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Review Article

Pharmaceutical and clinical development of phosphonate-based radiopharmaceuticals for the targeted treatment of bone metastases

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ABSTRACT

Therapeutic phosphonate-based radiopharmaceuticals radiolabeled with beta, alpha and conversion electron emitting radioisotopes have been investigated for the targeted treatment of painful bone metastases for >35 years. We performed a systematic literature search and focused on the pharmaceutical development, preclinical research and early human studies of these radiopharmaceuticals.

The characteristics of an ideal bone-targeting therapeutic radiopharmaceutical are presented and compliance with these criteria by the compounds discussed is verified. The importance of both composition and preparation conditions for the stability and biodistribution of several agents is discussed. Very few studies have described the characterization of these products, although knowledge on the molecular structure is important with respect to *in vivo* behavior.

This review discusses a total of 91 phosphonate-based therapeutic radiopharmaceuticals, of which only six agents have progressed to clinical use. Extensive clinical studies have only been described for ^{186}Re-HEDP, ^{188}Re-HEDP and ^{153}Sm-EDTMP. Of these, ^{153}Sm-EDTMP represents the only compound with worldwide marketing authorization. ^{177}Lu-EDTMP has recently received approval for clinical use in India.

This review illustrates that a thorough understanding of the radiochemistry of these agents is required to design simple and robust preparation and quality control methods, which are needed to fully exploit the potential benefits of these theranostic radiopharmaceuticals. Extensive biodistribution and dosimetry studies are indispensable to provide the portfolios that are required for assessment before human administration is possible. Use of the existing knowledge collected in this review should guide future research efforts and may lead to the approval of new promising agents.

Contents

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1. Introduction

A serious complication of many solid and hematological cancers is the development of bone metastases, which often lead to severe pain, skeletal fractures, neurological symptoms and hypercalcaemia. These complications result in a significant decrease of the quality of life, increased health costs and shorter survival [1–3]. At this later stage of the disease, pain palliation with strong analgesics (typically opioids) or external beam radiation can have serious side effects, and are not always feasible or effective. Bone-seeking therapeutic radiopharmaceuticals constitute an attractive alternative treatment option for osteoblastic bone metastases - especially for multiple lesions - because of their specific targeting, effectiveness and good tolerability [4–6]. The development of therapeutic bone-seeking radiopharmaceuticals was first evaluated in the 1940s with the investigation of phosphorus-32 [7]. Because of the large patient population and effectiveness of this approach, significant research concerning bone metastases seeking radiopharmaceuticals has been pursued up to now [8–10].

Bone-seeking therapeutic radiopharmaceuticals can be divided into calcimimetic radiopharmaceuticals and phosphonate-based radiopharmaceuticals. The localization of calcimimetic agents is controlled by the same physiological and metabolic regulatory mechanisms as calcium and may thus be variable and unpredictable. Examples in this category include phosphorus-32 (^{32}P), strontium-89 (^{89}Sr) and radium-223 (^{223}Ra).

As an alternative strategy, the speed and efficacy of bone accumulation of radionuclides can be enhanced by coupling with phosphonates, for example the well-known bisphosphonates (also called diphosphonates). Phosphonates are non-hydrolyzable analogues of the natural occurring pyrophosphate (see Fig. 1), which has high affinity for bone mineral and regulates bone mineralization.

The general molecular structure of a bisphosphonate is shown in Fig. 2. Different non-radioactive bisphosphonates have been developed as bone resorption inhibitors and are applied clinically as pharmaceuticals for the treatment of several bone diseases [11–13].

These agents are adsorbed by attachment to the calcium atoms in hydroxyapatite (HA), and suppress osteolytic activation and bone resorption, inhibit the functioning of osteoclasts and the maturation of osteoclast precursors and stimulate skeletal osteoblasts. They are able to reduce pain by induction of apoptosis of osteoclasts, inhibition of proliferation of malignant cells, reduction of production of cytokines and secretion of metalloproteinase [14]. The HA affinity is strongly dependent on the molecular structures of these compounds. 'Small' bidentate bisphosphonates, like MDP (methylenediphosphonate, medronate), have the weakest binding capacity. HDP (hydroxymethylenediphosphonate, oxidronate), HEDP (1-hydroxyethylidene-1,1-diphosphonate, etidronate), pamidronate and alendronate act more or less like a tridentate because of the presence of a hydroxyl group [15]. Bisphosphonates with larger side chains, like ibandronate, risedronate and zoledronate, have the highest HA affinity.

Phosphonates are well-known chelators of radiometals and radiolanthanides [16,17]. For the diagnosis of skeletal metastases by using bone scintigraphy, gamma emitting ^{99m}Tc-based bisphosphonates are the most widely applied radiopharmaceuticals [18,19]. For the treatment of bone metastases, many therapeutic phosphonate-

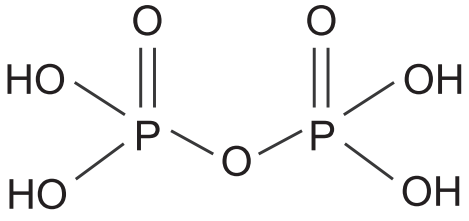

Fig. 1. Pyrophosphate.