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Review

Palliative treatment of metastatic bone pain with radiopharmaceuticals: A perspective beyond Strontium-89 and Samarium-153

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HIGHLIGHTS

- An overview of several radiopharmaceuticals is presented.;
- Clinical outcomes are reviewed and summarized.
- It is suggested a lack of substantial differences in terms of palliative efficacy.
- ^{177}Lu and ^{188}Re-labeled radiopharmaceuticals appear to be the most suitable.

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ABSTRACT

Purpose: The present review article aims to provide an overview of the available radionuclides for palliative treatment of bone metastases beyond ^{89}Sr and ^{153}Sm. In addition, it aims to review and summarize the clinical outcomes associated with the palliative treatment of bone metastases using different radiopharmaceuticals.

Materials and methods: A literature search was conducted on Science Direct and PubMed databases (1990 - 2015). The following search terms were combined in order to obtain relevant results: “bone”, “metastases”, “palliative”, “care”, “therapy”, “treatment”, “radiotherapy”, “review”, “radiopharmaceutical”, “phosphorus-32”, “strontium-89”, “yttrium-90”, “tin-117m”, “samarium-153”, “holmium-166”, “thulium-170”, “lutetium-177”, “rhenium-186”, “rhenium-188” and “radium-223”. Studies were included if they provided information regarding the clinical outcomes.

Results and conclusions: A comparative analysis of the measured therapeutic response of different radiopharmaceuticals, based on previously published data, suggests that there is a lack of substantial differences in palliative efficacy among radiopharmaceuticals. However, when the comparative analysis adds factors such as patient’s life expectancy, radionuclides’ physical characteristics (e.g. tissue penetration range and half-life) and health economics to guide the rational selection of a radiopharmaceutical for palliative treatment of bone metastases, ^{177}Lu and ^{188}Re-labeled radiopharmaceuticals appear to be the most suitable radiopharmaceuticals for treatment of small and medium/large size bone lesions, respectively.

Contents

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1. Introduction

Bone metastases are a common and severe complication in patients diagnosed with primary tumors. It develops in up to 70% of patients diagnosed with prostate cancer and breast cancer and in up to 30% of those with cancers of the lung, bladder and thyroid. The major complications associated with bone involvement are severe pain, spinal cord compression, hypercalcemia and pathological fracture, all of which compromise the patient's quality of life. Several therapeutic approaches targeting bone metastases and its associated effects are available, including the use of analgesics, chemotherapy, external beam radiotherapy and radionuclide systemic therapy. The latter, systemic palliative targeted therapy with suitable radiopharmaceuticals, has emerged as a particularly appealing and efficient treatment modality for patients with multiple skeletal metastases (Maini et al., 2003; Pandit-Taskar et al., 2014; Pillai et al., 2003; Silberstein and Drive, 1996).

Radionuclide therapy is characterized by the reasonably selective delivery of therapeutic doses of radiation to systemically dispersed target tissues, with generally limited toxicity and few long-term side-effects (Unak, 2002). The basis of successful radionuclide therapy relies on a high concentration and adequate retention of the radiopharmaceutical at the tumor site. The concept of targeted therapy introduced in 1898 by Paul Ehrlich, i.e. the "magic bullet" concept, has paved the way for the development of successful approaches for treatment of different diseases based on radiopharmaceutical systemic administration (Ehrlich and Herter, 1904; Vial and Callahan, 1957). A notable example is the treatment of hyperthyroidism and thyroid cancer using Na^{131}I. Since then, a wide variety of radiolabeled agents has been used clinically for treatment of different types of diseases, but only a limited number of these preparations have obtained regulatory approval for routine clinical use in patients and are commercially available (Das and Pillai, 2013). Examples of diseases that have been treated by nuclear medicine therapy are: thyroid carcinoma, hyperthyroidism, metastatic bone pain, polycythemia rubra vera, neuroendocrine tumors (NETs), liver metastases, lymphoma and neuroblastoma. Among these, treatment of thyroid cancer with ^{131}I is the most widely used radionuclide-targeted therapy. The second most widely used application is for bone pain palliation in the context of metastatic cancer (Das and Pillai, 2013).

There are essentially three main types of particulate radiations that are of interest for palliative treatment of bone metastasis using radiopharmaceuticals: beta minus ($\beta-$) particles, alpha (α) particles and Auger electrons. Traditionally, tumor-targeted radiotherapy has used $\beta-$ emitting radionuclides. However, high-energy $\beta-$ particles, with a range of several millimeters in tissues, can irradiate cells nearby the targeted tumor. Conversely, α particles (typical penetration range of less than 100 μm) (Harrison et al., 2013) and Auger electrons (penetration range of several nanometers to micrometers) have shorter penetration ranges and higher linear energy transfer (LET) (Unak, 2002). Radiopharmaceuticals deposition sites in the cell is another important factor to consider during palliative treatment of bone metastases using radiopharmaceuticals. For instance, if deposition occurs in the cell nucleus, an Auger electron emitter radionuclide may be adequate for cell killing, while in the case of cell surface deposition, $\beta-$ or α particle-emitting radionuclides may be preferable. Therefore, the design of the carrier molecule to be labeled with the radionuclide should consider the physical properties of the radionuclide to be used. For short-range particles, such as Auger electrons, this means the carrier molecule should be able to cross the cellular membrane either by passive diffusion or via specific carrier mediated process, in order to reach the cell nucleus and to associate with the deoxyribonucleic acid (DNA) complex for a time corresponding to the radionuclide half-life (Unak, 2002). Cell and tissue studies have shown that once Auger electron emitters are introduced into the cell's cytoplasm, they will present similar effects to those induced by low LET radiations, but when they are introduced close to DNA, the survival curves will be similar to those obtained with high LET α particles (Sastry, 1992). Dosimetric calculations have also supported these observations. For example, the decay of ^{125}I has been shown to lead to the deposition of a very high dose ($\approx$ 109 cGy/decaying atom) in the immediate vicinity ($\approx$ 2 nm^3) of the decay site and a sharp and significant drop in the energy deposited (from $\approx$ 109 to $\approx$ 106 cGy) as a function of increasing distance (few nanometers) from the decaying ^{125}I atom (Kassis, 2011). For example, when ^{125}I is localized within the cytoplasm, the survival curve is of the low LET type and the number of decays needed to reduce survival is $\approx$ 80 times that of DNA-incorporated ^{125}I (Kassis, 2011).