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Formulation of Patient Dose of ^{177}Lu-DOTA-TATE in Hospital Radiopharmacy in India: Preparation Using *In Situ* Methodology Vis-a-Vis Freeze-Dried Kit

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Dear Editor:

Peptide receptor radionuclide therapy (PRRT) using radiolabeled somatostatin analogs, particularly ^{177}Lu-DOTA-TATE, is now an established therapeutic modality for the treatment of patients suffering from a wide variety of inoperable neuroendocrine tumors.[1] In the past 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 to date, more than 1000 patient doses have been administered in 10 nuclear medicine centers across the country. India, with a large population, has a significant number of patients who require PRRT, and need to be provided at a reasonable cost due to the poor affordability in a large part of the population. This demands the formulation of the agent using ^{177}Lu obtained through the more economical and indigenously produced direct (n,γ) route using enriched ^{176}Lu as a target.[2] 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 shutdowns, power fluctuation, etc.) and variation in irradiation cycles used. In addition, variation in logistical factors, such as transportation delay, the distance of the hospitals from the radionuclide production site, and the date and time of actual administration, contributes to the variation in the specific activity of ^{177}Lu available to the end user.

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.[3] Since the radiopharmaceutical is prepared at the hospital radiopharmacy, the available specific activity of ^{177}Lu at the time of preparation should be considered for formulation of the agent with highest specific activity and thus ensuring the maximum therapeutic efficacy. Accordingly, a suitable method for the preparation of patient dose of ^{177}Lu-DOTA-TATE has been developed in our laboratory,[4] and the methodology has been successfully adopted by the nuclear medicine centers in India.[2] Preparation of the agent following this methodology requires the calculation of amount of peptide, radioprotecting agent (gentisic acid), and buffer to be used before every single formulation, and these vary depending on the specific activity of ^{177}Lu.[4] The main advantage of this method is that it ensures preparation of the agent with maximum possible specific activity.

The experience of regularly working with various hospitals made us realize that the success of this method largely depends on the working personnel in the respective radiopharmacies, as this procedure requires careful adjustment of certain critical reaction parameters. Particularly, adjustment of pH of the highly radioactive reaction mixture before incubation is very crucial and challenging for obtaining the agent with adequately high radiochemical purity. Consequently, there is an increased possibility of radioactive contamination of the workplace as well as radiation exposure to the working personnel. Moreover, a small deviation from the standard procedure or error in calculation may lead to batch failure and consequently loss of expensive peptide and radioactivity. This, in turn, sometimes adversely affects the treatment schedule of the patients. Additionally, stringent fulfillment of certain other parameters, such as facility to prepare in an environmentally controlled atmosphere, utilization of high-quality chemicals, and use of pyrogen-free and autoclaved glasswares, is essential for the successful implementation of this methodology in the hospital radiopharmacy units. Finally, the preparation needs to be made sterile through Millipore® filtration before it can be administered in patients. The whole procedure should be accomplished according with the principles and requirements of Good Manufacturing Practice as developed by World Health Organization.[5]

On the other hand, clinical grade ^{177}Lu-DOTA-TATE could also be prepared at the hospital radiopharmacy using

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freeze-dried DOTA-TATE kits.[6,7] Toward this, the authors have reported the detailed formulation and radiochemical evaluation of a novel freeze-dried DOTA-TATE kit, which can be used for the preparation of up to 7.4 GBq of ^{177}Lu-DOTA-TATE.[8] This single-vial kit, which enables a convenient and single-step preparation of the agent using ^{177}Lu having specific activity of $\geq$740 MBq/μg, is presently being used for the treatment of patients in a couple of nuclear medicine centers in India.[7] As the preparation of the agent using the kit requires only the addition of water and $^{177}LuCl_3$ before incubation, the formulation is relatively simple at the end user. This also reduces the possibility of contamination, radiation exposure, batch failure, and the preparation time of the radiopharmaceutical. However, this methodology has the drawback of using a fixed amount of DOTA-TATE, and thus, the preparation may contain more DOTA-TATE than required, particularly when ^{177}Lu of higher specific activity is used for the preparation.

Both the methods, with respective merits and limitations, have been proven to be useful in preparing patient dose of ^{177}Lu-DOTA-TATE with adequately high radiochemical purity. In consideration, it is advantageous to follow the *in situ* preparation methodology in centers having a well-equipped radiopharmacy and well-trained radiochemists as it always ensures the formulation of ^{177}Lu-DOTA-TATE with highest possible specific activity. On the other hand, the use of the freeze-dried kit may be a more desirable option in other centers to make PRRT an accessible therapeutic modality to a large number of patients.

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