occurs 1–3 weeks after infusion with a duration of 5–12 months. After approximately one week a pain flare does occur in up to 50% of patients. Toxicity has been shown to consist of thrombocytopenia whereas leucopenia seems to play a minor role [59]. Grade 2 and 3 thrombocytopenia occurs in 12% and 7% respectively but rarely is clinically relevant. The same applies for neutropenia that is seen in 29% of cases but rarely results in clinical interventions. In a randomized trial the Re186-HEDP was shown to be superior over placebo: 27% of patients reported pain relief compared to still 13% in the placebo group [12]. Twenty of 131 men did not receive Re186-HEDP due to rapid progression suggesting that the population in this study was in a poor condition. Since a low serum hemoglobin and poor performance were shown to be associated with poor pain response [7,35] this may explain the relatively low response rate compared to the 50% of pain responses reported in other analyses [35,60].

At higher doses the use of Re186-HEDP is limited by its myelosuppressive toxicity. Re186-HEDP at higher doses (up to 5000 MBq) with autologous blood stem cell rescue and re-infusion 2 weeks after Re-186 injection was shown to result in a partial PSA response in 20% of cases that received more than 3500 MBq [61]. No grade IV thrombocytopenia or leucopenia was reported. These initial findings resulted in a phase-II trial of 38 patients treated with high dose Re186-HEDP (dose range 4770–5100 MBq). In this second study 21% of patients

![Fig. 1 – Comparison of Technetium-99 (Tc-99M) and Rhenium-186 (Re186) bone scan. Gamma-emitting radionuclides such as Rhenium and Samarium can be used for imaging to confirm correct uptake of the therapeutic radionuclide to the areas of bone activity found on the Technetium bone scan.](image)
experienced grade 3 thrombocytopenia with a nadir platelet count value after 3 weeks. In 29% of cases a PSA decrease of at least 50% was observed that lasted for more than 4 weeks. The median duration of PSA response was 5.6 months.

Re186-HEDP results in considerable pain relief and mild toxicity at lower doses. At high dose, Re186-HEDP resulted in a modest PSA response, but significantly more bone marrow suppression.

5. Rhenium-188 (Re188)

Another radionuclide derived from Rhenium is Re188. Compared to Re186 it has a shorter half-life (12 hours for the entire body and 16 hours in bone metastases) [62]. In a dose-escalation analysis the maximal tolerated dose was determined on 3.3 GBq [63]. Pain palliation is reported in 66–77% of patients with a complete response percentage of 16–25% [6,11,64]. Moreover, an improvement in quality of life-score was noted in the 6–12 week period following Re188-HEDP infusion [6]. Similar to Re186-HEDP, Re188 complexed to HEDP resulted in hematological toxicity with a reduction in platelet count in 20% of cases and a reduction in leucocyte count in 25% of cases. These parameters return to normal within 3 months and proper patient selection rarely results in serious toxicity [6,62,65,66]. An alternative to Re188-HEDP is Re188 chelated to dimercaptisuccinic acid (Re188-DMSA). Re188-DMSA was shown to target bone metastases from prostate cancer specifically but clinical experience is limited to one report [67].

Palmedo et al. (2003) [68] studied the effects of repetitive Re188-HEDP injections for pain palliation in osseous metastases from prostate cancer. In a randomized fashion patients were assigned to either a single Re188-HEDP injection or 2 injections with an 8 week interval. Repetitive dosing not only improved pain response but also resulted in a higher percentage of PSA responses (39% versus 7%) and significantly improved median overall survival from 7 months in the single dose group to 12.7 months in the repetitive dosing group. Maximal toxicity in both groups was transient grade-2 thrombocytopenia and leukopenia.

A non-randomized comparison of Re188-HEDP and Sm153-EDTMP in patients with painful metastases from prostate and breast cancer Liepe et al. [11] showed comparable response and toxicity for both agents.

Re188-HEDP was shown equally effective and toxic to Sm153-EDTMP in non-randomized analyses and repetitive dosing is feasible.

6. Samarium-153 (Sm153)

Bombardment of enriched Samarium-152 with neutrons in a nuclear reactor results in samarium-153 (Sm153). Sm153 has no natural affinity for bone but can be complexed with several aminocarboxylates and aminophosphonates such as ethylenediamine-tetramethylene phosphonate (EDTMP) directing osseous targeting. Clearance from the bloodstream is completed 6 hours after injection and excretion is done in the urine [69] whereas nuclear decay half-life is 1.9 days with 0.22 MeV beta-emission and 103 keV gamma rays. Hence, similar to Rhenium-based radionuclides Sm153-EDTMP can be used for imaging. Bone metastases bind 5 × more Sm153 compared to normal bone [70]. Dose limiting toxicity consists of thrombocytopenia and is seen in 20–42% of patients. In more than 95% of patients platelet count normalizes within 5 weeks [70–73]. Pain relief from osseous metastases after Sm153-EDTMP occurs in 30–85% of patients in a variety of tumors [74].

Several randomized, double-blind studies have analyzed the efficacy of Sm153-EDTMP. A higher dose (37 MBq/kg) was shown to be more effective for palliation of pain from osseous metastases in both breast and prostate cancer compared to a lower dose (18.5 MBq/kg) [75]. In breast cancer patients, but not in prostate cancer patients, the highest dose of Sm153-EDTMP was associated with improved survival.

Another three-arm randomized trial comparing low dose (18.5 MBq/kg) and high dose Sm153-EDTMP (37 MBq/kg), versus placebo reported an improvement in pain for both low dose (42%) and high dose (67%) Sm153-EDTMP after 4 weeks [76].

A more recent randomized phase-III trial compared Sm153-EDTMP to placebo [77]. Analgetics use decreased significantly after a 2–4 week interval. Moreover, 9% of patients in the Sm153-EDTMP group showed a reduction of more than 50% in serum PSA levels.

In all three trials only mild thrombocytopenia and neutropenia were reported with platelet count reduction between 43–55% and white-blood cell count reduction between 45–60% at 3–4 weeks after infusion. Normalization of hematological parameters was reported in all trials by 8 weeks.

Sm153 in repetitive dosing was shown to be effective [70]. Repetitive dose was studied in 15 patients of which 13 (87%) showed pain improvement after secondary treatment. Both the median duration of pain control (24 versus 8 weeks) and survival (9 versus 4 months) in the retreated group were substantially greater than for patients treated...
with a single dose. However, 60% of the patients in the re-treatment group required blood transfusions for anemia. This increased efficacy of repeat dosing was not observed in other studies [35]. Selection of patients may have caused this inconsistency.

Repetitive dosing of Sm153 is feasible. When treatment intervals exceed 6 weeks toxicity is limited and reversible.

7. Comparing radionuclides for efficacy

Based on effects of myelosuppression it can be expected that radionuclides with shorter half-life would potentially be less toxic. The local availability and approval of use by regulatory bodies of radionuclides with shorter half-lives dictate the use in different countries. So far, based on clinical efficacy and toxicity data, none of these radionuclides has shown convincing superiority of the others neither with respect to efficacy nor with respect to toxicity. Based on limited comparison analyses the shorter half-life of Re188 compared to Re186 and Sm153 may favor its use in the light of toxicity. The need for a production facility close by the hospital with the use of short half-life radionuclides such as Re188 may prohibit the extensive use of the agents (Table 3).

8. Combination therapy

8.1. Radionuclides and chemotherapy

Based on several findings there is reason to believe that a combination of radionuclides and chemotherapeutic agents may have synergistic antitumor activity. The radiosensitizing effects of for example cisplatin and docetaxel are known and exploited to increase efficacy of external beam radiotherapy [78,79]. On the other hand, both radionuclide and chemotherapy result in myelotoxicity and, therefore, hematological toxicity may increase with the combination therapy. In the 2005 EAU-guidelines for prostate cancer [80] the authors mention (section 16.10) that palliative treatment with Samarium and Strontium radionuclides may be effective but could compromise later chemotherapy due to myelotoxicity of both treatments. Recent data, however, suggests that radionuclide treatment does not prohibit further chemotherapy and that the effects on bone marrow function is limited to the first 6 to 12 months after administration [81].

8.2. Chemotherapy and Sr89

Sr89 was shown to be of benefit to patients that earlier received and were resistant to chemotherapy [36]. Conversely, Sr89 treatment did not inhibit future chemotherapy application [81]. Akerley et al. (2002) [82] showed that Sr89 (2.2 MBq/kg) in combination with estramustine (600 mg/m²) and vinblastine (4 mg/m²) resulted in a PSA decline of more than 50% for longer than 6 weeks in 48% of patients. Pain response was not assessed in this non-randomized-study.

Pain response was improved upon the addition of low-dose cisplatin (18 mg/m²) to Sr89 (148 MBq) [83,84]. Any reduction in pain was experienced by 91% of patients in the combination arm against 63% in the Sr89 monotherapy arm. However, the rate of “complete” response was not significantly different for both arms. Interestingly, none of the hematological toxicity parameters was significantly different for both arms. No significant difference in overall

<table>
<thead>
<tr>
<th>Table 3 – Available radionuclides for bone metastases targeting</th>
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<tr>
<td><strong>Radionuclide</strong></td>
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<tr>
<td>-----------------</td>
</tr>
<tr>
<td>32P</td>
</tr>
<tr>
<td>89Sr</td>
</tr>
<tr>
<td>153Sm-EDTMP</td>
</tr>
<tr>
<td>186Re-HED</td>
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<tr>
<td>188Re-HEDP</td>
</tr>
<tr>
<td>117mSn-DTPA</td>
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<td>223Ra</td>
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survival between Sr89 and S89+cisplatin was observed.

The combination of Sr89 and doxorubicin after two or three courses of induction doxorubicin was found to prolong survival in a small randomized trial. The addition of doxorubicin to Sr89 extended median survival from 16.8 months in the doxorubicin only group to 27.7 months in the combined treatment group [85].

These data suggest that a combination of Sr89 and chemotherapeutic agents may potentially improve survival in a subgroup of patients and has mild toxicity. The limited data available prohibit widespread use of the combination, in particular with respect to the effects on bone marrow suppression.

### 8.3. Chemotherapy and Sm153-EDTMP

The ongoing TAXSAM study is a non-randomized phase II analysis to evaluate the tolerability and efficacy of a combination of Sm153-EDTMP and docetaxel in patients with hormone refractory prostate cancer. Docetaxel was administered at a dose of 30 mg/m² weekly for 5 weeks. Eighteen to twenty-four hours prior to the fourth administration of docetaxel, the approved dose of Sm153-EDTMP (1 mCi/kg) was injected. Patients received a second cycle of the TAXSAM combination regimen at PSA and/or clinical progression. Grade 3 and 4 neutropenia was observed in 3 of 29 patients between 2–6 weeks after Sm153-EDTMP infusion. Thrombocytopenia higher than grade 2 did not occur. Within 12 weeks 34% and 18% of patients had a more than 50% reduction in serum PSA after the first and second Sm153-EDTMP, respectively [86]. Higher PSA response rates were reported by Fizazi et al. [87] combining Sm153-EDTMP with docetaxel after a positive response to 4 courses of 70 mg/m² docetaxel and estramustine 3-weekly. Twenty-five of 36 (69%) of patients had a PSA decrease of more than 50% and 80% of patients reported a decrease in VAS-score pain assessment by more than 2 points after the initial 4 docetaxel induction cycles. Patients that experienced a positive response after the initial 4 cycles of docetaxel were treated with a maintenance protocol with a single Sm153-EDTMP infusion combined with weekly docetaxel 20 mg/m² for 6 weeks. For the patients that completed 6 weeks maintenance treatment the pain response was 94%.

These data suggest that a single Sm153-EDTMP treatment increases the incidence of grade 3–4 neutropenia of weekly docetaxel: 5% grade 3–4 neutropenia in docetaxel [88] compared to 10% in the combination. Thrombocytopenia was not more frequent in the combined treatment, whereas PSA response and pain response were higher. Data from ongoing randomized studies is needed here to evaluate both pain response and survival of the combination of chemotherapy and Sm153-EDTMP treatment but initial findings seem promising.

### 8.4. Bisphosphonates and radionuclide treatment

Bisphosphonate treatment was shown to result in a modest reduction in pain from osseous metastases in prostate cancer but pain relief occurred after considerable longer intervals compared to radionuclide treatment [89]. Since bisphosphonates are used to target Re186, Re188, and Sm153 to bone metastases it was studied whether earlier treatment with bisphosphonates may influence efficacy of these radionuclides. Recently, a non-randomized comparison in a small group of patients found that the combination of zoledronic acid and Sr89 was more effective for pain relief than either of the two agents in monotherapy [90]. These limited findings suggest that bisphosphonates not necessarily counteract the efficacy of radionuclide treatment and patients experiencing pain while on bisphosphonates could continue these while receiving radionuclide treatment.

### 9. Recommendations for radionuclide use

Data from both retrospective and prospective studies do indicate that pain palliation obtained by radionuclide treatment is most likely in patients with relatively good performance status and pain reduction can be obtained in over 50% of patients which seems higher than for chemotherapy. Pretreatment a bone scan be done to confirm metastases and exclude patients with a so-called super-scan, since it is generally assumed that bone marrow toxicity may be higher in these patients. Hematological parameters showed be assessed and be higher than lower normal limits. It is recommended to use radionuclides only in patients with renal clearance over 60 ml/min. As for chemotherapy, the likely of pain relief decreases when serum hemoglobin starts to drop, this reflecting a poor overall condition. Radionuclides with shorter physical half-lives, such as Sm153, Re186 and Re188, that, based on the earlier recovery of bone marrow toxicity compared to initially used radionuclides (Sr89) could potentially be given at higher frequency which favors repetitive use and supports treatment earlier in the course of disease. Moreover, data now clearly show that radionuclide treatment not necessarily precludes further chemotherapy.
Considering the milder side-effect profile for radio-nuclides compared to chemotherapy it should be considered first choice in patients with multiple painful osseous metastases where external beam radiotherapy is not feasible due to the number of metastases. Moreover, radionuclide treatment should be considered in patients with painful metastases after chemotherapy. Combination of radionuclide treatment and chemotherapy should be considered experimental. Although increased efficacy was has been observed for the combination, the incidence of grade 3 and 4 neutropenia also increased. A combination of bisphosphonates with radionuclides was not associated with increased toxicity and potentially increases efficacy of pain relief.

- Bone marrow suppression with thrombocytopenia and neutropenia occurs in similar frequency and grade in all radionuclides but a shorter half-life seems to be associated with earlier recovery to baseline blood cell counts.
- Repetitive dosing of all radionuclides was shown to be feasible when the intervals were at least 6 weeks.
- Combination of radionuclides with external beam radiotherapy and chemotherapy was shown to be beneficial, but toxicity increased significantly.
- Combination of radionuclides with chemotherapeutic agents should be considered an experimental treatment and study data are awaited.

10. Future

Combination of chemotherapy and radionuclide treatment and a direct comparison of both modalities should be studied. The initial findings of a combination of Samarium based radionuclides and docetaxel hold promise. Alpha-particle emitters deliver a higher energetic and localized radiation with a much smaller range in tissue than beta-particles. These alpha-particle radiation induces predominantly non-reparable DNA double-strand breaks which may kill dormant cells but alpha-emitters are potentially more toxic and mutagenic than beta-emitters. Further evaluation of alpha-emitters such as Ra223 that has a natural affinity for bone like Sr89 is awaited but initial data suggests reduced thrombocytopenia in patients with prostate cancer [14,15].

11. Remarks

- Pain response is seen in approximately half the patients treated with radionuclides for painful osseous metastases of prostate cancer.
- P32 and Sr89 show a natural affinity for bone, whereas Re186, Re188, and Sm153 require chelation to bisphosphonates for targeting.
- Of the different radionuclides used those with a shorter half-life such as Re186-HEDP, Re188-HEDP, and Sm153-EDTMP showed similar efficacy compared to Sr89, with a longer half-life.
- Several parameters are associated with a favorable pain response: higher performance score and lower pain score at treatment, higher serum hemoglobin, and a limited number of osseous metastases.
- Bone marrow suppression with thrombocytopenia and neutropenia occurs in similar frequency and grade in all radionuclides but a shorter half-life seems to be associated with earlier recovery to baseline blood cell counts.
- Repetitive dosing of all radionuclides was shown to be feasible when the intervals were at least 6 weeks.
- Combination of radionuclides with external beam radiotherapy and chemotherapy was shown to be beneficial, but toxicity increased significantly.
- Combination of radionuclides with chemotherapeutic agents should be considered an experimental treatment and study data are awaited.

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**CME questions**

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1. $^{89}\text{SrCl}_2$ is a radionuclide for which one of the following applies:
   A. It does not have a natural ability to bind bone.
   B. Its physical half-life is $< 1$ d.
   C. Its efficacy for pain relief is markedly shorter than other radionuclides.
   D. It has a natural ability to bind bone.

2. Physical half-lives differ between radionuclides. What is the correct order when ordered from short to long physical half-life?
   A. $^{89}\text{Sr}$; $^{186}\text{Re}$; $^{153}\text{Sm}$
   B. $^{153}\text{Sm}$; $^{186}\text{Re}$; $^{89}\text{Sr}$
   C. $^{186}\text{Re}$; $^{153}\text{Sm}$; $^{89}\text{Sr}$
   D. $^{188}\text{Re}$; $^{89}\text{Sr}$; $^{153}\text{Sm}$

3. The $\alpha$-emitting radionuclides are relatively new in the field of palliation for bone pain from metastases. Which of the following is true:
   A. $\alpha$-particles travel longer ranges in tissue compared to $\beta$-particles.
   B. $\alpha$-particles are potentially less toxic to cells than $\beta$-particles.
   C. $\alpha$-particles cannot be used for the treatment of prostate cancer.
   D. $\alpha$-particles result in DNA double-strand breaks.

4. The most prevalent typical toxicity of all radionuclides is:
   A. Neuropathy
   B. Hepatotoxicity
   C. Nephrotoxicity
   D. Thrombocytopenia

5. Which of the following radionuclides is not dependent on a bisphosphonate for bone targeting?
   A. $^{153}\text{Sm}$
   B. $^{186}\text{Re}$
   C. $^{188}\text{Re}$
   D. $^{223}\text{Ra}$

6. Pain response to radionuclide treatment was shown to be associated with:
   A. Serum hemoglobin level
   B. Patient age
   C. Renal function
   D. Location of bone metastases