Adverse Reactions Mediated by Strontium-89, Samarium-153, Rhenium-186 and Rhenium-188: A Systematic Review of Literature

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Abstract. *One of the therapies used for the palliative treatment of pain associated with bone metastases is radiopharmaceutical therapy. Radiopharmaceuticals can cause adverse reactions, and, therefore, the aim is to systematize the results and conclusions of studies on the use of the radiopharmaceuticals ^{89}Sr, ^{153}Sm, ^{186}Re and ^{188}Re in the palliative treatment of pain associated with bone metastases. A systematic literature review was conducted according to PRISMA statement, using the databases MEDLINE and EBSCO. After the selection process, 20 articles were included. The studies showed that the 4 radiopharmaceuticals analysed presented very similar results regarding pain relief after treatment, decrease in analgesic consumption, side effects at the time of administration, hematologic toxicity and disease progression after treatment. Concluding, the use of radiopharmaceuticals for pain palliation seems to be safe and an alternative to existing treatments.*

Keywords. Pharmacovigilance, adverse reactions, radiopharmaceuticals, bone metastases, pain palliation

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1 Introduction

The World Health Organisation (WHO) defines pharmacovigilance as "the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other medicine/vaccine related problem" [1]. Pharmacovigilance must constantly adapt to rapid developments in new technologies and new therapies, and their regulation. This field includes radiopharmaceuticals (RF), that can be used for diagnostic or treatment purposes, with the scope of nuclear medicine [2].

Bone metastases are one of the most frequent complications of advanced cancers and can significantly affect the quality of life of patients [3], [4]. One of the therapies used for the palliative treatment of pain associated with bone metastases is radiopharmaceutical therapy.

Like any other drugs, RF can cause adverse reactions (AR), and, therefore, the objective of the present study is review the results and conclusions of studies on the use of RF in the palliative treatment of pain associated with bone metastases, namely, Strontium-89 (^{89}Sr), Samarium-153 (^{153}Sm), Rhenium-186 (^{186}Re) and Rhenium-188 (^{188}Re), and provide up to date information on AR associated with this drugs.

2 Methods

A systematic literature review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement [7]. The research question was the "what is the characterization of the AR described associated with the RF ^{89}Sr, ^{153}Sm, ^{186}Re and ^{188}Re, in patients with pain associated with bone metastases, until the year 2022?".

A computerized literature search was performed using the databases MEDLINE (PubMed) and EBSCO (Academic Search Complete). Two researchers developed a search string for each database. Controlled trials, cohort studies, case-control studies and case series, in English, Spanish and Portuguese, were considered, between 1983 and 2022 (the date range comprises the appearance of the first studies in the literature until the moment when the search ended). The analysis and selection of the literature was performed using the Rayyan Software. The two researchers independently accessed all articles obtained and analysed its title and abstract for the inclusion or exclusion of each one. In case of doubt, the full article was read. Initially, 2583 articles were obtained from the two databases, of which 2563 were excluded. After analysing the title and abstract, 139 and 319 articles were obtained from reviewer 1 and 2, respectively. Review articles, articles that didn't contain complete data on the AR under study, articles where AR weren't well characterized or weren't written in English, Portuguese or Spanish were rejected. After resolving the articles selected as "maybe" and "conflict", 306 articles were selected to be included. Only 14 articles focused on the RF above mentioned. Six other articles were obtained by cross-referencing and manual search. The difficulty to find studies related to RF adverse events forced the acceptance of low-quality studies (with fewer than 10 reported cases), but those provided information not found in other literature. The AR described were classified according to the SOC-MedDRA hierarchy.

3 Results

From the 20 selected articles, an analysis was carried out which resulted in table 1 and graphic 1, with an overview of the evidence collected.

Table 1. Overview of included studies with their characteristics.

Study	Radiopharmaceutical	Patients
Collins *et al.* [8]; Ashamalla *et al.* [9]; Berger *et al.* [10]; Ribera *et al.* [11]	153Sm-EDTMP	101
Maxon *et al.* [12], Klerk *et al.* [13]	186Re-HEDP	22
Liepe *et al.* [14]; Palmedo *et al.* [15]; Li *et al.* [16]; Liepe *et al.* [17]; Zhang *et al.* [18]; Cheng *et al.* [6]; Beiki *et al.* [4]; Shinto *et al.* [3]	188Re-HEDP	287
Hesslewood *et al.* [19]; Baziotis *et al.* [20]; Kraeber-Boderé *et al.* [21]	89Sr	160
Dafermou *et al.* [22]	89Sr and 186Re-HEDP	510
Liepe *et al.* [23]	188Re-HEDP and 153Sm-EDTMP	46
Liepe *et al.* [5]	188Re-HEDP and 186Re-HEDP and 153Sm-EDTMP	79

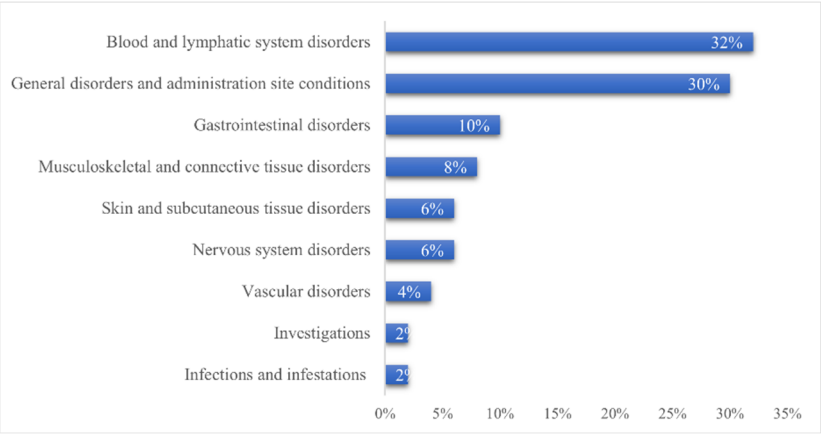

Figure 1. Overview of adverse reactions by SOC.

4 Discussion

In addition to some other cancers, such as myeloma or lung cancer, skeletal metastases can develop in around 50% of women with breast cancer, the most prevalent cancer in women, and in 80% of patients with prostate carcinoma, the second most frequent disease in men [24]. The pain phenomenon is directly caused by tumor invasion. After traditional surgical and/or non-radiologic therapy options have been explored, almost half of the patients will still experience significant

bone pain. A particularly significant therapeutic option is provided by metabolic radiotherapy [25].

All the studies recovered, show that these drugs can provide safe, symptomatic relief from painful osseous metastases and in most cases the hematological toxicity was reversible [3]–[6], [8], [9], [11]–[22]. There is also evidence of secondary outputs for health and quality of life. Collins *et al.* [8] , Baziotis *et al.* [20]; and Zhang *et al.* [18] showed a reduction in analgesic requirements and the works of Kraeber-Boderé *et al.* [21] observed an improvement in quality of life in terms of better sleep or increased activity after 65% of administered injections [8], [18], [20], [21].

The case report of Klerk *et al.* [13] describes an uncommon side effect which is transient cranial neuropathy after treatment with ^{186}Re-HEDP and the explanation for this side effect could be the direct radiation injury of cranial nerves surrounded by metastatic bone tissue [13].

The flare response is a reaction that some studies have observed in their patients, after the injection of the RF [3]–[6], [10], [12], [15]–[18], [20]–[23]. There are different explanations provided for this phenomenon. Dafermou *et al.* [22] suggested that the pain flare phenomenon is a positive predictive factor for the efficacy of the radionuclide therapy. In their trial, patients with pain flare showed slightly lower favourable response rate in comparison to those who did not experience this reaction. This difference may be due to the known psychological component of pain and to some individual variability in pain threshold [22]. Shinto *et al.* [3] explain that this probably related to transient inflammatory reactions that modify intratumoral pressures. In their study flare reactions occurred in more than half of patients and could be due to the patient's awareness of the probable short-term worsening of bone pain, higher administered dose, or greater fluctuations in the level of pain. Despite this fact, the authors showed that flare reactions can be managed by analgesic or steroid agents, are reversible and are not predictive of pain palliation [3].

In conclusion, pain is one of the most common and distressing symptoms described by patients with bone metastases. The analysed studies presented similar results regarding pain relief, decrease in analgesic consumption, AR at the time of administration, hematologic toxicity and disease progression after treatment. The use of RF for pain palliation seems to be a safe alternative to standard treatments, however more studies are needed to evaluate safety and toxicity.

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