

THERANOSTICS - NEUROENDOCRINE TUMOURS

Theranostics is the term used to define targeted therapy based on targeted diagnostic tests. This phenomenon has been in use in nuclear medicine since the 1940s when isotopes of radioactive iodine (I-131 and I-123) were introduced to diagnose and treat benign and thyroid diseases.^[1] Radioiodine labelled metaiodobenzylguanidine, an analogue of noradrenaline, is another example of theranostics at play in the treatment of metastatic neuroblastoma since decades.^[2] Radionuclide therapies for bone pain palliation (i.e., strontium-89, samarium-153 and radium-223) work on the similar principle by targeting the osteoblastic metastases documented on the conventional bone scintigraphy.^[3]

In the 21st century, theranostics is a part of the personalized and precision medicine. New radiotracers are available for use with hybrid single-photon emission computed tomography (SPECT) and positron emission tomography (PET) scanners, the latter being the more superior modality. PET tracer i.e., Fluoride-18 and Gallium-68 labelled somatostatin analogues have higher affinity than the SPECT-based tracers such as indium-111 (In-111) or technetium (Tc-99m) octreotide.^[4] On the therapeutic front high-energy β (beta) emitters such as lutetium-177 (Lu-177) and yttrium-90 (Y-90) lead the way along with radium (Ra 223) an α (alpha) emitter.^[5,6]

One area where theranostics is making promising headway is the metastatic neuroendocrine tumours (NETs). NETs are relatively rare and heterogeneous neoplasms which are grouped together due to their distinct features, which are hormone production and metabolism, histology and expression of somatostatin receptors (SSRs) on the cell surface.

Functional imaging of the NETs can be done using the metabolic or peptide radiotracers. The metabolic radiotracers are modified precursors which are further modified by the NET cell. The peptide radiotracers

bind to specific receptors on tumour cell surface. The peptide radiotracers which are internalized after binding to the receptors are 'agonists' while those which are not internalized are the 'antagonists'.^[6,7]

Patients with NETs may present with local tumours and with or without regional or distant metastases with liver being the most common site. These tumours may remain clinically silent until a significant liver tumour burden is present. Therapeutic options for NET include surgery, somatostatin analogues, interferon, chemotherapy, molecularly targeted agents, locoregional therapies and peptide receptor radionuclide therapy (PRRT). Basic underlying principle remains that the disease with high SSR receptor expression documented with somatostatin analogue scintigraphy can be treated with similar analogues labelled with Lu-177 and Y-90. Individual β -emitters elicit variation in energy and path length.

Lu-177 PRRT was supposed to be more suited for smaller tumour volumes compared with Y90 which emits more energetic particles with longer path length.^[7,8] However, Kunikowska *et al.* demonstrated that overall survival is significantly higher in patients treated with the combination of Y-90/Lu-177 DOTA-TATE compared with Y-90 DOTA-TATE alone.^[9]

The most significant breakthrough for the role of PRRT has been the NETTER-1 Phase III Trial of Lu-177 DOTA-TATE for midgut NET.^[10] Strosberg *et al.* conducted an international multicentre randomized, controlled trial across 41 centres in eight countries. The trial evaluated the efficacy and safety of Lu-177 DOTA-TATE (7.4 GBq every 8 weeks \times 4 administrations) and octreotide LAR (60 mg) in 229 patients with advanced, progressive and somatostatin-receptor-positive midgut NET. The trial results showed evidence for a clinically meaningful and statistically significant increase in progression-free survival (65.2% vs. 10.8%) and objective radiographic response (18% vs. 3%). Clinically significant myelosuppression was noted in <10% of patients treated with Lu-177 DOTA-TATE. Trial findings suggested a potential survival benefit in treating advanced midgut NET with Lu-177 DOTA-TATE.^[10,11,12]

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In 2013, the international atomic energy agency along with the European Association of Nuclear Medicine and the Society of Nuclear Medicine and Molecular Imaging (SNMMI) issued a joint practical guidance on PRRT.^[13] This joint effort was based on review of experience and data acquired over 15 years, initiated in Europe. Past 2 years have been very favourable for the clinical use of NET theranostics given that in 2016 FDA approved Ga-68 DOTA-TATE for imaging followed by Lu-177 DOTA-TATE for therapy in 2018 following the NETTER-1 trial results.

PRRT for NET represents the tip of the iceberg in terms of theranostics. Prostate cancer is yet another area of significant focus.^[14] Promising results for Lu-177 PSMA are breaking ground at the 2018 SNMMI meeting in Philadelphia as these lines are drafted.^[15]

Precision and personalized medicine is the way that things are headed. In the process, terminologies are being invented and modified to reflect the changes and highlight the focus. Theranostics is lately changing to theragnostics to highlight the importance of prognosis amidst diagnosis and treatment.^[16] Let's see what more future has to offer.

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