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Radiopharmaceuticals for Palliation of Bone Pain in Patients with Castration-resistant Prostate Cancer Metastatic to Bone: A Systematic Review

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Abstract

Context: The majority of patients with castration-resistant prostate cancer develop bone metastatic disease. It is often challenging to optimally palliate malignant bone pain. In case of multifocal pain due to diffuse osteoblastic metastases, treatment with bone-seeking radiopharmaceuticals can be considered.
Objective: This systematic review evaluates the efficacy of different bone-seeking radiopharmaceuticals for palliation of malignant bone pain from prostate cancer.
Evidence acquisition: The PubMed (Medline) and Embase databases were searched for publications on 89-strontium-chloride (^{89}Sr), 153-samarium-EDTMP (^{153}Sm), 186-rhenium-HEDP (^{186}Re), 188-rhenium-HEDP (^{188}Re), and 223-radium-chloride (^{223}Ra). Randomised controlled trials and prospective cohort studies were included. Metastatic bone pain had to be registered as outcome measure for prostate cancer patients separately.
Evidence synthesis: This review included 36 articles of which 13 randomised trials and 23 prospective studies. Of all trials, 10 studies used ^{89}Sr, 7 ^{153}Sm, 12 ^{186}Re, 2 ^{188}Re, and 2 ^{223}Ra; three reported on a combination of different radionuclides. Only a few trials contained a blinding procedure and several studies contained incomplete follow-up or lack of intention-to-treat analysis. It was not possible to calculate a pooled estimate of pain response to treatment with any of the radionuclides because different definitions of pain response were used.
Conclusions: Overall, pain response percentages greater than 50–60% were seen with each radionuclide. Haematological toxicity was reported in 26 of the 36 studies and more than half of these trials stated no grade 3/4 leukopenia or thrombocytopenia occurred.
Patient summary: In this report we reviewed the efficacy of bone-seeking radionuclides for treating bone pain from metastatic prostate cancer. Overall, treatment with bone-seeking radionuclides resulted in pain responses greater than 50–60%.

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1. Introduction

Bone is the most common site for metastases in patients with castration-resistant prostate cancer (CRPC) [1]. These skeletal metastases, mostly localised in the lumbar spine, vertebrae, and pelvis, are frequently complicated by pain [1]. Hormonal therapy, chemotherapy, and immunotherapy are systemic treatment strategies for metastatic prostate cancer that can result in a decrease of pain, prolongation of time to first skeletal related event, and improvement of overall survival [2]. However, it is challenging to optimally palliate malignant bone pain [3]. Analgesics such as opioids and nonsteroidal anti-inflammatory drugs are frequently used, but may have unpleasant side effects.

Localised pain due to a single metastasis can be controlled with external beam radiotherapy in about 80% of patients [4]. In case of multifocal pain due to diffuse osteoblastic metastases, treatment with bone-seeking radiopharmaceuticals can be considered [5]. Most bone-seeking radiopharmaceuticals are beta-emitting agents, except for the alpha emitter radium-223-chloride (^{223}Ra). The most commonly used bone-seeking radiopharmaceuticals are strontium-89-chloride (^{89}Sr), samarium-153-EDTMP (^{153}Sm), rhenium-186-HEDP (^{186}Re), rhenium-188-HEDP (^{188}Re), and ^{223}Ra (Table 1). These radionuclides are bound to a ligand that binds to the bone matrix and accumulates in sites of increased bone turnover. Subsequently, radiation is delivered at the osteoblastic metastatic sites. The most important side effect of these radiopharmaceuticals is bone marrow suppression.

Many studies have been conducted to determine the benefit from treatment with bone-seeking radiopharmaceuticals on bone pain. Interpretation of these trials is difficult because of their often retrospective design, small sample-sizes, inclusion of patients with bone metastases from different primary tumours, and variable definitions of pain response. In 2011 a Cochrane Systematic Review was published of randomised controlled trials (RCTs) using beta-emitting radiopharmaceuticals in metastatic bone pain [6]. All other prospective studies about the efficacy of bone-seeking radiopharmaceuticals in palliating bone pain were excluded. There was no selection of studies based on tumour type. Bone metastases from prostate cancer are predominantly osteoblastic and sclerotic of nature, whereas bone metastases from other cancer forms are often mixed type (both osteoclastic and osteoblastic). Consequently, quantitative uptake of the radiopharmaceuticals in skeletal metastases of prostate cancer is expected to be higher than in metastases from other tumour types, hypothetical leading to increased efficacy of bone-seeking radiopharmaceuticals in prostate cancer. Thus, skeletal metastases from prostate cancer are an attractive target for bone-seeking radiopharmaceuticals.

The purpose of this systematic review was to determine the efficacy of currently available alpha- and beta-emitting bone-seeking radiopharmaceuticals to reduce bone pain in patients with CRPC.

2. Evidence acquisition

We conducted a literature search of the PubMed (Medline included) and Embase databases on October 17th, 2014 and November 21st, 2014, respectively with an English language restriction. We developed a search strategy using both medical subject headings and text words for 'bone metastases' and the following bone seeking radiopharmaceuticals ^{89}Sr, ^{153}Sm, ^{186}Re, ^{188}Re, and ^{223}Ra (search strategy displayed in Supplementary Data 1). Finally, we performed manual cross-referencing.

Inclusion criteria were: RCTs and prospective cohort studies; at least 10 patients with CRPC and osteoblastic metastases; treatment with at least one of the following radiopharmaceuticals: ^{89}Sr, ^{153}Sm, ^{186}Re, ^{188}Re, or ^{223}Ra. For studies that examined the efficacy of a radiopharmaceutical in metastatic bone pain from any cancer type, metastatic bone pain had to be registered as an outcome measure for the prostate cancer patients separately.

Two reviewers (J.D. and D.O.) independently identified the eligible studies. Study selection was initially based on title and abstract, and subsequently by reading the full text articles. The methodological quality of the included articles was independently assessed by the same reviewers. Differences were resolved by consensus. For RCTs and comparative prospective studies we used the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011 version 5.1.0). Methodological quality of prospective cohort studies was evaluated using the Newcastle Ottawa Scale. The complete criteria lists as applied in this systematic review, including the applied levels of bias are shown in Supplementary data 2.

Data were independently extracted by the two reviewers using a data extraction form that included patient characteristics, methodological quality, trial characteristics, details of the intervention, and outcome measures (see Supplementary data 3). Besides pain response percentages, data on overall survival and toxicity (pain flare and haematological toxicity) were also extracted. Haematological toxicity had to be described following the National Cancer

Table 1 – Physical characteristics of different bone-seeking radiopharmaceuticals

Radio-pharmaceutical	Half-life (d)	Type of radiation	Maximum energy (MeV)	γ-emission MeV (%)	Maximum range (mm)
^{89}Sr	50.5	β	1.46	Nihil (0.01%)	7
^{153}Sm	1.9	β	0.81	0.103 (29%)	2.5
^{186}Re	3.7	β	1.07	0.137 (9%)	5
^{188}Re	0.7	β	2.12	0.155 (15%)	10
^{223}Ra	11.4	α	5.78 average	0.154 (1.1%)	<0.01