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Comparative studies of ^{177}Lu–EDTMP and ^{177}Lu–DOTMP as potential agents for palliative radiotherapy of bone metastasis

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Abstract

^{177}Lu is presently considered as an excellent radionuclide for developing bone pain palliation agents owing to its suitable nuclear decay characteristics [$T_{1/2} = 6.73$ d, $E_{\beta(\max)} = 497$ keV, $E_{\gamma} = 113$ keV (6.4%) and 208 keV (11%)] and large-scale production feasibility with adequate specific activity using moderate flux research reactors. Multidentate polyaminophosphonic acids have already been proven as the carrier molecule of choice for radiolanthanides and similar +3 metal ions in designing agents for palliative radiotherapy of bone pain due to skeletal metastases. The present paper describes a comparison between ^{177}Lu complexes of two potential polyaminophosphonic acid ligands, namely Ethylenediaminetetramethylene phosphonic acid (EDTMP) and 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetramethylene phosphonic acid (DOTMP) with respect to their radiochemical and *in-vivo* biological characteristics. Although both the agents have exhibited promising features, the study reveals that ^{177}Lu–EDTMP has marginally higher skeletal accumulation in comparison to that of ^{177}Lu–DOTMP, while the latter has slightly faster blood clearance along with lower retention in liver and kidneys in animal models.

Keywords: Bone pain palliation; ^{177}Lu; EDTMP; DOTMP

1. Introduction

A large percentage of patients suffering from primary carcinoma of breast, lung and prostate develop metastasis in bone in the advanced stage of their diseases (Maini et al., 2004; McEwan, 1999; Goeckeler et al., 1987). This often leads to excruciating pain and other complications such as, hypercalcemia, lack of mobility, depression and neurological deficits which adversely affect the quality of life (Kvinnsland et al., 2002; Lewington, 2005; Pandit-Taskar et al., 2004; Twycross and Fairfield, 1982). Compared to the other conventional methods, such as use of analgesics and external beam radiotherapy, systematic palliative therapy using suitable radionuclides linked to bone seeking ligands have emerged as the most efficacious treatment modality for patients with multiple skeletal lesions (Hoskin, 2003; Maini et al., 2004; Pandit-Taskar et al., 2004; Silberstein, 1996). The major challenge in developing effective radiopharmaceuticals for palliative treatment of bone pain due to skeletal metastasis is to deliver adequate dose of ionizing radiation at the skeletal lesion sites with minimum radiation-induced bone marrow suppression (Hosain and Spencer, 1992; Volkert and Hoffman, 1999). To meet these challenging requirements, a great deal of research efforts have been devoted in identifying potential therapeutic radionuclides for use in palliative care of metastatic bone pain with more favorable radiation properties. It has been demonstrated that the energy and hence the penetrating ability of the particulates emitted from the radionuclides contribute significantly to the efficacy of the radiotherapeutic. This factor determines the dose delivered to the bone marrow and consequently moderate energy β^-/conversion electron-emitting radionuclides are

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considered to be the most efficacious candidates (Bishayee et al., 2000; Bouchet et al., 2000; Goddu et al., 2000).

^{177}Lu is presently being considered as a promising candidate for use in the palliative care of metastatic bone pain due to its suitable nuclear decay characteristics [$T_{1/2} = 6.73$ d, $E_{\beta(\max)} = 497$ keV, $E_{\gamma} = 113$ keV (6.4%) and 208 keV (11%)] (Chakraborty et al., 2002; Das et al., 2002; Sola et al., 2000). The energies of β^- particles from ^{177}Lu being adequately low, it is expected to have minimum bone marrow suppression on accumulation in skeletal lesions while simultaneously delivering the appropriate dose (Chakraborty et al., 2002; Das et al., 2002; Pillai et al., 2003). Emissions of adequate energy gamma photons in low abundances are suitable for carrying out simultaneous scintigraphic studies and dosimetric evaluation. The logistic advantages obtained from the use of ^{177}Lu having comparatively longer half-life as well as the possibility of its large-scale production in adequately high-specific activity in moderate flux reactors [$\sigma = 2100$ b for ^{176}Lu (n, γ) ^{177}Lu] are additional and definitive advantages towards envisaging this isotope for bone pain palliation (Pillai et al., 2003).

In designing suitable radiolabeled agents for palliative care of bone pain due to metastatic skeletal lesions, multidentate polyaminophosphonic acids are found to be the most promising candidates as carrier ligands owing to their high bone affinity, selective localization in skeletal lesions and ability to form metal chelates with high *in-vivo* stability, especially with lanthanides (Chakraborty et al., 2002; Das et al., 2002; Deligny et al., 1990; Goeckeler et al., 1987; Hosain and Spencer, 1992; Ketring, 1987; Laznicek et al., 1994; Volkert and Hoffman, 1999). Ethylenediaminetetramethylene phosphonic acid (EDTMP) (Fig. 1(a)) is one of the most widely used ligands which forms stable complexes with various radiometals, particularly lanthanides, and all the complexes showed high bone affinity and other favorable pharmacological characteristics in biological systems (Ando et al., 1998, 2000; Goeckeler et al., 1987; Laznicek et al., 1994; Sola et al., 2000). ^{153}Sm–EDTMP (Quadramet®) is currently being used extensively for pain palliation due to skeletal metastases. The agent shows excellent pharmacokinetics, such as preferential localization in osteoblastic lesions and rapid excretion of the residual activity via the kidneys, as well as clinical efficacy in patients (Collins et al., 1993; Maini et al., 2004; Serafini, 2001; Singh et al., 1989). The macrocyclic analog of EDTMP, viz. 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetramethylene phosphonic acid (DOTMP) (Fig. 1(b)), yet another tetramethylene phosphonic acid, could be chosen as another efficacious carrier ligand in developing bone pain palliation agents using radiolanthanides. This is based on the well-documented phenomenon that macrocyclic chelators form thermodynamically more stable and kinetically more inert complexes with lanthanides compared to their acyclic analogs (Caravan et al., 1999; Liu and Edwards, 2001; Volkert and Hoffman, 1999). Thermodynamic stability as well as kinetic inertness of the metalloradiopharmaceutical are very important parameters to be considered in designing agents since the dissociation of the radiometal from the chelate in blood circulation could result in the accumulation of radioactivity in non-target organs (Liu and Edwards, 2001; Volkert and Hoffman, 1999). It is pertinent to note that ^{166}Ho–DOTMP has indeed shown excellent pharmacokinetic properties as well as clinical efficacy in the treatment of patients suffering from multiple myeloma (Bayouth et al., 1995; Breitz et al., 2006; Rajendran et al., 2002).

Bearing in mind the specific advantages of using ^{177}Lu in palliative radiotherapy of bone pain, we have already reported the preparation and preliminary biological studies of five different ^{177}Lu-labeled acyclic and cyclic polyaminophosphonates (Chakraborty et al., 2002; Das et al., 2002, 2008). Among these agents, ^{177}Lu–EDTMP and ^{177}Lu–DOTMP complexes showed encouraging results with respect to complexation yield, stability and biological behavior in Wistar rats. In the present article, we report a comparative study of the ^{177}Lu complexes of EDTMP and DOTMP in terms of their radiochemical properties and biological behaviors in animal models.

2. Experimental

2.1. Materials and methods

Natural lutetium oxide (spectroscopic grade, >99.99% pure, 2.6% ^{176}Lu) used as the target for production of ^{177}Lu was obtained from American Potash Inc., USA. EDTMP and DOTMP were synthesized in-house as per

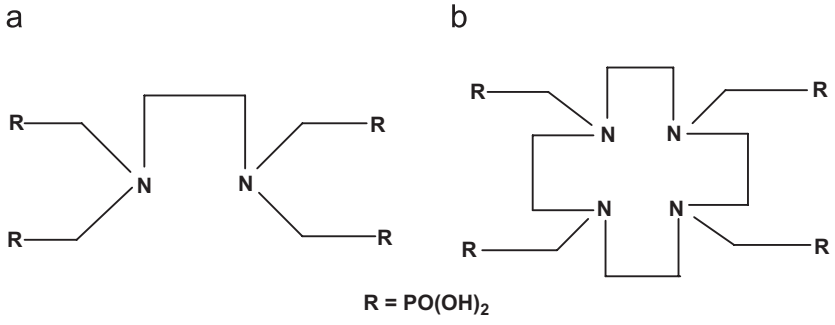

Fig. 1. Structure of (a) EDTMP and (b) DOTMP.