Emerging Role of ^{177}Lu in Nuclear Oncology: A Brief Review

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Abstract: With the innovations in nuclear medicine techniques, Lutetium 177 (^{177}Lu) has epitomized as a revolutionary theranostic agent- with both scintigraphic and therapeutic properties. The present review focusses on the introduction of ^{177}Lu as a promising modality for tumor diagnosis and therapy in widespread metastases . Being a shorter β-range emitter providing better irradiation of smaller tumor volumes, ^{177}Lu- based PRRT is being increasingly used in patients with somatostatin receptor positive neuroendocrine tumors. Clinical trials with ^{177}Lu–DOTATATE and ^{177}Lu–DOTATOC have gained considerable interest in recent years with successful tumor regression in patients with malignant metastatic neuroendocrine tumors. Especially, therapy with ^{177}Lu-DOTATATE PRRT has reported to significantly improve the quality of life of Gastroenteropancreatic NET patients because of higher affinity of DOTATATE for the somatostatin type 2 receptors. In addition, this review also sheds light on the diagnostic and palliative aspects of ^{177}Lu which also serves to be an attractive candidate for the preparation of radiopharmaceuticals for radiation synovectomy of small to medium sized joints. Enlisting all the said features, ^{177}Lu is strongly emerging as a promising theranostic agent that could possibly endow Nuclear Medicine an edge over other conventional therapies in near future.

Keywords: Theranostic agent, somatostatin receptor, radionuclide therapy, radioimmunotherapy, imaging agent.

INTRODUCTION

Following the introductory research paper on the diagnostic use of ^{177}Lu in 1968 for bone imaging, the β-emission characteristics harbored minor interest for therapy until *Bard et al*. described the pioneer use of ^{177}Lu in the treatment of arthritis in rabbits in 1985 [1-3]. ^{177}Lu belongs to a family of elements called Lanthanides (rare earth isotopes) and has emerged as a promising diagnostic and therapeutic candidate in the field of clinical nuclear oncology. Worldwide, the isotope is under extensive investigation for treatment of approximately 30 different clinical aspects including treatment of colon cancer, metastatic bone cancer, non-Hodgkin's lymphoma, lung cancer, radiation synovectomy, neuroendocrine and gastroentero-pancreatic tumors [4,5].

Endoradiotherapeutic treatment employing radiolabeled, receptor avid peptides are a burgeoning aspect of nuclear medicine. Particularly, advances in sophisticated molecular carriers that target tumor associated antigen ie. Targeted Radiotherapy (TRT) is a promising new tool in management of inoperable or metastasized cancer [6]. A careful consideration for the appropriate radionuclide along with a suitable carrier moiety is essential to design a targeted, highly specific radiopharmaceutical. The major criteria defining the choice of radioisotope to be used for therapeutic purposes are suitable pharmacokinetic properties resulting in good *in vivo* biolocalization and desired clearance [7-9], decay characteristics (biological half-life of the radiopharmaceutical should match to the physical half life of the radionuclide) and the energy of the emitted corpuscular emission should be compatible to the volume of lesion allowing uniform irradiation of the tumors [6].

Whether designed for therapeutics or diagnostics, targeted radiopharmaceutical complexes often use a radiometal that is irreversibly and stably attached to the targeting moiety (antibody or peptide) by a bifunctional chelator rendering thermodynamic stability to the radiocomplex [10].

The radiolanthanides mostly exist in an oxidation state of +3 and are often stabilized by macrocyclic, polyamino-carboxylate-multidentate ligands (DTPA, DOTA), though the 1,4,7,10- Tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA) analogues have resulted in more stable bifunctional chelate frameworks for the +3 radiometals [10-12]. Owing to its favourable physicochemical characteristics as well as the feasibility of isotopically enriched largescale production in adequate specific activity,^{177}Lu is presently being considered as a potent radionuclide for use in *in vivo* therapy.

RADIONUCLIDE CHARACTERISTICS

^{177}Lu is a medium energy β-emitter with a maximum energy of 0.5 MeV, a long half life of 6.7 days and having a maximal tissue penetration of 2 mm [13]. It also emits low energy γ-rays at 113 and 208 keV and with 6% and 10% abundance respectively [14] that are ideally suited for *ex vivo* evaluation of the *in vivo*

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localized ^{177}Lu biomolecular targeting agent and subsequent dosimetric calculations [1]. The shorter β- range and lower energy provides better irradiation of small tumor volumes [15] and the longer half life provides logistic advantage for production, as well as feasibility to supply the products to places far away from the reactor site [16]. In this framework, ^{177}Lu is also envisioned as a successful alternative to Iodine-131.

PRODUCTION

^{177}Lu can be produced by two alternate routes, namely, the direct route based on neutron activation of ^{176}Lu. The ^{177}Lu thus obtained is of relatively high specific activity. Natural abundance of ^{176}Lu is only 2.6% thereby requiring enriched Lu_2O_3 target for this route of production, the limitation being only carrier-added ^{177}Lu preparations can be obtained. Thus the stable isotopes (^{175}Lu,^{176}Lu) present in the target reduce the specific activity of ^{177}Lu obtained in (n,ϒ) activation[6,17].

In indirect production route, ^{177}Lu is obtained in carrier-free form from beta decay of ^{177}Yb produced by neutron capture on ^{176}Yb in a nuclear reactor. Carrier free production requires enriched target material that in principle should be recycled as the neutron capture cross section of ^{176}Yb is low. Radiochemical separation of Yb/Lu in the irradiated target also forms a crucial parameter for high specific yield of ^{177}Lu [17].

PEPTIDE RECEPTOR RADIONUCLIDE THERAPY

In 1990s, peptide receptor radionuclide therapy (PRRT) was introduced as a promising treatment modality for tumor diagnosis and therapy. The characteristic overexpression of specific peptide receptors on tumor cells form the molecular basis of the high affinity targeting of these receptors for imaging or radionuclide therapy purposes in nuclear medicine. The naturally occurring biologically active regulatory peptides when exploited by labeling with a radionuclide of interest is used as a probe to target particular receptor expressing tissues [18]. Several peptides such as somatostatin analogs, bombesin etc are being actively investigated as agents for use in PRRT. Among the several classes of radiolabeled peptides for targeted therapy, radiolabeled somatostatin analogs are nowadays the most successfully established ones in the clinical practices. Somatostatin is a cyclic hormone expressed in the central and the peripheral nervous systems, have been identified to be in two forms, SST-14 and SST-28 and inhibits the release of hormones (insulin, growth hormones and glucagon) by binding to G-protein coupled SST receptors which are further categorized into five subtypes [19]. Neuroendocrine tumors overexpress somatostatin receptors, predominantly the receptor subtype 2 [20,21]. Somatostatin analogues such as lanreotide and octreotide provides symptomatic relief in patients with metastasized Gastroenteropancreatic neuroendocrine tumors (GEPNETs) not only by decreasing hormonal overproduction but it has also been shown to increase time of tumor progression [1]. These low molecular weight peptides (M_W = 5.5 kDa) favors rapid sequestration of the receptor peptide ligand facilitating retention of tracer in receptor expressing tumors and rapid clearance from non target tissues resulting in appreciable tumor to background ratio [13,22].

^{177}LU AS RADIOTHERAPEUTIC AGENT

Started initially with [^{111}In-DTPA^{0}] octreotide, Peptide receptor radionuclide therapy (PRRT) did not prove to be very useful in clinical practice with its pioneer radionuclide. Its small particle range and subsequent low tissue penetration provided symptomatic relief but tumor regression was rare [1,23-24]. The next generation of PRRT targeted somatostatin receptors with metabolically stable radiolabeled somatostatin analog, ^{90}Y-DOTA,Tyr3-octreotide (^{90}Y-DOTATOC) with DOTA instead of DTPA to ensure a more stable binding [25]. Lastly ^{177}Lu-based PRRT represents the third generation of somatostatin receptor targeted radionuclide therapies [1,26]. Clinical trials with (^{177}Lu–DOTA–Tyr^3)-Octreotide {DOTATOC} and (^{177}Lu– DOTA–Tyr^3)-Octreotate {^{177}Lu–DOTATATE} have shown symptomatic improvement as well as successful tumor regression in patients with different types of NET [27-29]. The somatostatin analogue [DOTA, Tyr3-octreotate] and [DOTA, Tyr^3-octreotide] differs only in that the C-terminal threoninol of DOTA is replaced with threonine [25,26]. As a result, DOTATATE has been reported to display ninefold higher affinity for somatostatin receptor positive tissues as compared to DOTATOC [30,31] leading to a significantly higher tumor uptake and radiation dose. On comparison of ^{177}Lu-DOTATATE with ^{177}Lu-DOTATOC, the mean residence time ratios of TATE to TOC-peptide was evaluated to be ≈2.1 for tumors. However, a lower whole body retention potentially implying lower bone marrow toxicity, a longer tumor residence time and fewer negative side effects while exhibiting superior tumor responses and improving the quality of life [28], ^{177}Lu-DOTATATE concludes to be a better peptide for use in PRRT [1].

^{177}LU AS RADIOIMMUNOTHERAPEUTIC AGENT

About a century ago, Paul Ehrlich envisioned that antibodies as "magic bullets" could be developed to selectively target disease [32]. The concept of localizing radiolabeled tumor specific monoclonal antibodies to specific overexpressing receptors on cancer cells forms the basis of Radioimmunotherapy [33]. Gastrin-Releasing Peptide Receptors (GRPr) are overexpressed in a wide variety of cancer cells including breast, lung, prostate and pancreatic cancers. Bombesin is an amphibian analogue of the human gastrin releasing peptide (GRP) that binds to GRP receptors with high affinity and specificity.

Development of ^{177}Lu based bombesin agonists as agents for systemic radiotherapy and diagnostic imaging and has stimulated research in the field of targeted diagnosis and therapy. Studies are in development with novel radiopharmaceutical ($BEFG_2$) radiolabeled with ^{177}Lu as a useful tool to evaluate bombesin receptor-positive tumors [34].

An important cell surface protein antigen Human Epidermal growth factor receptor 2 (HER2) leads to uninhibited cell proliferation and is commonly overexpressed in 20-30% early stage breast cancer. Trastuzumab (Herceptin), an IgG1 monoclonal antibody directed against HER2 protein, attaches to the receptor and thus prevents the epidermal growth factor from reaching the cancerous breast cells. Herceptin has recently been conjugated with ^{177}Lu to be used in imaging and radioimmunotherapy of human breast cancer [35].

Radioimmunotherapeutic intervention presents a curative treatment for advanced prostate cancer stages as it often gets metastasized as small foci in lymph nodes or bone marrow where a high number of antibodies are in circulation [36]. PSMA is considered as the most suitable cell surfaced antigen overexpressed in all prostate cancers. Radioimmunotherapy with ^{177}Lu-Labelled Anti-Prostate specific membrane antigen (PSMA) antibodies is also under way as a promising new option for patients with prostate cancer [36,37].

^{177}LU AS IMAGING AGENT

^{177}Lu emits Υ photons of 113 keV (6.4%) and 208 keV (11%) concomitantly with the therapeutic β - radiation allows post therapeutic scintigraphic detection of the tracer *in vivo* along with subsequent dosimetry. Also as discussed above peptides are non-immunogenic, demonstrate good tumor penetration properties and low bone marrow uptake that makes them suitable probes for tumor imaging, staging and therapy [13,19]. Internalization by receptor mediated endocytosis of ^{177}Lu labeled agonist peptides leads to longer retention time of radioactivity in tumor cells followed by rapid clearance by kidneys [38,39]. Thus post therapeutic peptidal imaging form an important tool for establishing response assessment in patients with somatostatin positive NET.

Radiolabeled antibodies, a promising class of diagnostic probes are also being explored as potent radiopharmaceuticals having specific target oriented therapeutic properties. Scintigraphic images obtained using a gamma camera equipped with a low energy high resolution collimator shows ^{177}Lu-Herceptin accumulated in mammary tumors of mice to a greater extent than in any other organ [35].

Expression of hCG (Human Chorionic gonadotrophin) and its subunits is reported in a number of cancers. Therefore, possibilities of using antibodies raised against hCG-expressing tumors, are also being explored to develop immune-imaging and therapeutic agents for cancer management. Studies showing radiolabeling of anti-β-hCG antibody with ^{177}Lu shows a significant uptake in tumors providing a platform for enhancing the potential of radiolabeled antibodies to work as diagnostic and therapeutic radiopharmaceutical [40].

POTENTIAL TO BE USED AS BONE SEEKING AGENT

Treatment of multiple osseous cancer metastases forms one of the major concerns in patient management in oncological practice. Successful palliation improves quality of life in those afflicted with wide spread skeletal mets. Multiple palliative treatment modalities such as external beam radiotherapy, bisphosphonates, morphine derived analgesics fail to provide adequate relief due to multiplicity of tumors and potential to be used repetitively [16]. In this context, intravenous radionuclide therapy targeted skeletal lesions by delivering adequate dose of ionizing radiation with complexes showing high affinity towards bone [16,41-42].

Ethylene diamine-N,N,N′,N′- tetrakis(methylene phosphonic acid) (EDTMP) is one of the most popular ligands that when complexed with lanthanides show high bone seeking properties and other favorable

pharmacological characteristics along with minimal toxicity issues [43,44]. EDTMP chelated to ^{153}Sm targets the bone matrix as polyphosphonate and has been applied in clinical practice for more than a decade however short half life being the major impediment limits its wide use [16,45]. On the other hand, the conventionally used ^{89}Sr used for bone pain palliation with a half-life of 50.5 days and less than .01% of the gamma ray emission doesn't allow post-injection imaging unlike ^{177}Lu that has imageable gamma emission with comparatively short half-life giving it an advantage over ^{89}Sr for bony metastasis.

The adequately low energy of β-particles is expected to have minimum bone marrow suppression on accumulation in skeletal lesions for effective bone pain palliation [46]. Studies have been conducted wherein diagnostic dose of ^{177}Lu-EDTMP have shown prominent uptake in vertebral column and metabolically active bone lesions [16].

POTENTIAL TO BE USED FOR MISCELLANEOUS THERAPEUTIC APPLICATIONS

^{177}Lu-Hydroxy apatite is considered as an attractive candidate for radiation synovectomy and is found to be very effective in treatment of medium size joints, owing to higher dose accumulation per mCi activity, besides a longer half life [6]. Moreover, ^{177}Lu is a good substitute for the difficult to produce ^{169}Er and could also reduce radiation dose to patient (compared to ^{153}Sm) during radiation synovectomy of small joints [47].

CONCLUSION

^{177}Lu based radiopharmaceuticals have proved to possess tremendous potential to become a successful alternative to conventional therapeutic approaches. Beside palliative aspects, the suitable chemical and nuclear characteristics, image-able gamma photons along with particulate β (-) emission and subsequent patient dosimetry substantiates its emerging role as a successful theranostic agent. Treatment with ^{177}Lu somatostatin analogues of NETs by means of Peptide Receptor Radionuclide Therapy in the management of patients with inoperable or metastasized neuroendocrine tumours has by far given very encouraging results in terms of tumor regression. With this spectacular evolution of use of ^{177}Lu over the years, it may soon emerge as the therapy of preferred choice in patients with NETs. Further endeavors warrants studies with new agonist and antagonist peptides to be labeled suitably with ^{177}Lu [21] that could possibly change the facet of rapidly growing field of Nuclear Medicine.

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