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Theranostics in India: a Particularly Exquisite Concept or an Experimental Tool

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Abstract

The term theranostics is a combination of a diagnostic tool that helps to define a right therapeutic tool for specific disease and paves the approach towards personalized or precision medicine. In Nuclear Medicine, a diagnostic radionuclide is labeled with the target and once expression is documented, the same target is labeled with a therapeutic radionuclide and treatment is executed. The theranostic concept was applied first time in 1964 in the treatment of thyroid cancer with I-131 (RAI). Over the years, other theranostic radiotracers became available indigenously from the Bhabha Atomic Research Centre (BARC) in the country. Currently Lu-177 is produced in India and peptides like DOTATATE and PSMA are available in a kit form indigenously. At the present time, the radionuclide therapies of oncological disorders which are being performed in India are mainly for neuroendocrine tumors (NET) and metastatic castration resistant prostate cancer (mCRPC). The main constraints pertaining to this concept is the cost of treatment and awareness among the clinicians which are gradually being taken care of by the private health insurance and our participation in disease management group meetings respectively. The theranostic concept has become popular over the years and has the potential for sustained growth.

Keywords Theranostics · India · History · Current status · Constraints

Introduction

Personalized medicine enables the use of diagnostic and screening methods to manage the individual patients' disease or predisposition towards a disease in a better way. It enables risk assessment, diagnosis prevention, and therapy specifically tailored to a particular individual's type of disease or a disease phenotype thus enhancing the outcome or quality of life. The term theranostics is a combination of a diagnostic tool that helps to define a right therapeutic tool for specific disease and paves the approach towards personalized or precision medicine. A diagnostic radionuclide is labeled with the target and once expression is documented, the same target is labeled with a therapeutic radionuclide and the treatment is executed. It signifies the concept of "we treat what we see and see what we have treated". In Nuclear Medicine, theranostics is easy to apply and understand because of an easy switch from diagnosis to therapy with the same vector. It helps in maximizing tumor dose, sparing normal tissue with high specific and rapid uptake in metastasis with a high effective T1/2 thus delivering high absorbed tumor dose. Imaging and treatment of neuroendocrine tumors (NET) and prostate cancer (PCa) are current examples of successful implementation of this concept worldwide including India [1].

History of Nuclear Medicine in India

To understand the implementation and growth of theranostics in India, it is essential to understand the journey of the specialty in this country. The history of Nuclear Medicine in India began in the mid-twentieth century shortly after independence in 1947 from British rule. The Atomic Energy Establishment Trombay (AEET) was first established in 1954. In 1956, the first research reactor was established in India at the same location and named APSARA. The second reactor became operational in 1960 in the same campus named CIRUS and the indigenous production of various radionuclides like I-131 (RAI), P-32, Cr-51, etc. started. The AEET was renamed as

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Bhabha Atomic Research Centre (BARC) in 1967 after Dr. Homi Jehangir Bhabha, a renowned nuclear scientist who shaped India's nuclear journey and future. BARC took up the responsibility of production and commercial supply of radioisotopes and radiopharmaceuticals to the medical institutions in the country since early 1960s and is continuing till today. Over the years India went on to build institutions, infrastructure, and instrumentation with the result that Nuclear Medicine became an integral part of patient management both in the Government and private sector healthcare system. India graduated from the rectilinear scanner era in the early 1960s to its first gamma camera in late 1960s and single-photon emission computed tomography (SPECT) in 1984. In 2002, India's first medical cyclotron and PET scanner was commissioned at the Radiation Medicine Centre (RMC) in Mumbai which is the pivotal training center for Nuclear Medicine Physicians and technologists since early times. This is the center from where most of the Nuclear Physicians (including me) took their baby steps during training and went on to become established professionals today. India's first PET-CT scanner was commissioned at the Tata Memorial Hospital (TMH) in 2004 which is an internationally acclaimed cancer hospital (where I began my career in 1990). With this, the revolution of an ever increasing molecular imaging facilities in the country started witnessing a sustained exponential growth. This was complemented by the parallel development of human resources in the form of postgraduate trainings in different premier institutions in the country [2].

Evolution of Theranostics in India

The practice of theranostics in oncology made a beginning in 1964 when RMC became the first institution to use RAI for the treatment of thyroid cancer by using its two–three beds indoor facility. This has now grown to a 16 bed isolation ward and is the largest radionuclide treatment facility in the country having the distinction of treating the maximum number of thyroid cancer cases in the world. This institution has also been treating NET with 177-lutetium (Lu-177) dotatate since 2010 and PCa with Lu-177 PSMA since 2017. I-131 MIBG therapy for neuroblastoma and malignant pheochromocytoma are also administered. Although the molecular imaging facilities have showed an exponential growth in the last five decades, more so in the last one, the growth of institutions performing radionuclide therapies have not taken place at the same pace. This is mostly due to logistic issues and very stringent regulatory requirements of the Atomic Energy Regulatory Board (AERB) which is the Government of India regulatory body for looking after the radiation safety aspects pertaining to radionuclide therapies. The most prominent among the logistic issues is the requirement of a large capacity delay and decay tank for the effluents from toilets attached to the isolation wards for radionuclide therapy. This requirement has been an infrastructural compliance challenge especially in an already functioning hospital. At the present moment, there are 92 isolation wards in the country with a total capacity of about 200+ beds. Our institution has the facility of isolation ward for radionuclide therapy since its inception in 1996 with 3 patient beds [2].

Availability of Indegenous Theranostic Radionuclides and Pharmaceuticals

As mentioned earlier, the BARC has been involved in the production of radionuclides since the early 1960s and gradually over the years, the scientists from different divisions of BARC have developed radiopharmaceutical kits for theranostic use, thus benefitting such patients from all over the country as well as few neighboring countries. This has kept pace with the rapid development worldwide.

The practice of theranostics have grown many folds in clinical practice in the country in the last 5 years. This has been possible partly due to the availability of radionuclides and radiopharmaceutical kits indigenously as well as importing from overseas at competitive prices. The awareness among clinical oncologists and the patients about this form of treatment has also helped in its sustained growth.

The radionuclides for therapy which are being indigenously available for routine use have been RAI, P-32 and now Lu-177. The use of Lu-177 in the treatment of NET and CRPC is well documented in the world literature now and is now practiced regularly in institutions accredited for performing radionuclide therapy in the country, including ours. In addition to the treatment in these diseases, the indigenously produced Lu-177 have also been used in the palliation of metastatic bone pain. Lu-177 is produced in the BARC reactor by irradiating isotopically enriched Lu_2O_3 target (82% in Lu-176) at a thermal neutron flux of $\sim 1 \times 10^{14}$n cm^{-2} s^{-1} for a period of 21 days. The irradiated target was cooled for 24 h and subsequently dissolved in 0.01 M supra pure HCl by gentle warming. $^{177}LuCl_3$ thus obtained was directly used for preparing the patient doses of Lu-177 DOTA-TATE and EDTMP [3]. The indigenously produced Lu-177 which has been quality controlled with TLC and HPLC has been successfully labeled with PSMA-617 as well. In a series of 7 patients with metastatic CRPC treated with 200 mCi of Lu-177 PSMA-617, significant accumulation of the therapeutic dose of the radiopharmaceutical was seen at the metastatic sites as seen in the diagnostic scan performed with Ga-67 PSMA prior to the therapy. [4]. Similarly the isotope division in BARC has developed ready to use freeze dried single vial kit of PSMA-11 [5] and DOTA-TATE [6]. These have been clinically validated and now used for patient treatment in many institutions.

Current Status of Practice

There has been significant theranostic work done in India both in our institution and other accredited premier institutions in the country. Most of these work has been published and cited in the world literature.

We have shown that initial risk stratification and staging in prostate cancer can be done with Ga-68 PSMA as a one stop shop with a reasonably correct *N* stage estimation and kappa coefficient showing substantial agreement between PSMA PET-CT and histopathological confirmation of lymph node metastasis ($k = 0.734$). Fair agreement was seen ($k = 0.277$) with *T* staging [7–9]. Ga-68 PSMA PET-CT can provide useful incremental information in patients with high PSA and negative TRUS biopsy and has a potential to guide management [10]. Ga-68 PSMA PET-CT has been successfully evaluated to assess treatment response in metastatic prostate cancer with biochemical progression undergoing systemic therapy [11] and Lu-177 PSMA ligand therapy [12]. Molecular response evaluation criteria was found to be better in both the studies.

Safety and efficacy of Lu-177 PSMA radio ligand therapy were also highlighted in a few studies from India. Lu-177 DKFZ PSMA radionuclide therapy was found to be a safe and effective approach in the treatment of mCRPC. In a series of 31 patients with progressive disease despite second-line hormonal therapy and/or docetaxel chemotherapy, the mean activity administered in the 31 patients was 5069 ± 1845 MBq ranging from one to four cycles. There was a decline in the mean serum PSA levels from the baseline. Biochemical response criteria had complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD), respectively. The mean VAS max score also decreased from 7.5 to 3. The mean analgesic score decreased from 2.5 to 1.8 after therapy. The mean KPS score improved from 50.32 to 65.42 after therapies. The mean ECOG performance status improved from 2.54 to 1.78 after therapy. Two patients experienced grade I and grade II hemoglobin toxicity each. None of the patients experienced nephrotoxicity or hepatotoxicity [13, 14].

In our series of 25 histologically proven mCRPC patients with progression on standard treatment protocols were administered Lu-177-PSMA therapy on compassionate grounds. All patients were previously treated with at least first line antiandrogens and first line chemotherapy with docetaxel. A Ga-68 PSMA-11 PET-CT was performed on all patients to document adequate receptor expression for inclusion. Our initial results of efficacy and toxicity of one cycle of Lu177-PSMA therapy have showed adequate palliation of pain and PSA response in heavily pretreated mCRPC patients with low performance status with no clinically significant hematological or other toxicity [15].

The use of Actinium-225 (Ac-225) labeled PSMA-617 for the treatment of mCRPC is also being performed in one or two institutions in India with promising initial results. Ac-225 is being made available as unit patient dose from overseas and the labeling with PSMA is being carried out in individual hospital-based radiopharmacy. Targeted alpha therapy with its high level of ionization and short range in tissue has the potential to deliver highly localized cytotoxic radiation to cancer cells with minimal toxicity to surrounding healthy tissues. The commonly used alpha emitting radiotracers used in therapy are Bi-213, actinium-225, and astatine-211. At present, there is some initial human experience with Ac-225 DOTANOC, Ac-225 PSMA, and Bi-213 DOTATOC. Thirty-two patients of metastatic castration resistant prostate cancer who have failed multiple lines of hormonal therapy, taxane-based chemotherapy, and other therapies like abiraterone and enzalutamide underwent Ac-225 DKFZ-PSMA617 therapy as an end of life salvage therapy. Based on data from phase I and phase II studies, an empiric dose of 100 kBq/kg body weight was administered every 2 months. The patients were followed with S. PSA levels at the end of 1 month and hematological parameters every 2 weeks. Clinical performance, QOL scoring, and Ga-68 PSMA scan was done before each cycle with a median duration of follow-up of 15 months. The median progression-free survival was 7.06 months. Median survival from first Ac-225 PSMA treatment was 12.23 months. There was an 81% median PSA reduction. Nearly all the patients including those who did not show PSA response showed improvement in the quality of life. None of the patients demonstrated any serious adverse effect. Xerostomia was the principal adverse effect with nearly 90% of patients showing Gr I and II xerostomia.

The results with Ac-225 DOTATOC were even better than the Ac-225 PSMA results. Ten patients of well-differentiated NET with evidence of progressive disease following Lu-177 Peptide Receptor Radiopharmaceutical Therapy (PRRT) underwent Ac-225 DOTATOC therapy as a salvage procedure. The average duration of follow-up was 15 months. All patients except one showed evidence of partial response to therapy. There was significant improvement of quality of life with no serious toxicity till the time of censure. Five patients also underwent selective intra-arterial Bi-213 DOTATOC infusion with excellent responses. [16]

Constraints and Possible Remedies

In India, most of the patients pay themselves for their treatments. These high-end and new treatment facilities are available in a very few premier public hospitals with subsidized cost. It is therefore imperative that majority of such patients have to be treated in private hospitals at higher cost which many of them are not able to afford. The health insurance industry is still in its developing stage and patients having private health insurance have been gradually increasing over the last couple of years. This is making things easier for the patients having access to it. The availability of indigenously produced radionuclides and

radiopharmaceutical kits also contributes to the increasing number of patients availing these new form of treatment. Theranostics for well-differentiated thyroid cancer (DTC) with RAI has been well accepted and is being regularly performed in India for remnant ablation, as adjuvant and for treatment of metastatic disease [17]. The use of other theranostic form of treatments are progressing slowly but steadily. We are trying to get over the constraints, increase the indigenous production of radionuclides and kits. We are also looking into the safety profile of these new therapeutic radionuclides in conjunction with AERB with an objective to make these treatments available as a day care procedure so that it could be made available to institutions without the facility of an isolation ward. We are actively participating in disease management groups and tumor boards of individual institutions to increase the awareness among clinicians about the safety and efficacy so that the patients can avail these in the earlier stages of their disease rather than when they are already heavily pretreated with other forms of treatment with both treatment related and "financial" toxicity.

Conclusion

We believe that the theranostic journey in India is on the right track and it is only a matter of time when we will be able to overcome the constraints and put these form of treatment to optimal use in a larger number of patients. We are trying to perfect the art of theranostics and learning new things regularly. Patient selection appears to be a key factor and performance status also plays a very important role in predicting outcome. We expect to perfect this art with more experience as it is believed that "perfection comes with experience and experience comes with bad judgements."

Compliance with Ethical Standards

Conflict of Interest Partha S Choudhury and Manoj Gupta declares that they have no conflict of interest.

Ethical Approval This article does not contain any studies with human participants or animals performed by any of the authors.

Informed Consent The institutional review board of our institute approved this retrospective study, and the requirement to obtain informed consent was waived.

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