

PREPARATION OF PATIENT DOSES OF ¹⁷⁷LU-DOTA-TATE USING INDIGENOUSLY PRODUCED ¹⁷⁷LU: THE INDIAN EXPERIENCE

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Introduction: ¹⁷⁷Lu labeled DOTA-TATE, a somatostatin analog, is presently being considered as a promising agent for the treatment of patients suffering from inoperable neuroendocrine tumors which over-expresses somatostatin receptors. One of the challenges involved in carrying out targeted tumor therapy using ¹⁷⁷Lu-DOTA-TATE is to prepare the radiolabeled agent with adequately high specific activity in order that sufficient activity can be deposited in the cancerous lesions without saturating the limited number of receptors present in the cancerous site. As the specific activity of ¹⁷⁷Lu available at the time of preparation of the agent may vary considerably, it is crucial and poses a challenge to optimize the labeling protocol, more importantly with respect to the amount of peptide, in order that it can be prepared with high radiochemical purity using minimum amount of DOTA-TATE. The present paper describes our studies towards preparing several batches of ¹⁷⁷Lu-DOTA-TATE for clinical application in human patients using indigenously produced ¹⁷⁷Lu.

Experimental: ¹⁷⁷Lu was produced by thermal neutron bombardment on enriched (64.3% to 82% in ¹⁷⁶Lu) Lu₂O₃ target at a neutron flux of 6×10¹³-1×10¹⁴ n/cm².s for 21 days in our Institute's reactor. For the preparation of a patient dose of ¹⁷⁷Lu-DOTA-TATE (typically 150-200 mCi, 5.55-7.40 GBq), first the amount of Lu required to obtain that dose was calculated from the specific activity of ¹⁷⁷Lu after the necessary decay correction. The requirement of DOTA-TATE was subsequently determined considering that DOTA-TATE: Lu molar ratio to be 4:1 (minimum requirement for achieving adequate stability post-preparation). A stock solution of the DOTA-TATE, prepared in de-ionized water with a concentration of 1 µg/µL, was used for the preparation of the agent. Required volume of DOTA-TATE solution and ¹⁷⁷LuCl₃ were added to three times of their volume equivalent of 0.1 M ammonium acetate buffer (pH ~5) containing 40 mg/mL gentisic acid. The pH of the reaction mixture was adjusted, if required, within 4-5. The preparation was then subsequently heated in at 90°C (boiling water bath) for 60 min. Quality control was performed by employing paper chromatography (PC) and high performance liquid chromatography (HPLC) techniques. Finally, the preparation was subjected to Millipore filtration and administered to the patients.

Considering typical specific activity of ¹⁷⁷Lu available during the preparation of the agent to be 25 Ci/mg (925 GBq/mg), a 200 mCi (7.40 GBq) patient dose requires the use of 8 µg i.e. 0.045 µM Lu. This implies that 260 µg of DOTA-TATE needs to be used for the preparation. Therefore, for the actual preparation of the agent 260 µL of DOTA-TATE stock solution was added to ~1.4 mL of 0.1 M ammonium acetate buffer containing 56 mg of gentisic acid followed by 200 mCi (typical volume 200 µL) of ¹⁷⁷LuCl₃.

Results: ¹⁷⁷Lu was obtained with a specific activity range of 20-40 Ci/mg (740-1480 GBq/mg). Several batches of ¹⁷⁷Lu-DOTA-TATE were prepared using the ¹⁷⁷Lu and the amount of DOTA-TATE required to prepare a patient dose of 200 mCi varied from 175-350 µg. A patient dose is typically achieved in a total volume of 1.5-2.2 mL.

In PC performed using 50% acetonitrile in water, ^{177}Lu -DOTA-TATE moved from the point of spotting ($R_f > 0.4$) while uncomplexed ^{177}Lu remained at the point of application ($R_f = 0$). In HPLC carried out employing gradient elution technique using water and acetonitrile mixed with 0.1% trifluoroacetic acid as the eluting solvent, ^{177}Lu -DOTA-TATE exhibited a retention time of 900 s, while uncomplexed ^{177}Lu eluted out within 250 s. The radiochemical purity of the ^{177}Lu -DOTA-TATE complex was determined to be $98.25 \pm 1.1\%$. The agent was obtained with a specific activity of 0.57-1.14 Ci/mg (21.14-42.29 GBq/mg) or 0.82×10^3 - 1.63×10^3 Ci/mMole (30.23-60.46 TBq/mMole).

Conclusion: An optimized protocol was developed for the preparation of injectible ^{177}Lu -DOTA-TATE with high specific activity taking into account the variable specific activity of ^{177}Lu available during the preparation of the agent. Several batches of the agent were prepared with high radiochemical purity following this protocol. ^{177}Lu -DOTA-TATE prepared following this protocol is regularly being administered to the patients suffering from neuroendocrine tumors.