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Lu-177 - A Noble Tracer: Future of Personalized Radionuclide Therapy

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Abstract

Radionuclide therapy using radiopharmaceuticals is in existence for over sixty years. Iodine-131 remains the work-horse for the treatment of thyroid cancer due its efficacy and ease of administration. Lutetium-177 (Lu-177) is one of the most promising targeted radionuclides therapy agents. 177Lu (half-life of 6.67 days) decays into the stable Hafnium-177 (177Hf). It emits beta radiation (maximum energy of 498 keV) and gamma rays of 208 and 113 keV. Owing to its beta as well as gamma ray emission, 177Lu is a near-to-ideal 'theranostic' radionuclide. In India the potential of 177Lu in designing agents for targeted radiotherapy was initially realized in 2000, in the Radiopharmaceuticals Division, Bhabha Atomic Research Centre (BARC). Now clinical grade 177LuCl3 is commercially supplied by BARC, to nuclear medicine centers all over India. At our institute, we have also experienced good results of PRRT with 177 Lu- DOTA-NOC in well-differentiated inoperable and metastatic neuroendocrine tumors. Dazed by the above results, we are pushing the efforts for the utilization of 177Lu –PSMA therapy in patients with metastatic prostate cancer.

Main Text

Radionuclide therapy using radiopharmaceuticals is in existence for over sixty years. Iodine-131 remains the work-horse for the treatment of thyroid cancer due its efficacy and ease of administration. Apart from the tumor therapy, targeted radionuclide therapy is also being used in certain other diseases as bone pain palliation, loco regional applications for treatment of liver cancer by Trans Arterial Radioembolisation (TARE) and Radiosynovectomy for patients with different types of arthritis. The development of new and improved approaches for targeted radionuclide therapy is currently one of the most focused areas of radiopharmaceutical research. Recent advances in this area have lead to the development of receptor-avid and immune-derived molecular radiopharmaceuticals as well as other new therapeutic radionuclides. Lutetium-177 is one of the most promising targeted radionuclides therapy agents. The first publication on the use of 177Lu for radiopharmaceuticals development was in 1988 by Keeling et al. [1] on the uptake of 177Lu on hydroxyapatite particles. In the year 1991, radio labeling of CC-49, a murine monoclonal antibody that recognized the tumor associated glycoprotein 7 (TAG-72) with 177Lu for the development of a radio immunotherapeutic agent, was tried [2], Later on, many papers were published to describe the labeling of Lu-177 with different radiopharmaceuticals [3]. like *in 1998* for the preparation of 177Lu-EDTMP for bone pain palliation [3], In 2001, for the preparation of 177Lu-DOTATATE and its clinical use in patients of metastatic neuroendocrine tumors [4] and the synthesis of a 177Lu labeled vitronectin receptor antagonist peptide, RGD [5]. International Atomic Energy Agency (IAEA) has initiated two Coordinated Research Projects (CRPs), with the objective to enhance the production of 177Lu and the development of 177Lu radiopharmaceuticals [6]. These projects accelerate the development and different type of 177Lu based radiopharmaceuticals. Now targeted therapy using 177Lu radiopharmaceuticals is one of the fastest growing branches of therapeutic nuclear medicine [7-13]. For the wide use of radiopharmaceuticals, it is mandatory to carefully consider the choice of the radionuclides along with the vector molecules, for suitable pharmacokinetic properties and adequate therapeutic efficacy. An ideal radionuclide for therapy should have suitable nuclear decay characteristics, high radionuclide purity and specific activity in production, low production cost and comfortable delivery logistics. Among the various radionuclides suitable for radionuclide therapy, 177Lu has emerged as one of the ideal therapeutic agents with suitable imaging and cytotoxic properties. 177Lu (half-life of 6.67 days) decays into the stable Hafnium-177 (177Hf). It emits beta radiation (maximum energy of 498 keV) and gamma rays of 208 and 113 keV with 10%

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and 6% abundance, respectively [14]. The production -177Lu requires a very high thermal neutron capture cross-section of the target 176Lu [176Lu (n,γ) 177Lu (σ = 2060 barns)], thus making it an excellent radionuclide for labeling with different pharmaceuticals. Its cross-section requirement is highest among all (n,γ) produced radionuclide used for therapy now a days. In the long run, the cost of this radionuclide is expected to decrease significantly with the entry of more producers and clients into the market. The long half-life of 177Lu also provides logistic advantage for facilitating supply to places far away from the production site. Owing to its beta as well as gamma ray emission, 177Lu is a near-to-ideal 'theranostic' radionuclide. By administration of sub-therapeutic activity of the 177Lu-based radiopharmaceutical, successful preclinical dosimetric studies have been performed in few patients that have helped in studying the pharmacokinetics of the radiopharmaceutical [15]. This aids in tracing the initial localization of the labeled radiopharmaceutical and subsequently post therapy imaging. In India the potential of 177Lu in designing agents for targeted radiotherapy was initially realized in 2000, in the Radiopharmaceuticals Division, Bhabha Atomic Research Centre (BARC). The first trial to produce 177Lu from natural Lu_2O_3 target was carried out in 2000; subsequently the production of high specific activity 177Lu from enriched target was tried in 2001. For carrying out research on preparation of 177Lu-labeled agents for receptor-mediated targeted radiotherapy, indigenous sourcing of the isotope in high specific activity and adequate radionuclide purity became a necessity. As a result of the extensive research on standardizing the production methodology of this isotope with high specific activity, clinical grade 177LuCl3 is commercially supplied by Radiopharmaceuticals Division, BARC, to nuclear medicine centers all over India. As per the need, 177Lu can be produced with different specific activities. High specific activity of 177Lu is necessary to produce receptor-specific radionuclide therapy agents, which target limited number of receptors over-expressed in tumors, while low to medium specific activity of 177Lu is needed to produce non- targeted radionuclide therapy agents, like the ones for bone pain palliation (177Lu-EDTMP) and radiation synovectomy. Extensive research on utilizing indigenously produced 177Lu has unraveled its immense potential in radio therapeutic applications, and led to development of agents like 177Lu–DOTMP, 177Lu-EDTMP for palliative care of bone pain due to skeletal metastases and 177Lu-DOTATOC, 177Lu-DOTATATE, or 177Lu-DOTANOC for the treatment of well-differentiated neuroendocine malignancies. 177Lu based agents also find use in radiation synovectomy of small/medium-size joints and targeted therapy of a variety of other malignant disorders when labeled with peptides like substance P, Bombesin etc. Aforementioned, the results of 177 Lu- DOTA-TAE and 177 Lu- DOTA-TOC therapies in the well differentiated neuroendocrine tumors are overwhelming and encouraging. At our institute, we have also experienced good results of PRRT with 177 Lu- DOTA-NOC in well-differentiated inoperable and metastatic neuroendocrine tumors. The therapy was given along with reno-protective amino acid infusion (European association of nuclear medicine guidelines) and before the administration, the marrow, renal and liver function of the patients was evaluated, to be enrolled for the therapy. The quality control of the 177 Lu- DOTA-NOC was done each time before injecting in the patient. Out of 5 patients with metastatic and inoperable Gastroentropancreatic Neuro Endocrine Tumors (GEP-NET), carcinoids and gastrinoma, marked reduction in the serum gastrin, serum chromogrannin and urinary 5-HIAA (Hydroxyindoleacetic acid) levels were noted with significant improvement in the Quality of Life status, according the internationally approved European Organization Of Research and Treatment of Cancers (EORTC) quality of Life (QoL) score. No therapy is devoid of the adverse effects and the 'appropriate use' of the any radionuclide administration is a must in the management of a patient. In our study, transient thrombocytopenia was the most common hematological derangement associated with the PRRT. The thrombocytopenia was more severe in those with skeletal metastasis, due to higher marrow radiation dose. Dazed by the above results, we are pushing the efforts for the utilization of 177Lu –PSMA therapy in patients with metastatic prostate cancer. The role of 177Lu-PSMA has been successfully illustrated in the published literature [16,18]. At our institute, the patients with known metastatic carcinoma prostate evaluated with the sensitive 68 Ga- PSMA study and adequate marrow and renal function will be enrolled in the therapy with 177Lu- PSMA. In summary 177Lu has been pursued with great interest for therapy in many countries all over the world, and the pioneer works have been published from Europe (Netherlands, Germany, Italy, Switzerland) in patients of well-differentiated neuroendocrine tumors with 177Lu-DOTA-TATE. This has encouraged other countries, including India to have a strong program on 177Lu. The beginning in clinical deployment of this isotope for treating patients has now grown and the demand of this isotope will multiply several folds in near future. From the studies reported in the past 10-15 years, 177Lu –DOTATATE can be seen to be the most effective PRRT for medium sized and inoperable lesions of well-differentiated neuroendocrine tumors. It is considered to have a great potential in future for use in therapeutic radiopharmaceuticals. Efforts and research to prepare and test a variety of molecules labeled with 177Lu are being pursued for two decades in different countries and it is expected that a few of them will be suitable for deployment in clinics for the benefit of patients.

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