Preparation of \([{}^{177}\text{Lu}]\text{PSMA-617}\) Using Carrier Added (CA) \(^{177}\text{Lu}\) for Radionuclide Therapy of Prostate Cancer

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Abstract

Objective: Lutetium-177 labelled PSMA-617 is an emerging radiopharmaceutical for targeted radionuclide therapy of prostate cancer (PCa) and hence there is an interest in the formulation and clinical application of this novel tracer. This paper summarises the studies undertaken to prepare clinical doses of \([{}^{177}\text{Lu}]\text{PSMA-617}\) for therapy of prostate cancer patients.

Experimental: \([{}^{177}\text{Lu}]\text{PSMA-617}\) was prepared by reacting \(177\text{LuCl}_3\) (5.4 GBq to 15.8 GBq, specific activity 650 MBq/μg to 860 MBq/μg) with 100 μg to 300 μg of PSMA-617 at pH 4.5-5. Radiochemical (RC) yields were estimated by thin layer and paper chromatography. When RC yields were lower than 95% the product was purified using a C18 cartridge which removed unreacted \(177\text{LuCl}_3\). Two patients having histopathologically proven PCa and having significant levels of metastasis were given freshly prepared \([{}^{177}\text{Lu}]\text{PSMA-617}\).

Results: \([{}^{177}\text{Lu}]\text{PSMA-617}\) could be prepared in high yields using CA low specific activity \(177\text{Lu}\) and using modest amounts of ligand. Purification using a C18 cartridge provided the product with high RC purity. The product formed was stable for several days when stored at 4°C. SPECT images acquired post therapy showed that the \([{}^{177}\text{Lu}]\text{PSMA-617}\) accumulated in most lesions identified by \(^{68}\text{Ga}\text{PSMA-11 PET-CT imaging. No redistribution of activity accumulated in lesions was seen in images acquired up to 7th day, post therapy. Therapy was well tolerated by the patients with no adverse reaction reported.}

Conclusion: The studies carried out suggest that therapeutic doses of \([{}^{177}\text{Lu}]\text{PSMA-617}\) could be prepared by using low specific activity, carrier added \(177\text{Lu}\). Clinical studies demonstrated the uptake and retention of the tracer in prostate cancer lesions.

Keywords: Enzyme inhibitor; Lutetium-177; \([{}^{177}\text{Lu}]\text{PSMA-617}\); PET-CT imaging; Prostate cancer; Radionuclide therapy

Introduction

Prostate cancer (PCa) is one of the major cancers affecting men and a significant population of elderly patients suffers from this the world over. There are several options such as prostectomy, orchidectomy, chemotherapy and radiation therapy to treat PCa [1,2], targeted radionuclide therapy is emerging as an option to treat patients having multiple metastasis.

Targeted therapy using bone seeking agents such as \(^{89}\text{SrCl}_2\), \(153\text{Sm-EDTMP}\) or \(^{188}\text{Re-HEDP}\) is in vogue for over 30 years for palliative treatment of advanced PCa patients [3]. However, this class of tracers is not taken up by the primary or soft tissue lesions. The discovery and cloning of prostate specific membrane antigen (PSMA) as well as the fact that PSMA is over expressed in PCa cells has opened the possibility of using it as the target for radiopharmaceuticals [4,5]. Prostascint\(^*\) is the first tracer of this category which is an \(111\text{In}\) labelled monoclonal antibody (Capromab) targeting an intracellular portion of the enzyme [6]. Yttrium-90 and \(177\text{Lu}\) labelled J591, a humanized monoclonal antibody targeting the extracellular portion of PSMA was used for targeted therapy of hormone and chemo-refractory prostate cancer [7]. However, the above products did not penetrate into large scale clinical practice. Monoclonal antibodies being macromolecules show slow pharmacokinetics thereby taking long time to reach the target and hence not the ideal vector for carrying radionuclides which exponentially decay as time passes.

The ability of certain molecules called enzyme inhibitors to block the reaction of the enzyme with the substrate is widely taken advantage for the discovery of new drugs [8]. Several low molecular weight inhibitors have been developed for the enzyme PSMA also called glutamate carboxypeptidase II (GCPII) as it is responsible for the release of the neurotransmitter glutamate [9-11]. Radiolabelling of such inhibitor molecules has resulted in the development of several radiotracers for SPECT and PET-CT imaging of prostate cancer [5,12]. \(^{68}\text{Ga}\text{PSMA-11, introduced by the German Cancer Research Centre, is one such tracer which is finding wide clinical use [13,14]. This radiopharmaceutical uses a remarkably simple yet potent molecule, Lys-urido-Glu which is attached to a chelating molecule called HBED-CC}.\)

\(\left(N,N'-\text{bis[2-hydroxy-5-(carboxyethyl)benzyl]ethylene diamine-}N,N'\text{-diacetic acid}\right)\) through a spacer [13,15]. The same group developed another molecule, PSMA-617[\(2-[3-(1-\text{Carboxy-5-[3-naphthalen-2-yl-2-[(4-[(2-(4,7,10-tris-carboxymethyl-1,4,7,10-tetraaza-}
\text{cyclohexanecarbonyl})-amino]}
\text{propionylamino]-methyl]-}
\text{acetylaminol-methyl]-}
\text{propionylamino]-pentyl]-ureido}]\).
tetraethylenepentanedioc acid) having DOTA attached to Lys-uriedo-Glu molecule through another linker molecule. Figure 1 gives the structure of PSMA-617 and PSMA-11. The two phenolic groups in the HBED-CC are responsible for imparting favourable lipophilicity to PSMA-11. As DOTA chelating agent is hydrophilic two phenyl groups are introduced in the spacer molecule to induce lipophilicity to PSMA-617. The chelating agent DOTA is capable of radiolabelling radionuclides such as ⁶⁸Ga, ⁹⁰Y or ¹⁷⁷Lu [16]. The favourable biokinetic properties of PSMA-617 has been reported by PET-CT imaging with [⁶⁸Ga]PSMA-617 [17]. Preliminary results of the clinical studies are emerging from multiple centres [18-28].

![Figure 1: The structure of PSMA-617 used for ¹⁷⁷Lu labelling for therapy (top) and PSMA-11 used for labelling with ⁶⁸Ga for PET-CT imaging (bottom).](image-url)

The preparation of ¹⁷⁷LuPSMA-617 can be done relatively easily thanks to advances in ¹⁷⁷Lu chemistry in the last 20 years [29]. The current practice in most countries is to prepare ¹⁷⁷Lu agents in the radio pharmacy of the nuclear medicine departments using commercially available ¹⁷⁷LuCl₃ and ligands. Hence, development of robust standard operating procedures that give consistently high yields and high radiochemical purity is important. This is critical while preparing ¹⁷⁷Lu agents for targeted therapy as the specification of ¹⁷⁷LuCl₃ vary significantly from manufacturer to manufacturer.

Lutetium-177 is available from several suppliers and the product comes under two different categories, non-carrier added (NCA) or carrier added (CA) depending upon the route of production [30]. NCA ¹⁷⁷Lu has advantages as the specific activity is high (~110 Ci/mg; 19.5 Ci/mol) and post production decay will reduce the activity but have minimum effect on specific activity. However, the specific activity of CA ¹⁷⁷Lu is significantly low and depends on the irradiation conditions as well as the neutron flux of the reactor. Also the reduction in Lu metal content will be less prominent as compared to reduction in activity due to decay. Hence, the specific activity can be very different from the quoted specific activity depending upon the time taken for the product to reach the radio pharmacy. Lutetium-177 having specific activity of ~20 Ci/mg (740 GBq/mg or 3.54 Ci/μmol) is available thanks to local production in the Dhruka reactor using the direct route [31]. This paper describes the preparation of ¹⁷⁷LuPSMA-617 using locally produced CA ¹⁷⁷Lu and its biodistribution in two patients.

**Materials**

PSMA-617 was purchased from ABX Advanced Biochemicals Compounds, Germany. Hydrochloric acid (30%, Suprapur), trisodium citrate dihydrate (Empura), ethanol (Emsure), water (Emsure) and pH paper (MColorpHast, pH 0-6) were from Merck, Germany. Ascorbic acid and sodium ascorbate were (Sigma-Aldrich). C18 light cartridges were purchased from Waters. 0.22 μm pore size syringe filters were of Millipore or Sartorius, Germany. All radioactivity measurements were done using Capintec CRC® 25 dose calibrator or by using a NaI(Tl) solid scintillation counter adjusted for the 106 keV and 211 keV gamma photons.

[⁶⁸Ga]PSMA-11 used for PET-CT imaging studies was prepared in iQs® Ga-68 fluidic labelling module and ⁶⁸Ge/⁶⁸Ga generator purchased from Isotope Technologies Graching (ITG), Germany [32].

¹⁷⁷LuCl₃ having specific activity 23 Ci/mg to 29 Ci/mg (850 MBq to 1070 MBq) at the time of despatch was purchased from Board of Radiation and Isotope Technology (BRIT), Department of Atomic Energy, Mumbai, India.

**Experimental**

**Preparation of reagents**

One mg of PSMA-617 (MW 1042 Da) was dissolved in 1 mL of emsure water and aliquots of 100 μL (100 μg, 96 nmol) were dispensed in 1 mL Eppendorf tubes and frozen at -20°C. Ascorbate buffer for the reaction was prepared by mixing 100 mg of ascorbic acid with 400 mg of sodium ascorbate and dissolving in 5 mL of emsure water. Trisodium citrate was weighed for 1.47 g and dissolved in 50 mL of Emsure water, 500 μL of 30% HCl was added to this solution to give a final pH ~5-5.5 and was used for thin layer chromatography.

**Preparation of ¹⁷⁷LuPSMA-617**

¹⁷⁷LuPSMA was prepared by addition of (200 μg to 300 μg) of PSMA-617 to one mL of ascorbate buffer (pH ~4.5-5). ¹⁷⁷LuCl₃ (200 μL to 400 μL) was added to the solution and the pH of the solution was confirmed to be 4.5-5.0. The reaction mixture was heated for 30 min at 95°C in a water bath. An aliquot of the reaction mixture was withdrawn for estimation of radiochemical yields as discussed in the next section.

When the radiochemical yield was <95%, a C18 cartridge purification was performed. The C18 cartridge used for purification was conditioned by passing 5 mL of 70% ethanol followed by 10 mL of Emsure water. A membrane filter used for sterilization of the product was conditioned by passing 2 mL of 60% ethanol. The waste vial.

A vent was created by plunging a sterile needle through the rubber septum of the collection vial. The product was eluted by passing 1 mL of 70% ethanol followed by 5 mL of 0.9% saline solution. The products not needing purification was passed through a 0.22 micron membrane filter for sterilization. At the end of synthesis, the activity in the
product, waste, cartridge and filter were measured using the dose calibrator.

Quality control

Thin layer chromatography (TLC) and paper chromatography (PC) were used for estimating the RC yields and RC purity. TLC was done on a 7 cm × 1 cm ITLC-SG sheet. A 5 μL aliquot of the reaction mixture or the purified product was spotted about 1.5 cm from one end of the strip and the strip was developed in sodium citrate buffer till the solvent migrated to the top. PC was done on a 10 cm × 1 cm Whatman 3 MM chromatography sheet. A 5 μl aliquot of the reaction mixture was spotted and the paper was developed in 1:1 (v/v) acetonitrile: water mixture. TLC and PC strips were cut into three pieces, point of spotting, middle and solvent front. The activity in the strips was estimated using a dose calibrator. At lower activity levels the strips were counted in a NaI(Tl) well counter.

Patient studies

Patients for \([^{177}\text{Lu}]\text{PSMA-617}\) therapy were referred from the Oncology Department of the Hospital. The tumour board of the Institution discussed every case prior to approval for therapy. Patients with proven chemo/hormone refractory PCa and progressive disease were approved for this procedure.

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Age (yr)</th>
<th>Brief history</th>
<th>Gleason score</th>
<th>PSA ng/ml</th>
<th>Activity administered (mCi)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>65</td>
<td>Metastatic PCa underwent bilateral orchidectomy, radiotherapy and 6 cycles of chemotherapy.</td>
<td>9/10</td>
<td>58.7</td>
<td>128 (4.7 GBq)</td>
</tr>
<tr>
<td>2</td>
<td>76</td>
<td>Metastatic PCa underwent hormonal treatment.</td>
<td>8/10</td>
<td>4.4</td>
<td>184 (6.8 GBq); 195 (7.2 GBq)</td>
</tr>
</tbody>
</table>

@ Second cycle after 11 weeks

Table 1: Clinical history of the patients who underwent \([^{177}\text{Lu}]\text{PSMA-617}\) therapy.

The patients underwent \([^{68}\text{Ga}]\text{PSMA-11}\) PET-CT imaging to document the extent of metastasis. The inclusion criteria were a Karnofsky score >60; creatinine ≤ 1.7 mg/dl; WBC > 4000/μL; platelets > 75000/μL; RBC > 300000 and hemoglobin >9g/dl. A detailed information sheet explaining the therapy procedure was provided to the patient and relatives on first consultation for therapy. An informed consent was obtained on the day of therapy. Relevant details of the first two patients who received \([^{177}\text{Lu}]\text{-PSMA-617}\) are given in Table 1.

Hemodynamic parameters of the patients are recorded prior to therapy. A resuscitation cart and trained emergency team was kept ready. Premedication included intravenous administration of 8 mg of Ondansetron and dexamethasone. 1000 ml to 1200 mL of amino acid infusion (lysine 22.3 mg/mL and arginine 8.0 mg/mL) was started 30 min before the \([^{177}\text{Lu}]\text{PSMA-617}\) infusion and continued till 3.5 h after the termination of activity infusion. \([^{177}\text{Lu}]\text{PSMA-617}\) was diluted in normal saline solution to a volume of 20 mL and infused by means of an indwelling IV catheter in about 30 min. The line is flushed with normal saline after completion of the radiotracer infusion. Five hundred mL of 0.9% saline solution was administered intravenously before and after administration of \([^{177}\text{Lu}]\text{PSMA-11}\).

Whole body SPECT imaging was done using a low energy all purpose (LEAP) collimator using 208 keV gamma photons of \(^{177}\text{Lu}\). Scanning time of 30 min was used in a Siemens Ecam Signature series dual head camera. Whole body images or spot views of the upper abdomen and all involved sites are acquired at three time points, preferably at 24 h, 72 h and 7 day post-injection. Pathological parameters such as CBC, RFT and LFT were estimated at intervals after therapy.

Results

Preparation of \([^{177}\text{Lu}]\text{PSMA-617}\)

During the course of this study, three batches of \([^{177}\text{Lu}]\text{PSMA}\) were prepared for therapy; the results of which are summarized in Table 2. The radiopharmaceutical is prepared immediately after receipt of \(^{177}\text{LuCl}_3\) at which time the decay corrected specific activity was 17.7 Ci/mg to 23.3 Ci/mg (654 MBq/mg to 860 MBq/mg). The first batch was prepared with 148 mCi (5.45 GBq) of \(^{177}\text{Lu}\) and 100 μg of peptide. The radiochemical yield estimated at the end of synthesis was only 68% and hence an additional 100 μg of ligand was added and heated for another 15 min.

Table 2: Details of the preparation of \([^{177}\text{Lu}]\text{PSMA-617}\) using CA \(^{177}\text{Lu}\).

<table>
<thead>
<tr>
<th>Specific activity of (^{177}\text{Lu}) (Ci/mg)</th>
<th>Activity used (mCi)</th>
<th>([^{177}\text{Lu}]) (nmol)</th>
<th>Amount of ligand (μg)</th>
<th>[Ligand] (nmol)</th>
<th>M:L ratio</th>
<th>RC (%)</th>
<th>yield (%)</th>
<th>RC purity (%)</th>
<th>Specific activity (^{177}\text{Lu}) (mCi/μg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. 23.35</td>
<td>148</td>
<td>0.036</td>
<td>100</td>
<td>0.096</td>
<td>2.66</td>
<td>68.0</td>
<td>-</td>
<td>-</td>
<td>1.065</td>
</tr>
<tr>
<td>2. 23.35</td>
<td>148</td>
<td>0.036</td>
<td>200</td>
<td>0.192</td>
<td>5.32</td>
<td>100</td>
<td>100</td>
<td>0.74</td>
<td></td>
</tr>
<tr>
<td>3. 17.74</td>
<td>428</td>
<td>0.136</td>
<td>300</td>
<td>0.288</td>
<td>2.11</td>
<td>89.1</td>
<td>99.0</td>
<td>1.27</td>
<td></td>
</tr>
<tr>
<td>4. 18.71</td>
<td>213</td>
<td>0.084</td>
<td>200</td>
<td>0.192</td>
<td>2.98</td>
<td>99.7</td>
<td>99.9</td>
<td>1.065</td>
<td></td>
</tr>
</tbody>
</table>

The radiochemical yield increased to 100%. The metal-ligand (M:L) ratio in the final preparation was 1:5.36. The product was used without purification. In the second batch, 428 mCi (15.8 GBq) of \(^{177}\text{Lu}\) was used with 300 μg of ligand (M:L: 2.11) and a radiochemical yield of 89% could be obtained. Purification through cartridge was done and 87% of the product was recovered which had an RC purity of 100%. The third batch was prepared with 213 mCi (7.8 GBq) of activity and 200 μg of peptide; final metal ligand ratio was 1:2.98. The
radiochemical yield was 100% and hence no purification was done in this batch of product. From the limited number of batches done in these studies it is difficult to accurately predict the desired M:L for quantitative complexation however maintaining a ratio of 1:3 could yield good high radiochemical yields.

Purification

The results of the purification study (n=1) suggest that the C18 cartridge purification developed is adequate for the removal of unreacted \(^{177}\)LuCl\(_3\) from the final product. Near quantitative recovery of the product could be achieved.

Quality control

We adapted two solvent systems for the quality control of \(^{177}\)LuPSMA-617. In TLC, \(^{177}\)LuPSMA-617 is retained at point of spotting whereas free \(^{177}\)Lu moves to the solvent front. In PC, \(^{177}\)Lu-PSMA-617 moves to the solvent front and free \(^{177}\)Lu remains at the point of spotting. This dual chromatography procedure having different migration pattern for the labelled ligand and free \(^{177}\)Lu is found very useful for estimating the yield as well as radiochemical purity of the product. The radiochemical yields and radiochemical purities obtained for different batches were identical in both the chromatography techniques as well as consistent with the activity recovered after cartridge purification.

Stability studies

Stability of the purified product stored at 4°C was estimated over a period of 7 days, by estimating the RC purity by performing PC and TLC. The product was in saline media and contained 3% to 5% ethanol. The product was found to be stable over the time period studied (Figure 2). The stability of an un-purified batch was lower as the RC purity fell to 92% over a period of 3 days.

Clinical studies

The patients underwent \(^{68}\)GaPSMA-11 PET-CT imaging prior to therapy to assess their suitability for getting therapy. Post therapy, SPECT imaging were done at 24 h, 72 h and on the 7th day. Figure 3 gives the results of the imaging studies of Patient 1. In PET-CT imaging (Figure 3A), intense tracer uptake is seen in lymph nodes, bone and liver with a mild tracer uptake in left lobe of lung. 128 mCi (4.73 GBq) of activity was administered in the isolation ward of the nuclear medicine department following a protocol developed by the authors based on the experience with \(^{177}\)LuDOTATATE therapy [33].

![Figure 3: PET-CT image of head (A) and abdomen (C) region taken 1 h post injection of tracer. SPECT images of head (B) and abdomen (D) region, taken 24 h after therapy.](image)

![Figure 4: MIP projection PET-CT imaging at one hour post administration of 3.24 mCi (120 MBq) of \(^{68}\)GaPSMA-11 in Patient 1. Whole body SPECT images after administration of 128 mCi (4.7 GBq) of \(^{177}\)LuPSMA after 24 h (B), 72 h (C) and 7 days (D).](image)

SPECT images taken 24 h, 72 h and 7th day post administration are given in Figure 3B, 3C and 3D, respectively.

Uptake of the $^{177}$LuPSMA-617 in all the lesions identified in PET-CT imaging could be observed. In one hour PET-CT images, the tracer uptake was more intense in the salivary and lachrymal glands than in the occipital bone (Figure 4A).

However, in 24 h SPECT images (Figure 4B) the tracer intensity was higher in the occipital bone rather than in the salivary and lachrymal glands. Correspondingly higher tracer uptake seen in soft tissues and other organs in PET-CT images (Figure 4C) was not seen in SPECT images (Figure 4D). The patient did not complain of any discomfort during or after administration of the tracer. The patient was discharged after 24 h at which time the radiation dose at 1 metre was ~ 1 μSv.

The patient was recalled for examination as well SPECT imaging on 3rd and 7th day post therapy. The lesion accumulated activity did not redistribute as time passed. More over the whole body images are clean except activity in the lesions depicting a good target to background ratio.

![Figure 5](image)

**Figure 5**: (A): Patient 2: MIP projection PET-CT imaging at one hour post administration of with 3.03 mCi (112 MBq) of $^{68}$GaPSMA-11. Whole body SPECT images after administration of 184 mCi (6.8 GBq) of $^{177}$LuPSMA-617 after 24 h (B), 72 h (C) and 7 days (D).

Patient 2 was 76-year old male who underwent hormonal therapy. In PET-CT imaging, the patient showed tracer uptake in the right half of prostate as residual primary (Figure 5 A). Intense tracer concentration was seen in bilateral external iliac lymph nodes (SUVmax of 43.6 on the right side, measuring 1.45 cm × 1.29 cm in size). Bone metastasis was seen in left scapula, right 6th rib, L5 vertebra and sacrum near right SI joint.

Tracer uptake was also seen in a large hypodense lesion in the right lobe of the liver. SPECT images taken 24 h, 72 h and 7 day post therapy are given in Figure 5B-SD, respectively. Uptake and retention of the $^{177}$LuPSMA-617 was seen in most lymph nodes and bone metastasis identified in PET-CT images. This patient had a second cycle of therapy after 11 weeks; and the SPECT images obtained post 2nd cycle of therapy showed very similar pattern. Both the above patients are under follow up.

**Discussion**

Radionuclide therapy with radiotracers targeting disease at cellular level is useful for treating cancer that are inoperable and/or metastasised wherein surgery and external beam therapy have limited role and chemotherapy is either not responding or tolerated. In order to develop radiopharmaceuticals for targeted therapy, one of the biochemical reactions altered during the onset of disease is taken advantage of. The manifestation of the altered biochemical reaction could be the over expression of an antigen, a cellular protein, an enzyme etc. Such over expressed molecules are called tumour markers or simply biomarkers. Biomarkers which are over-expressed during cancer, yet not shed into circulation are ideal for targeting therapeutic radiopharmaceuticals. Radioimmunotherapy (RIT) and peptide receptor radionuclide therapy (PRRNT) are two such modalities which have emerged in the past [34-36]. In RIT, a monoclonal antibody specific to a tumour antigen is labelled with a therapeutic radionuclide ($^{90}$Y or $^{177}$Lu) and administered to deliver the therapeutic radiation dose to the tumour. RIT did not live up to the initial expectation and is only in very limited use. The main problem is the slow pharmacokinetics of the monoclonal antibody as a result of which a major part of the radionuclide decays before the radiopharmaceutical is targeted to tumour.

Targeting cellular receptor proteins over expressed during cancer by using radiolabelled peptides binding to the receptors is another successful strategy proposed in 1978 [35] and exemplified in the use of $^{177}$Lu-DOTATATE for the treatment of neuroendocrine tumors [33]. This mode of therapy commonly known as peptide receptor radionuclide therapy (PRRNT) is yet to be successfully developed for the treatment of any of the major cancers [36]. The major advantage of PRRNT is that it uses relatively small molecular weight peptides and hence the pharmacokinetics is fast, the non-targeted radiopptide is cleared within a short time allowing administration of very high levels of radioactivity without crossing the dose limit set for critical organs.

The concept of using an enzyme inhibitor as the target seeking moiety in radiopharmaceuticals is novel and unexplored till the development of a PSMA inhibitor labelled with the carbon-11, a PET radionuclide [37]. There are a large number of enzymes present in a living system as the chemical reactions required to maintain the body would not occur fast enough without them. However, over expression of these enzymes manifest in the development of several diseases and hence molecules that can inhibit certain specific enzyme reactions are used as drugs.

PSMA is one of the key biomarkers of PCA [38]. Though over expressed during disease, PSMA is not shed into circulation and hence an ideal target for radiotracers. Thanks to the interest in drug discovery a large number of PSMA inhibitor molecules have been developed [8]. Enzyme inhibitors are small molecules smaller than peptides and hence exhibit fast pharmacokinetics as well as fast clearance from non-targeted organs and tissues including muscles and blood.

Among the several class of inhibitor molecules developed for PSMA, Lys-uriedo-Glu has been adapted by several groups for the development of radiopharmaceuticals for SPECT, PET and therapy [5,12]. Among the new tracers, $^{68}$GaPSMA-11 have made a significant leap for PET-CT imaging [13]. PSMA-11 (Figure 1B) used HBED-CC as the chelating agent which while being very good for complexing $^{68}$Ga, it is not useful to chelate $^{177}$Lu. The German Cancer Research Centre which originally developed PSMA-11 came up with another molecule PSMA-617 which has DOTA as the chelating agent.
Preliminary results of radionuclide therapy with $^{177}$LuPSMA-617 are being published and look promising [18-27].

While it is advantageous to use NCA $^{177}$Lu having specific activity approaching theoretical value (110 Ci/mg), the availability is limited and at the same time expensive. Hence, it is necessary to develop protocols to use CA added low specific activity $^{177}$Lu produced by direct method [30]. In India, $^{177}$Lu having specific activity of ~25 Ci (925 MBq)/mg is available. However delivery to outstation nuclear medicine departments takes 48 h by which time the specific activity reduces by 20%. The product is modestly priced and hence preferred.

In this paper we reported the results of synthesis of $^{177}$LuPSMA-617 and the development of appropriate quality control techniques for estimation of radiochemical yield as well as purity. A cartridge based purification of the product is also developed to be used when radiochemical yields are low. The protocol developed by us and reported in this paper is readily adaptable.

The first patient who underwent this therapy in our centre had a Gleason score of 9/10. His PSA levels were rising and most therapy options were exhausted. The second patient had a Gleason score of 8/10 and had high PSA values (472 ng/ml). He underwent hormone therapy once in three months and the PSA levels were subdued to normal for a short time, however started rising again. In PET-CT imaging, several lesions were identified in this patient but the extent of disease was not as spread as that of the first patient. He got two cycles of therapy over a 11 week period with 184 mCi (first cycle) and 195 mCi (second cycle) and the uptake of tracer was nearly identical to $^{68}$GaPSMA-11.

One pertinent point to be noted is that the tracer remains in the lesions and does not get redistributed and also most likely not excreted as seen from the very clean late images of both the patients. This is a very favourable situation as the target radiation dose will be high and at the same time non-targets are spared thereby allowing the administration of higher levels of activity without crossing the critical organ dose limits.

Conclusion

$^{177}$LuPSMA-617 suitable for therapy is prepared by using CA low specific activity $^{177}$Lu prepared in a medium flux reactor. The product has adequate specific activity, stable in vitro and SPECT images with these formulations showed concordance with $^{68}$GaPSMA-11 PET-CT images. SPECT images taken 7 days post therapy showed that the accumulated activity is retained in the tumour without redistribution which is a favourable feature for a therapeutic radiopharmaceutical having a long lived radionuclide. Therapy is tolerated by the patients and no side effects were seen. Ascertainment clinical efficacy is planned by having therapy in larger number of patients.

References


