Development of $^{177}$Lu-Based Agents for Targeted Radiotherapy: Laboratory to Clinics

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Abstract: In the last one and half decade, $^{177}$Lu has emerged as one of the most important and useful radionuclides for the development of a wide variety of targeted radiotherapy agents owing to its suitable nuclear decay characteristics, comparatively longer half-life and production feasibility using medium flux research reactors. Radiopharmaceuticals Division (RPhD), BARC has done pioneering work in the field of production of clinical-grade $^{177}$Lu and development of $^{177}$Lu-based agents for targeted radiotherapy and palliative care. The efforts undertaken by the author and his colleagues in the past 15 years have paved the way towards the development of several potential radiopharmaceuticals and freeze-dried kits. A few of these radiotherapeutic agents and lyophilized kits are being regularly used in various hospitals of our country for the treatment of cancer patients. This has not only ensured the availability of some state-of-the-art radiopharmaceuticals in our country, but also helped to make such radiotherapeutic modalities affordable to the cancer patients.

Key words: $^{177}$Lu, Bone pain palliation, Targeted radiotherapy, EDTMP, DOTMP, DOTA-TATE, PSMA-617, Freeze-dried kit

Introduction: Radionuclide therapy (RNT) using target-specific radiopharmaceuticals has been in existence for over sixty-five years for the treatment of thyroid cancer primarily due to the efficacy and ease of using radioiodine ($^{131}$I) [1]. Other than the applications in tumor therapy, targeted RNT finds applications in certain other diseased states, such as bone pain palliation for improving the quality of life of cancer patients, locoregional applications for treatment of liver cancer and radiation synovectomy for patients with rheumatoid arthritis [2]. The development of new and improved approaches for targeted radionuclide therapy is currently one of the most intensively pursued areas of radiopharmaceutical research. Recent advances in this area exploit the diversity of receptor-avid and immune-derived molecular vectors as well as a plethora of therapeutic radionuclides. In order to ensure the wider use of radiopharmaceuticals, it is essential to carefully consider the choice of radionuclides for a particular application. The criteria for the selection of a radionuclide for radiotherapy are suitable nuclear decay characteristics, ability to produce with high radionuclidic purity and specific activity as well as amenable chemistry [1,3]. However, the practical considerations in selecting a radionuclide for targeted therapy are the possibility to produce the radionuclide with high specific activity at low production cost and comfortable delivery logistics.

In the last one and half decade, therapeutic radionuclide $^{177}$Lu has emerged as one of the prime candidate for developing various types of radiotherapeutic agents [4]. Suitable nuclear decay characteristics [$E_{\beta_{\text{max}}}$ = 0.49 MeV, $E_{\gamma}$ = 208 keV (11%), 113 keV (6.4%)], comparatively longer half-life ($T_{1/2}$ = 6.71 d) along with its easy and cost-effective production feasibility with adequately high specific activity and radionuclidic purity using medium flux research reactors have made this isotope as one of the most widely used radionuclide, a close next to $^{131}$I, for non-thyroidal applications in RNT [4]. Moreover, possibility of using $^{177}$Lu for theranostic applications, which enables the use of same agent for diagnosis or staging of the disease during the course of
radionuclide therapy, are added advantages while using it for targeted RNT applications [5].

While the use of $^{177}$Lu for radiotherapy has been reported earlier by a few researchers, the concerted efforts to explore the potential applicability of this isotope in designing agents for therapeutic applications, more specifically targeted radiotherapy, was initiated in 2000, in the Radiopharmaceuticals Division, BARC [1]. A logical outcome therefore led to research towards envisaging methods to produce this logistically suitable radioisotope in adequate quantities and specific activities using the present reactor facilities in our Institute. The first (n,$\gamma$) irradiation of natural Lu$_2$O$_3$ target to produce $^{177}$Lu was carried out in 2000, following which the production of high specific activity $^{177}$Lu from enriched target was attempted in mid 2001 [6]. Owing to the extensive research on standardizing the production methodology of this isotope, high specific activity clinical-grade $^{177}$LuCl$_3$ had emerged as a new radiochemical for commercial deployment to nuclear medicine centres all over India.

$^{177}$Lu-based agents for bone pain palliation: Skeletal metastasis is one of the most common complications experienced by the patients suffering from prostate, breast and lung cancer at the advanced stage of their disease [7]. It is reported that 80-85% of patients with advanced breast or prostate cancer are likely to develop bone metastases [8]. These metastatic skeletal lesions often lead to excruciating pain and have a very detrimental impact on the quality of life of these patients. This clinical condition can lead to pathological fractures, immobility, hypercalcemia, neurological deficits and severe psychological trauma [7,8]. Such patients are subjected to palliative care, the major objective of which is to alleviate the pain and thus improving the quality of life enjoyed by these patients.

Clinical management of bone pain arising out of skeletal metastases is a challenging task and usually carried out through a multimodality approach which includes use of analgesics medications, cytotoxic chemotherapy, hormone-deprivation therapy, radiation therapy as well as administration of bisphosphonates and bone-seeking radiopharmaceuticals [7,8]. Although the conventional treatment modalities such as administration of analgesics and external beam radiotherapy are continuing practices, these approaches have multiple side effects. It is reported that amongst the methodologies usually employed for metastatic bone pain palliation, use of bone-seeking radiopharmaceuticals is considered to be the most desirable for the patients having multiple metastatic lesions, as it is most well tolerated by the patients [9].

The major challenge in developing effective agents for palliative treatment of bone pain arising from skeletal metastasis is to ensure the delivery of adequate dose of ionizing radiation at the site of skeletal lesion with minimum radiation induced bone marrow suppression [10]. These in-vivo features are governed by the tissue penetration range and hence on the energies of the $\beta$- particles of the radionuclides used in the radiopharmaceutical preparations [10]. The important attributes of $^{177}$Lu as an attractive radionuclide for bone pain palliation emerge from its suitable $\beta$- energy which is adequately low and thereby it is expected to cause minimum bone marrow suppression on accumulation in skeletal lesions [4]. Therefore, attempts were made for the development of potential bone pain palliation agents based on $^{177}$Lu.

$^{177}$Lu-EDTMP: It is well reported in the literature that EDTMP (ethylenediaminetetramethylene phosphonic acid, Figure 1) forms stable complexes with different radionuclides [10] and $^{153}$Sm-EDTMP (Quadramet$^\text{®}$) is an already well-established radiopharmaceutical for bone pain palliation [7]. Since Lu$^{3+}$ has similar coordination chemistry as that of Sm$^{3+}$, it is pertinent to envisage EDTMP complex of $^{177}$Lu, expecting the pharmacokinetic properties of the agent to be similar to that of $^{153}$Sm-EDTMP. Therefore efforts were directed to develop $^{177}$Lu-EDTMP as an agent for metastatic bone pain palliation.

EDTMP was synthesized in-house following the reported procedure [11] and characterized by standard spectroscopic techniques. The radiolabeling protocol for the formulation of $^{177}$Lu-EDTMP was standardized and subsequently scaled-up to prepare patient dose equivalent of $^{177}$Lu-EDTMP. Preliminary biological studies were
performed in normal Wistar rats, normal New Zealand white rabbits as well as in diseased dogs [10]. Clinical studies with the agent were carried out in collaboration with AIIMS (All India Institute of Medical Sciences, New Delhi) and KMCH (Kovai Medical Centre and Hospital, Coimbatore).

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Figure 1: Structure of EDTMP

On the other hand, for the easy and convenient preparation of \(^{177}\text{Lu-EDTMP}\) patient dose at the hospital radio-pharmacy, formulation of suitable lyophilized EDTMP kit was also attempted. As the preparation of the agent using the kit requires only the addition of normal saline and \(^{177}\text{LuCl}_3\) in the kit vial prior to incubation at room temperature, the formulation becomes relatively simple at the end user. This also reduces the possibility of contamination, radiation exposure, batch failure as well as the preparation time of the radiopharmaceutical [12]. Freeze-dried EDTMP kits, each comprising a lyophilized mixture of 35 mg EDTMP, 14.1 mg NaOH and 5.8 mg of CaCO\(_3\) was prepared in our facility [12]. The kit was successfully used for the preparation of up to 3.7 GBq (100 mCi) patient dose of \(^{177}\text{Lu-EDTMP}\) with high radiochemical purity [12].

Clinical potency of \(^{177}\text{Lu-EDTMP}\), formulated using the freeze-dried EDTMP kit, was evaluated in human cancer patients in collaboration with KMCH, Coimbatore and RMC (Radiation Medicine Centre), BARC, Mumbai. Figure 2 shows the post-therapy whole-body scans of a prostate cancer patient recorded after administration of \(^{177}\text{Lu-EDTMP}\) (anterior and posterior views). It has now been proven that \(^{177}\text{Lu-EDTMP}\) is effective in providing significant pain relief to patients and the treatment considerably increased their mobility, resulting in an overall improvement in the quality of life [13]. A similar pain response efficacy, similar hematological toxicity profile and absence of renal toxicity exhibited by \(^{177}\text{Lu-EDTMP}\) coupled with almost identical improvement in the quality of life in comparison to those reported with \(^{153}\text{Sm-EDTMP}\) provided conclusive evidences that the agent is clinically safe for pain palliation of patients with disseminated skeletal disease [14].

It is important to mention that the use of both the \(^{177}\text{Lu-EDTMP}\) preparations, namely ready-to-use and that formulated using freeze-dried EDTMP kit, have been approved by the RPC (Radiopharmaceuticals Committee) of DAE (Department of Atomic Energy) for human application. Both these products are now being supplied from BRIT (Board of Radiation and Isotope Technology) for the benefit of the patients needing palliative care.

\(^{177}\text{Lu-DOTMP}:\) Lutetium-177-labeled DOTMP (1,4,7,10-tetraazacyclododecane-1,4,7,10-tetramethylene phosphonic acid) is another bone palliation agent whose clinical evaluation has recently been initiated. DOTMP (Figure 3), the macrocyclic analog of EDTMP, is reported to form complex with \(^{177}\text{Lu}\) with superior thermodynamic stability and improved kinetic inertness [15]. The
agent can be prepared following a simple wet-chemistry protocol akin to that of $^{177}$Lu-EDTMP mentioned above [15] or more conveniently using freeze-dried DOTMP kits [16]. Patient dose of $^{177}$Lu-DOTMP was prepared by using freeze-dried DOTMP kit, developed in-house, comprising 20 mg of DOTMP and 8.75 mg of NaOH in the lyophilized form [17]. Clinical evaluation of this agent is presently being carried out in collaboration with three nuclear medicine centres in India, namely, KMCH (Coimbatore), PGIMER (Post Graduate Institute of Medical Education and Research, Chandigarh) and AIIMS (New Delhi). Figure 4 shows the post-therapy whole-body scans of a patient recorded after administration of $^{177}$Lu-DOTMP (anterior and posterior views). Satisfactory pain palliation was achieved starting from 6th day post-administration and none of the patients have shown any significant hematological toxicity till date. Although the clinical studies, conducted till date, are limited by the number of patients recruited, the preliminary data obtained so far indicates the potential of the agent to emerge as an alternative radiopharmaceutical for bone pain palliation. The proposal seeking clearance of using freeze-dried DOTMP kits for the formulation of $^{177}$Lu-DOTMP for human administration has already been submitted to RPC. It is expected that RPC approval for the regular manufacture and supply of lyophilized DOTMP kits for the clinical use of $^{177}$Lu-DOTMP will be obtained in the near future.

![Figure 3: Structure of DOTMP](image)

![Figure 4: Whole-body scintigraphic images of a patient treated with $^{177}$Lu-DOTMP (Image courtesy: Dr. Ajit Shinto, KMCH, Coimbatore)](image)

$^{177}$Lu-DOTA-TATE for peptide receptor radionuclide therapy: Peptide receptor radionuclide therapy (PRRT) using radiolabeled somatostatin analogues is a novel therapeutic modality for the treatment of somatostatin receptor-positive tumors [18]. PRRT using $^{177}$Lu-DOTA-TATE, (TATE is a somatostatin analog octapeptide, Tyr$^3$-Octreotate, Figure 5) is now an established therapeutic modality for the treatment of patients suffering from a wide variety of inoperable neuroendocrine cancers [18]. In the last decade, PRRT has gained momentum and at present is being routinely used as a therapeutic regimen in a limited number of countries. In India, PRRT employing $^{177}$Lu-DOTA-TATE has been in regular use since 2008 and till date few thousand patient doses have been administered in thirteen nuclear medicine centres across the country [19]. India, with a large population, has a significant number of patients who require PRRT and the treatment needs to be provided at a reasonable cost due to the poor affordability of a large mass of population. This required the formulation of the agent using $^{177}$Lu obtained via the more economical and indigenously produced direct (n,$\gamma$) route using enriched $^{177}$Lu as the target [4]. However, specific activity of $^{177}$Lu produced following this route varies significantly from batch to batch due to the
variable operating conditions of the reactor (scheduled and unscheduled shut-downs, power fluctuation etc.) and variation in irradiation cycles used. Additionally, variation in logistical factors such as transportation delay, the distance of the hospitals from the radionuclide production site, date and time of actual administration etc. contribute to the variation in the specific activity of $^{177}$Lu available to the end user [19]. Therefore, the radiopharmaceutical challenge associated with PRRT using $^{177}$Lu-DOTA-TATE lies in its preparation with adequately high specific activity so that the required dose could be deposited in the cancerous lesions without saturating the limited number of receptors available on the target [20]. Accordingly, a suitable method for the preparation of patient dose of $^{177}$Lu-DOTA-TATE was developed in our laboratory [21] and the methodology had been successfully demonstrated to various nuclear medicine centres in India. Figure 6 shows the post-therapy whole-body scans of a neuroendocrine cancer patient recorded after administration of $^{177}$Lu-DOTA-TATE (anterior and posterior views).

$^{177}$Lu-PSMA-617 for treatment of prostate cancer: Prostate cancer is the sixth leading cause of cancer related deaths and is estimated to be the second most frequently encountered cancer in males worldwide [22]. Therefore, development of suitable and efficient therapeutic agents is of high clinical importance, specifically, to combat the metastatic and hormone refractory prostate carcinoma. Prostate-specific membrane antigen (PSMA) is a surface protein that is usually present on healthy prostate cells and significantly over-expressed on prostate cancer cells [23]. In prostate cancer, PSMA expression has been shown to correlate with disease progression, with highest levels expressed in hormone-refractory and metastatic disease [24]. Moreover, pathology studies have shown that PSMA is expressed by virtually all types of prostate cancers and PSMA-negative prostate carcinoma are relatively rare [25].

During the last two decades, significant work has been carried out in order to develop suitable low molecular weight prostate-specific ligands, which can be labeled with diagnostically or therapeutically important radionuclides [26]. Amongst these prostate-specific ligands, PSMA-617 (Figure 7) developed at the German Cancer Research Center of Heidelberg (DKFZ), has emerged as the most promising PSMA vector till-date. This molecule is reported to exhibit strong binding affinity to PSMA and demonstrated highly...
efficient internalization in prostate carcinoma cells [26]. Therefore, use of DOTA (1,4,7,10-tetraaza-cyclododecane-1,4,7,10-tetraacetic acid) coupled PSMA-617, which enables its labeling with either diagnostically ($^{68}$Ga) or therapeutically (radiolanthanides) useful radionuclides, have opened up a new avenue in the management of prostate cancer.

Therefore, efforts were directed to standardize the methodology of formulation of patient dose of $^{177}$Lu-PSMA using the indigenously produced $^{177}$Lu. Patient dose of 7.4 GBq (200 mCi) of $^{177}$Lu-PSMA-617 was prepared with high radiochemical purity under the optimized reaction protocols and necessary biological evaluations were carried to facilitate the clinical translation of the agent [26]. Clinical evaluation of the agent in prostate cancer patients, having proven PSMA expression in primary and metastatic lesions, was initiated in collaboration with Jaslok Hospital and Medical Research Centre, Mumbai. Figure 8 shows the post-therapy whole-body scans of a prostate cancer patient (with extensive skeletal metastases) recorded after administration of $^{177}$Lu-PSMA-617 (anterior and posterior views). Our effort towards clinical translation of this potential agent using the indigenously produced $^{177}$Lu has ensured the availability of this agent at a comparatively much lower price to the cancer patients of India within 1-2 years of its first clinical utilization. The therapeutic efficacy of $^{177}$Lu-PSMA in treating prostate cancer patients is presently being evaluated in few reputed nuclear medicine centres of India.

Conclusion
$^{177}$Lu has been pursued with great interest for therapy in many countries all over the world, owing to its attractive features detailed earlier and in the last one and half decade it has emerged as one of the prime radioisotopes for developing agents for targeted radiotherapy. Our modest beginning in clinical deployment of this radioisotope for treating patients a decade ago has now grown into a robust program, which is reflected in the continuous increase of demand of clinical-grade $^{177}$Lu, presently supplied through BRIT. Extensive research carried out with this radionuclide in the Radiopharmaceuticals Division, BARC in the past ten years has helped in development of several important radiopharmaceuticals, such as $^{177}$Lu-EDTMP and $^{177}$Lu-DOTMP for bone pain palliation, $^{177}$Lu-DOTA-TATE for treatment of neuroendocrine cancers, $^{177}$Lu-PSMA-617 for treatment of prostate cancer. This has ensured the availability of state-of-the art $^{177}$Lu-based radiopharmaceuticals in India at an affordable cost and thus helped the much-needed radiotherapeutic intervention to reach a wider mass of cancer patients of our country.
References


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