Clin Transl Imaging (2015) 3:167–168
DOI 10.1007/s40336-015-0099-x

SPOTLIGHT

The emerging potential of ^{177}Lu-EDTMP: an attractive novel option for radiometabolic therapy of skeletal metastases

Sara Mazzarri · Federica Guidoccio · Giuliano Mariani

Received: 23 December 2014 / Accepted: 6 January 2015 / Published online: 22 January 2015

Between 60 and 84 % of patients with solid cancers develop bone metastases, the main complication that severely impairs quality of life and performance status and constitutes one of the major challenges of oncological practice. Among other palliative treatments, therapy with bone-seeking radiopharmaceuticals is part of the armamentarium available in the clinical setting to treat bone pain caused by skeletal metastases. Although several radionuclides have been proposed to this purpose, the most widely used radiopharmaceuticals are the β^- emitters ^{89}Sr-chloride and ^{153}Sm-ethylenediamine-tetra-methylene phosphonate (^{153}Sm-EDTMP), while the more recently approved α^{++} emitter ^{223}Ra-chloride plays an increasing role in this scenario.

Based on clinical experience acquired for over two decades, ^{153}Sm-EDTMP has an excellent profile in terms of both efficacy and toxicity, as confirmed by a recent systematic review and meta-analysis of literature on therapy with ^{89}Sr-chloride and ^{153}Sm-EDTMP published between 2001 and 2011 [1]. Compared with an overall efficacy for bone palliation of 70 % (either partial or complete) when used as single agents and 74 % when combined with other therapies, the overall toxicity as single agents was 11 %, mostly reversible mild-to-moderate side-effects. Furthermore, interest is growing also on the potential antitumor efficacy of these agents, especially if combined with chemotherapy agents.

The market cost of ^{153}Sm-EDTMP is a drawback limiting a more widespread use of this radiopharmaceutical in low-income countries, thus reviving interest in earlier studies that had explored the potential of ^{177}Lu as a therapeutic radionuclide to be coupled with EDTMP (US Patent 4898724, 1990. Organic amine phosphonic acid complexes for the treatment of calcific tumors. Wilson DA, Volkert WA, Troutner DE, Goeckeler WF). Lutetium-177 has favorable characteristics such as the low energy β^- emission, which should reduce toxicity, and a 6.73 day half-life, which is advantageous for the distribution logistics to distant areas. Moreover, the most important feature which makes the production of ^{177}Lu especially attractive is the very high thermal neutron capture cross-section of the target ^{176}Lu, through the reaction ^{176}Lu(n,γ)^{177}Lu, the highest (σ = 2,060 barns) among all (n,γ)-produced radionuclides currently used for therapy. Such large cross-section of the reaction ensures that ^{177}Lu can be produced with adequately high specific activity for radionuclide therapy applications even when using moderate flux reactors, as those that can be employed for medical use even in several low-income countries. It also ensures that there will be no constraints in the large-scale production of ^{177}Lu and hence the increasing global demand for this radionuclide in the coming years can be met comfortably. In this regard, enriched ^{176}Lu (with isotopic abundance above 80 %) is relatively inexpensive (200 euros/mg) and available through multiple sources; furthermore, in the long run the cost of ^{177}Lu should decrease significantly, as more producers will entry into the market. Moreover, ^{177}Lu can also be produced through thermal neutron irradiation of natural ^{203}Lu.

Preliminary screening of ^{177}Lu-polyphosphonate complexes suggested that EDTMP has favorable properties to be considered for further investigations. Indeed, biodistribution studies in animals have revealed selective accumulation of ^{177}Lu-EDTMP in the skeleton (up to $\sim$60 % of injected activity) with major renal clearance, while a feasibility clinical study in 10 patients with skeletal

S. Mazzarri · F. Guidoccio · G. Mariani (✉)
Regional Center of Nuclear Medicine, University of Pisa, Via Roma 57, 56126 Pisa, Italy
e-mail: giuliano.mariani@med.unipi.it

metastases confirmed selective tracer accumulation in the skeletal lesions. Although mostly on a pilot study basis, ^{177}Lu-EDTMP has already been evaluated for bone pain palliation in patients with disseminated skeletal metastatic disease; work is also ongoing to develop a freeze-dried EDTMP kit suitable for the preparation of ^{177}Lu-EDTMP, suitable to be used within a 6–9 pH range with ^{177}Lu having specific activity as low as 925 GBq/g.

The favorable perspectives for further pursuing the potential of ^{177}Lu-EDTMP as an alternative option with respect to ^{153}Sm-EDTMP for the treatment of painful bone metastases can be summarized as follows:

- toxicology of the ligand EDTMP is well established;
- ^{153}Sm-EDTMP is already an approved radiopharmaceutical for the same indication, and a large body of evidence acquired in several thousands of patients is available;
- regulators, nuclear medicine physicians and oncologists are familiar with ^{153}Sm-EDTMP, hence their acceptability of ^{177}Lu-EDTMP is likely to be better than for other labeled polyaminophosphates such as ^{177}Lu-1,4,7,10-tetraazacyclododecane-1,4,7,10-tetramethylene phosphonic acid (^{177}Lu-DOTMP);
- rather than an altogether new product, ^{177}Lu-EDTMP might be considered as an analog of ^{153}Sm-EDTMP, a notion that is expected to facilitate fast-track approval procedures for clinical trials with ^{177}Lu-EDTMP.

Two pilot phase I/II clinical trials in limited groups of patients have recently reported significant reduction of bone pain scores, reduction in the use of major analgesics, improved mobility, and overall improved quality of life, even after administration of an activity as low as 18.5 MBq/kg body weight (or 0.5 mCi/kg) of ^{177}Lu-EDTMP—versus a standard activity of 37 MBq/kg as derived from experience with ^{153}Sm-EDTMP [2, 3].

Even more interesting are the results of a larger phase II clinical trial whereby the authors have assessed the efficacy and safety of ^{177}Lu-EDTMP for pain palliation in patients with bone metastases from castration-resistant prostate or from breast cancer, also comparing low-dose and high-dose ^{177}Lu-EDTMP (i.e., 18.5 versus 37 MBq/kg) [4]. The study included 44 patients who were randomized into two equal groups for the two ^{177}Lu-EDTMP dose levels. The overall response rate was 86 %; in particular, complete, partial and minimal responses were seen in 6 patients (13 %), 21 patients (48 %), and 11 patients (25 %), respectively. As to tumor type, favorable response was seen in 84 % of the prostate cancer patients and in 92 % of the breast cancer patients. Bone pain decreased significantly ($P < 0.001$) up to 16 weeks after administration (with maximum effect at 4–8 weeks), with ensuing improvement in quality of life; median duration of response was 3 months. Overall survival at one year post-treatment was 35 and 38 % in the two dose level groups, an important finding considering that all these patients had progressive disease at the time of treatment with ^{177}Lu-EDTMP. Mild hematological toxicity (grade I/II) was observed in 34 % of patients, while it was grade III/IV in 23 %. Interestingly, no differences in response of bone pain and in the other parameters considered for efficacy and toxicity was observed between the low-dose and the high-dose groups.

Thus, ^{177}Lu-EDTMP is emerging as a novel radiopharmaceutical for radionuclide-targeted therapy in patients with disseminated bone metastases from different types of cancer (primarily prostate and breast cancer). The major advantage of Lutetium-177 is the possibility to prepare it in large quantities, even in low-income countries, by "direct" neutron activation of an enriched target that is commercially available at a relatively low cost (Lutetium-176), or even using native Lutetium-203. Although the few clinical trials so far completed regarding therapy with ^{177}Lu-EDTMP have shown considerable efficacy and limited toxicity of this treatment, this observation must be validated by further large-scale studies directly comparing this agent with the other radiopharmaceuticals that are currently available commercially.

The promising results of the preliminary clinical trials described above have prompted an ongoing multicenter international phase II clinical trial sponsored by the International Atomic Energy Agency (IAEA, Vienna, Coordinated Research Project E1.30.33); the final results of this study are expected to shed further light on the actual perspectives of ^{177}Lu-EDTMP for efficient and convenient therapy of patients with painful skeletal metastases.

Conflict of interest Sara Mazzarri, Federica Guidoccio and Giuliano Mariani declare no conflict of interest.

Human and animal studies This article does not contain any studies with human or animal subjects performed by any of the authors.

References

1. D'Angelo G, Sciuto R, Salvatori M, Sperduti I, Mantini G, Maini CL, Mariani G (2012) Targeted "bone-seeking" radiopharmaceuticals for palliative treatment of bone metastases: a systematic review and meta-analysis. Q J Nucl Med Mol Imaging 56:538–543
2. Yuan J, Liu C, Liu X, Wang Y, Kuai D, Zhang G, Zaknun JJ (2013) Efficacy and safety of ^{177}Lu-EDTMP in bone metastatic pain palliation in breast cancer and hormone refractory prostate cancer: a phase II study. Clin Nucl Med 38:88–92
3. Shinto AS, Shibu D, Kamaleshwaran KK et al (2014) ^{177}Lu-EDTMP for treatment of bone pain in patients with disseminated skeletal metastases. J Nucl Med Technol 42:55–61
4. Agarwal KK, Singla S, Arora G, Bal C (2015) ^{177}Lu-EDTMP for palliation of pain from bone metastases in patients with prostate and breast cancer: a phase II study. Eur J Nucl Med Mol Imaging 42:79–88