Nuclear Medicine and Molecular Imaging (2019) 53:7–10
https://doi.org/10.1007/s13139-018-0562-5

REVIEW

ISSN (print) 1869-3482
ISSN (online) 1869-3474

Current Status of Theranostics in Jordan

Akram Al-Ibraheem[1] · Ali Mohamedkhair[1]

Received: 3 December 2018 / Accepted: 6 December 2018 / Published online: 11 December 2018

Abstract

Exploring the unknown is one of the key factors that lead to great discoveries in mankind history. With the advances in medicine and the development of new approaches towards patient care, like next-generation sequencing and patient-centered care, the need for treatments tailored to patient through personalized medicine has become more compelling. Theranostics has been introduced as a combination of a diagnostic tool and a therapeutic tool on the same vector for a specific disease, to facilitate personalized medicine. Nuclear medicine has shown the capability of providing a strong platform for this new approach through its arms, molecular imaging, and targeted molecular therapies. Though the prototype of theranostics has been practiced in Jordan since decades in the field of diagnosis and treatment of well-differentiated thyroid cancer, recently, the King Hussein Cancer Center (KHCC), a leading and comprehensive cancer center in Jordan and in the Middle East, has leaped forward to introduce the new approaches of theranostics through the nuclear medicine applications. This paper sheds the light on the most important aspects of this new theranostics practice in Jordan such as peptide receptor radionuclide therapy (PRRT) and prostate-specific membrane antigen (PSMA)–based theranostics.

Keywords Theranostics · Nuclear medicine · Peptide receptor radionuclide therapy · PSMA · Molecular imaging · Jordan

Introduction

In the era of personalized medicine, theranostics has been introduced as a new platform for precision medicine. The use of molecular imaging coupled with the therapeutic application of the same agent, or at least very similar one, to cover all aspects of patient management, from diagnosis, drug delivery, to response monitoring, is the corner stone of this field. It occurs through specific biological pathways inside the human body.

The application of theranostics results in giving the right treatment for the right patient in the right time and it is expected to decrease poor compliance due to side effects and enhance the therapeutic efficacy. For example, heterogeneity of cancer lesions, which is considered one of the biggest challenges of therapeutic success, can be determined through theranostics, thus determining which patient will benefit from therapy, avoidance of unnecessary conventional therapeutics, and applying other salvage treatments [1].

Nuclear medicine has many advantages to provide a robust platform for theranostics such as employing molecular targeting vectors which can be labeled with distinct radionuclides for diagnosis and therapy, high specific uptake sparing normal tissue and targeting metastases as identified by pre-imaging, non-invasive depiction and delivering high absorbed tumor dose, and considerably quantifying the tumor burden and the proportional response [2, 3].

There are many pairs of radioisotopes that have been employed in theranostics. After decades of practicing the conventional diagnostic and therapeutic nuclear medicine applications in thyroid cancer and some limit in neuroblastoma and palliation bone pain metastases, KHCC has recently established and introduced the service of Gallium-68 (^{68}Ga)-based positron emission computed tomography combined with computed tomography (PET/CT) into Jordan in both neuroendocrine tumors (NETs) and prostate cancer. This has been coupled with the targeted radionuclide peptide therapy utilizing the Lutetium-177 (^{177}Lu).

Theranostics Applications in NETs in Jordan

^{68}Ga DOTA-Peptide PET/CT in NET

PET/CT imaging with ^{68}Ga-labeled radioligand has become an established procedure for accurate staging of patients with

✉ Akram Al-Ibraheem
aibraheem@khcc.jo

[1] Department of Nuclear Medicine, King Hussein Cancer Center, 202 Queen Rania St., P.O. Box 1269, Amman 11941, Jordan

NETs [4]. It confers benefits like detection of more or smaller lesions, or those with low to moderate somatostatin expression, resulting in higher sensitivity and diagnostic accuracy when compared to Indium-111 (^{111}In) pentetreotide SPECT imaging, the previous old gold standard. Another added value is that it can be used to predict the potential benefit of PRRT to NETs patients [5]. In KHCC, the application of PET/CT with radiolabeled somatostatin analogs (^{68}Ga DOTA-peptide) in the diagnosis of NETs dated back to 2013 after the installation of the first Germanium-68/Gallium-68 (^{68}Ge/^{68}Ga) generator. Labelling has been performed using a manual synthesis module. Over 300 scans were done up to date, promoting and paving the road for other aspects of peptide PET imaging and peptide-based radionuclide targeted treatment. This molecular diagnostic imaging approach is currently considered the gold standard in our practice guidelines for staging, stratifying for treatments, monitoring response to treatment, and restating of most NETs.

PRRT in NETs

PRRT is a form of systemic endo-radiotherapy, which allows delivery of radionuclides to tumor cells expressing high levels of somatostatin receptors. It is composed of a radioisotope (^{111}In, ^{90}Y, or ^{177}Lu), a carrier molecule (octreotide, octreotate), and a chelator (DOTA, or DTPA) that binds them, stabilizing the complex [6]. Radiolabeled somatostatin analogs (SSA_s) bind to their receptor and internalized as per normal receptor recycle dynamics. The breakdown products of the radiolabeled peptide are stored in the lysosomes, thus enabling delivery and causing suspension of radioactivity inside tumor cells. As a consequence, radiation-induced DNA damage will occur to the tumor cell, leading to its eventual death [6].

We have demonstrated in our recent literature review that PRRT currently represents one of the treatment lines for patients with neuroendocrine tumors (NET_s). In particular, in patients with grade 1 and 2 gastroenteropancreatic NETs, that are inoperable and metastatic, who failed first-line somatostatin treatment, and whose tumor expresses high levels of somatostatin receptors ($SSRT_s$), PRRT would be a viable option [6]. Moreover, the tolerability of PRRT is good, in terms of short- and long-term side effects, and also when considering the safe and effective cumulative dose after progression following initial PRRT, which is up to 60.5 GBq [6, 7]. An additional value of PRRT and when compared to other systemic therapeutic options available is its efficacy in symptom control and prolongation of life [8, 9].

Radiolabeled somatostatin analogs (SSA_s) bind to their receptor and internalized as per normal receptor recycle dynamics. The breakdown products of the radiolabeled peptide are stored in the lysosomes, thus enabling delivery and causing suspension of radioactivity inside tumor cells. As a consequence, radiation-induced DNA damage will occur to the tumor cell, leading to its eventual death [6].

Our practice at King Hussein Cancer Center (KHCC) using ^{177}Lu DOTA-TATE started back in 2014. Following the international guidelines [10], patient's selection is based upon positive ^{68}GaDOTA-peptide PET/CT SCAN, objective disease progression, adequate blood profile, creatinine level, ECOG performance status score ≤ 2, and Ki-67 levels less than 20%. In a MDC with a nuclear medicine physician, surgeon, oncologist, radiologist, and pathologist approve the treatment plan. Preparations for the treatment include renal protection with amino acid infusion over 4 h, and half an hour before injection of ^{177}Lu DOTATATE.

Up to the date of this study, 14 patients were treated at our center by receiving 4 doses of ^{177}Lu DOTA-TATE spaced 8 weeks each. We currently use the dose empiric approach but also working on building our capacity in dosimetric methodology to keep the pace in this field. Our observations of our patients showed promising results in terms of patient's response rates and control of disease as the majority experienced partial responses or have had disease stabilization which are in line with the published results in this field. Our selection criteria for PRRT currently include patients with gastroenteropancreatic NETs but it is expected to have this treatment expanding to cover other types of NETs, provided those tumors showing overexpression of somatostatin receptors and the impact on patient's survival has been demonstrated by clinical trials.

Theranostics Applications in Prostate Cancer in Jordan

^{68}Ga PSMA PET/CT

PSMA ligands history started 20 years ago at John Hopkins University. However, its popularity and clinical acceptance were not appreciated until 2012 when first human studies were performed at Heidelberg in Germany [11]. Development in PSMA ligands' production and clinical use, which dates back to 2002, exposed them to comprehensive studies and publications. This development, including the invention of ^{68}Ga PSMA-11, resulted in a new platform for nuclear medicine imaging and personalized peptide radio nucleic therapy for prostate cancer [12].

PSMA is a type II transmembrane protein and an ideal target for molecular imaging of prostate cancer owing to its biological characteristics [13]. These characteristics include overexpression on the cell membrane of nearly all prostate cancer cells compared to normal non-target cells, and increased expression in advanced stage and castration-resistant prostate cancer [13].

In KHCC and Jordan, our practice includes the use of ^{68}Ga PSMA-HBED-CC for PET/CT imaging in primary staging of high-risk prostate cancer and in restaging of biochemical relapse. We published our experience in this regard; our study was the first of its kind in the region and one of the few studies investigating the impact of this imaging modality on clinical management [13]. We demonstrated that ^{68}Ga PSMA PET/CT outperforms CT, magnetic resonance imaging (MRI), and bone scintigraphy with respect to accuracy of primary staging of high-risk prostate cancer patients and concluded that ^{68}Ga PSMA PET/CT seems to be an invaluable imaging modality in the assessment of primary high-risk prostate cancer patients particularly if CT or MRI scans and bone scintigraphy show equivocal findings, with great potential for detection of lymph node spread and bone metastasis, thus impacting the management plan for more than half of our cohort in this study [13].

At KHCC, ^{68}Ga PSMA PET/CT is increasingly replacing the conventional imaging modalities in the setting of biochemical relapse and restaging of prostate cancer. Also it is being more widely employed in the staging of high-risk prostate cancer as it provides more accuracy and may stratify the treatment plan. ^{68}Ga PSMA PET/CT is changing the paradigm of the prostate cancer management plan, opening a wide door for personalized medicine in prostate cancer.

^{177}Lu PSMA Radionuclide Treatment

The PSMA-targeting radionuclide theranostics concept potentially offers advantages not only in regard to diagnosis but also the therapy of metastatic castration resistance prostate cancer (mCRPC) patients.

This targeted radionuclide treatment has been introduced in Europe particularly in Germany for many years as the last line of treatment in men with advanced stage prostate cancer who had exhausted all their treatment options [14]. The German multicenter study of ^{177}Lu PSMA radionuclide therapy revealed the advantageous efficacy and safety profile of this targeted treatment in mCRPC and demonstrated the superiority of this treatment to those of other third-line systemic in this retrospective study. Authors advocated that future prospective phase II/III studies are warranted to validate the added value and survival benefit of this new therapy [14].

This promising result of ^{177}Lu PSMA radionuclide treatment has been recently demonstrated in prospective phase two trial by group of researchers from the Peter MacCallum Cancer Centre in Australia. This study showed a significant response rate and improvement in quality of life in men with mCRPC who received this targeted radionuclide therapy after they progressed on standard treatment including chemotherapy and second-generation anti-androgens [15]. In this study, PSA declines 50% (or more) of the baseline value in almost 60% of the patients. Overall, there was a significant reduction in pain as well as measurable imaging response in 82% of the patients who had measurable disease [15].

In Jordan and KHCC, we have treated the first patient with ^{177}Lu PSMA-617 in 2017. This patient was referred for nuclear medicine department as a case of progressive metastatic prostate cancer to the bone who exhausted all other options. He received 3 cycles (7.4 GBq per cycle) every 8–10 weeks. Post-treatment ^{177}Lu scans and ^{68}Ga PSMA PET/CT scans showed very good response with decline in PSA level from 480 to 42 without any serious side effects. Genitourinary multidisciplinary clinic at KHCC has now ratified this treatment for limited cases of progressive mCRPC and more patients are being referred for nuclear medicine to be evaluated and checking the eligibility for this new radionuclide targeted treatment. We are now awaiting the results of the prospective phase II and III trials being conducted nowadays that expectantly would demonstrate the impact of ^{177}Lu PSMA on survival in comparison to standard treatments. This will certainly nurture this new effective treatment and make it a viable option for despairing prostate cancer patients and even at earlier stage before having extensive metastatic disease.

Theranostics by Metaiodobenzyle Guanidine in Jordan

Metaiodobenzyle guanidine (MIBG) is structurally similar to the neurotransmitter norepinephrine and enters neuroendocrine cells from the sympathetic nervous system either by endocytosis or by passive diffusion, before being stored in neurosecretory granules [3]. ^{131}I MIBG and ^{123}I MIBG constitute the radiolabeled molecules. Both used in scintigraphy to detect neuroendocrine tumors such as neuroblastoma, medullary thyroid cancer, paraganglioma, and pheochromocytoma. ^{123}I MIBG is more suitable for planar and SPECT imaging because of its lower gamma energy (159 kev) [3]. The use of I^{123} MIBG is invaluable in assessing therapy response and evaluation of potential ^{131}I MIBG therapy in patients with inoperable or metastatic neuroblastoma and pheochromocytoma [3].

^{131}I MIBG in high doses is an effective treatment in treatment-resistant neuroblastoma (NB), unresectable or metastatic pheochromocytoma (PC) and paraganglioma (PG) [16].

^{131}I MIBG has been used in Jordan in the diagnosis of NB for more than 10 years. In the last few years, KHCC has started employing ^{123}I MIBG in the diagnosis and stratifying for the treatment with ^{131}I MIBG [17]. Since 2015, ^{131}I MIBG treatment has been given to many patients suffering from metastatic neuroblastoma, metastatic paraganglioma, and unresectable pheochromocytoma according to the European guidelines [18].

In this regard, an intramural grant (17 KHCC 32) has been offered for nuclear medicine physicians at KHCC to evaluate the accuracy and diagnostic utility of functional imaging including ^{123}I MIBG, ^{68}Ga DOTA-TOC, and ^{18}F-FDG-PET in

pediatric high-risk neuroblastoma patients. Six patients have been recruited in this pilot study with interesting findings planned to be published next year.

Jordan Research and Training Reactor

Jordan Research and Training Reactor (JRTR) is the first nuclear reactor in Jordan which was inaugurated in December 2016. It is the first South *Korean* made nuclear reactor exported abroad. It aims to execute many activities, including both medical and industrial applications of radioisotopes to satisfy national needs and expectantly to cover the regional countries.

The JRTR will start producing I-131 and Mo99/Tc99m in the beginning of 2019. In the next phase, it will expand the radioisotopes production to include Lu-177. JRTR will rise as an evolving asset in the peaceful and medical nuclear technology applications to address needs both at national and hopefully international levels.

Conclusion

Theranostics in Jordan is moving forward with pace, getting the hype from the world and awaiting more robust clinical data and studies examining this innovative and promising field. The involvement of nuclear medicine physicians in the multidisciplinary teams at KHCC is expected to nurture the prosperity of theranostics approach in Jordan.

The new JRTR that recently inaugurated in Jordan is expected to ease the access to radionuclide materials such as ^{131}I and ^{177}Lu in Jordan and the region in the early future indeed.

Compliance with Ethical Standards

Conflict of Interest Akram Al-Ibraheem and Ali Mohamedkhair declare 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.

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

References

1. Ahn B-C. Contribution of radionuclide theranostics for managing intractable malignancies. Nucl Med Mol Imaging. 2018;52:168–9.
2. Taïeb D, Hicks RJ, Pacak K. Nuclear medicine in cancer theranostics: beyond the target. J Nucl Med. 2016;57:1659–60.
3. Yardanova A, Eppard E, Kürpig S, Bundchuh RA, Schönberger S, Gonzalez-Carmona M, et al. Theranostics in nuclear medicine practice. Onco Targets and Therapy. 2017;10:4821–8.
4. Putzer D, Kroiss A, Gabriel M, Traub-Weidinger T, Uprimny C, von Guggenberg E, et al. Somatostatin receptor PET in neuroendocrine tumors: 68Ga-DOTA0, Tyr3-octereotide versus 68Ga-DOTA0-lanreotide. Eur J Nucl Med Mol Imaging. 2013;40:364–72.
5. Barriuso J, Custodio A, Afonso R, Alonso V, Austudillo A, Capdivila J, et al. Prognostic and predictive biomarkers for somatostatin analogs, peptide receptor radionuclide therapy and serotonin pathway targets in neuroendocrine tumours. Cancer Treat Rev. 2018;70:209–22. https://doi.org/10.1016/j.ctrv.2018.09.008.
6. Hirmas N, Jadaan R, Al-Ibraheem A. Peptide receptor radionuclide therapy and the treatment of gastroentero-pancreatic neuroendocrine tumors: current findings and future perspective. Nucl Med Mol Imaging. 2018;52:190–9.
7. van der Zwan WA, Brabander T, Kam BLR, Teunissen JJM, Feelders RA, Hofland J, et al. Salvage peptide receptor radionuclide therapy with [^{177}Lu-DOTA, Tyr^3] octereotate in patients with bronchial and gastroenteropancreatic neuroendocrine tumours. Eur J Nucl Med Mol Imaging. 2018. https://doi.org/10.1007/s00259-018-4158-1
8. Prasad V, Bodei L, Kidd M, Modlin IM. Whither peptide receptor radionuclide therapy for neuroendocrine tumors: an Einsteinian view of the facts and myths. Eur Nucl Med Imaging. 2014;41:1825–30. https://doi.org/10.1007/s00259-015-2780-0.
9. Strosberg J, El-Haddad G, Wolin E, Hendifar A, Yao J, Chasen B, et al. Phase 3 trial of 177Lu-Dotatate for midgut neuroendocrine tumors. N Engl J Med. 2017;376:125–35.
10. Bodei L, Mueller-Brand J, Baum RP, Pavel ME, Hörsch D, O'Dorisio MS, et al. The joint IAEA, EANM, and SNMMI practical guidance on peptide receptor radionuclide therapy (PRRNT) in neuroendocrine tumours. Eur J Nucl Med Mol Imaging. 2013;40:800–16.
11. Virgolini I, Decristoforo C, Haug A, Fanti S, Uprimny C. Current status of theranostics in prostate cancer. Eur J Nucl Med Mol Imaging. 2018;45:471–95.
12. Rahbar K, Afshar-Oromieh A, Jadvar H, Ahmadzadehfar H. PSMA theranostics: current status and future directions. Mol Imaging. 2018;17:1–9.
13. Hirmas N, Al-Ibraheem A, Herrmann K, Alsharif A, Muhsin H, Khader J, et al. [68Ga] PSMA PET/CT improves initial staging and management plan of patients with high-risk prostate cancer. Mol Imaging Bio. 2018. https://doi.org/10.1007/s11307-018-1278-8.
14. Rahbar K, Ahmadzadehfar H, Kratochwil C, Haberkorn U, Schäfers M, Essler M, et al. German multicenter study investigating 177Lu-PSMA-617 radioligand therapy in advanced prostate cancer patients. J Nucl Med. 2017;58:85–90.
15. Hofman MS, Violet J, Hicks RJ, Ferdinandus J, Thang SP, Akhurst T, et al. [^{177}Lu]-PSMA-617 radionuclide treatment in patients with metastatic castration-resistant prostate cancer (LuPSMA trial): a single-centre, single-arm, phase 2 study. Lancet Oncol. 2018;19:825–33.
16. Kayano D, Kinuya S. Current consensus on I-131 MIBG therapy. Nucl Med Mol Imaging. 2018;52:254–65.
17. Bombardieri E, Giammarile F, Aktolun C, Baum RP, Bischof Delaloye A, Maffioli L. 131I/123I-Metaiodobenzylguanidine (mIBG) scintigraphy: procedure guidelines for tumour imaging. Eur J Nucl Med Mol Imaging. 2010;37:2436–46.
18. Giammarile F, Chiti A, Lassmann M, Brans B, Flux G. EANM procedure guidelines for 131I-meta-iodobenzylguanidine (131I-mIBG) therapy. Eur J Nucl Med Mol Imaging. 2008;35:1039–47.