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PERSPECTIVE

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Current Status and Growth of Nuclear Theranostics in Singapore

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Abstract

The concept of theranostics, where individual patient-level biological information is used to choose the optimal therapy for that individual, has become more popular in the modern era of 'personalised' medicine. With the growth of theranostics, nuclear medicine as a specialty is uniquely poised to grow along with the ever-increasing number of concepts combining imaging and therapy. This special report summarises the status and growth of Theranostic Nuclear Medicine in Singapore. We will cover our experience with the use of radioiodine, radioiodinated metaiodobenzylguanidine, peptide receptor radionuclide therapy, prostate specific membrane antigen radioligand therapy, radium-223 and yttrium-90 selective internal radiation therapy. We also include a section on our radiopharmacy laboratory, crucial to our implementation of theranostic principles. Radionuclide theranostics has seen tremendous growth and we hope to be able to grow alongside to continue to serve the patients in Singapore and in the region.

Keywords Theranostic · Singapore · Radioiodine · Lutetium · Yttrium · Radium

Introduction

The concept of theranostics has been deeply interwoven into the history of nuclear medicine. Since the 1930s when radioiodine began to be used in the customised therapy of individuals with thyroid disorders, nuclear medicine has grown alongside, whereby now, we have a large array of radionuclides at our disposal [1]. Because individual patient-level imaging information is used to tailor the optimal therapy for that patient, this fits with the paradigm shift in the modern era of 'personalised' medicine. There are increasing numbers of publications on the subject, including a journal called 'Theranostics' [2].

The nuclear medicine department of the Singapore General Hospital is the oldest in Singapore. It was started in 1967 as part of the Radiotherapy Department with the National University of Singapore Department of Medicine. In the 1970s, we started thyroid uptake studies. There was a dedicated radiopharmacy laboratory to conjugate and dispense radiopharmaceuticals to the whole of Singapore. Our first gamma camera was installed in 1979. With that, we started treating hyperthyroid and thyroid cancer patients with radioiodine (I-131) in the 1980s.

We started using metaiodobenzylguanidine (I-131 mIBG) for imaging in 1996 and for therapy in 2000. Zevalin was introduced in 2005 and the department was involved in phase III, multicentre trial to evaluate the efficacy and safety of subsequent Zevalin versus observation in patients with diffuse large B cell lymphoma who were in complete remission after first-line CHOP-R therapy. Several years later, Zevalin declined in clinical use. In 2012, we started using lutetium-177 DOTATATE (LuTATE) for the treatment of patients with somatostatin-positive metastatic tumours. Yttrium-90 for Selective Internal Radiation Therapy (Y-90 SIRT) has been used since 2006. Radium-223 (Ra-223) has also been used in our department since 2008. In 2018, we built on the knowledge gained from LuTATE and started lutetium-177 prostate specific membrane antigen (PSMA) radioligand therapy.

We discuss the status of each of these agents in Singapore in turn and present our local practice and clinical experience with them.

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Radiochemistry Synthesis

Theranostics can be effected by using different radioisotopes or doses of the same element (e.g. I-123 or I-124 for I-131) or by replacing a diagnostic radioisotope in a molecule with a therapeutic radioisotope with similar chemical properties (e.g. gallium-68 for lutetium-177 (Lu-177), technetium-99m for rhenium-188), whilst maintaining the biological properties of the radiopharmaceutical. Lu-177 is an attractive radionuclide as therapy can be effected via β-particle emission whilst post-therapy imaging can be performed with its gamma emission of 208 keV (11%) and 113 keV (6.4%) which is optimal for most gamma cameras.

Radiochemistry synthesis was performed manually in our department before the year 2016 (with the exception of F-18 fluorodeoxyglucose). With the arrival of new automated radiopharmaceutical synthesiser modules (Scintomics GmbH) in 2016, radiolabelling has been carried out in a more reliable manner.

Tracers for patient administration have to pass quality control tests including pH and radiochemical purity tests which we carry out in-house.

Radioiodine (I-131)

The first theranostic radiopharmaceutical used in Singapore General Hospital is sodium iodide I-131. There are several radioisotopes of iodine including I-123, I-124 and I-131. I-131 is the ubiquitous radionuclide used due to its widespread availability and lower cost.

Radioiodine is used in the diagnosis and treatment of Graves' disease; for remnant thyroid ablation and treatment of metastatic iodine-avid disease in patients with well-differentiated thyroid carcinoma (WDTC). In our department, an average of 330 and 300 patient treatments are administered annually for benign and malignant thyroid disease respectively. I-131 is available in our department as a capsule (of fixed-dose activity) or as a liquid whereby the desired activity is withdrawn from the vial and orally administered to patients.

Consultations are held with every patient referred to determine appropriate indication, proper patient preparation (including thyroid hormone withdrawal, use of recombinant human TSH, low iodine diet, etc.) and discussion on possible adverse effects. I-131 is generally well tolerated with nausea/vomiting and sialadenitis being the most frequent adverse effects. Long-term complications such as xerostomia are infrequent.

Due to the unavailability of I-123 and logistical complexities using I-131 for diagnostic scans prior to I-131 therapy, many centres had resorted to empirical radioiodine dose activity based on the initial patient risk profile following thyroid surgery. The Singapore Consensus on Multidisciplinary Care for Well-Differentiated Thyroid Cancer has also been published in 2016 [3]. An increase in the use of lower activities of I-131 for remnant thyroid ablation has been seen in our centre. Higher activities of I-131 (> 1110 MBq (megabecquerel)) require hospitalisation and discharge from radiation isolation when radiation levels fall below 80 μSv/h at 1 m as per local regulatory guidelines. Post I-131 whole body scans are performed 48 to 72 h after oral administration.

In selected patients, especially paediatric patients where radiation concern exists in cancer survivors, we have embarked on pretreatment dosimetry with a small dose of I-131. This allows more precise calculation of I-131 activity in a hope to minimise complications from radiation exposure.

Iodine-123 and Iodine-131 Metaiodobenzylguanidine

Metaiodobenzylguanidine (mIBG), the guanethidine analogue of norepinephrine, is specifically taken up by the norepinephrine transporter uptake mechanisms. Due to limited availability of I-123 mIBG, our department has been using I-131 mIBG for the diagnosis and treatment of patients with phaeochromocytomas, paragangliomas, neuroendocrine tumours and neuroblastomas (NB). Whilst LuTATE has increasingly been used to treat a similar patient population, mIBG therapy still has a therapeutic role to offer in NB and in patients who do not express significant somatostatin receptors.

I-131 mIBG is shipped frozen and requires thawing prior to administration. It is given as a slow intravenous infusion over 1 to 2 h with close monitoring of the vital signs during and after infusion. Initially started as empirical fixed activity treatments (3700–7400 MBq) for phaeochromocytoma and paragangliomas, since 2012, the department has embarked on high-dose I-131 mIBG treatments in high-risk NB patients. These are typically chemotherapy refractory or relapsed NB patients with administered activities beyond 12 mCi/kg body weight (to a maximum of 18 mCi/kg body weight) and autologous stem cell support. The quoted response rates in the medical literature are beyond 30%. Our current treatment number averages 1–2 a year.

As the administered activities are above 1110 MBq, all treatments require hospitalisation and radiation isolation. Therapy is straightforward with an expected hospital stay of 3–4 days. However, pretreatment consultation and preparation (Lugol's solution, appropriate dietary advice and avoidance of interfering medications) is crucial for a successful treatment. Close collaboration with medical oncology is paramount. Treatment protocols should be drawn up as the administered activity can be very high and concerns over radiation exposure to the healthcare worker may arise. The most common adverse effects we have encountered are nausea and vomiting. In patients with phaeochromocytoma and functional

paragangliomas, catecholamine surge should be anticipated and emergency measures prepared for. Myelosuppression is typical 4–6 weeks post-treatment with reports of hypothyroidism and possible second malignancies in the longer term. Typically, a post-treatment whole body scan is performed a few days after mIBG infusion to reduce excessive radiation exposure to staff.

Lutetium-177 DOTATATE (LuTATE)

Neuroendocrine tumour (NET) is a group of neoplasms with a common origin of neuroendocrine cells and common physiological feature of universal expression of transmembrane somatostatin receptors [4]. The latter is an ideal target for radionuclide theranostics, an endeavour started in Europe more than a quarter of a century ago, gained world recognition thereafter, and finally obtained FDA approval recently after a successful phase 3 clinical trial [5].

It was back in 2012, a decade after peptide receptor radionuclide therapy (PRRT) for NET became a clinical reality in Europe, Singapore General Hospital Department of nuclear medicine and molecular imaging (SGH/DNMMI) responded to the internal and external requests for this new radionuclide to become available locally, for the benefit of Singaporean as well as regional foreign patients.

SGH/DNMMI, the largest nuclear medicine centre in the region with an on-site cyclotron and well-equipped radiopharmacy, quickly formed a delegation comprising of nuclear medicine physicians, technologists, radiopharmacists, radiophysicists and specialised nurses. The delegation made a multi-week-long study tour to centres in Germany and Austria which were front-runners in the field of PRRT (Fig. 1).

Taking advantage of already available gallium-68 somatostatin analogue (^{68}Ga-SSA) PET imaging [6], and a multidisciplinary NET team, the first PRRT in this region was offered in SGH at the beginning of 2012 (Fig. 2), one of the earliest in Asia. The excitement for this therapy immediately went beyond Singapore and beyond the circle of nuclear medicine to reach patients and doctors in related fields in Southeast Asia.

Nowadays, PRRT in SGH/DNMMI is well known by referring doctors in Asia and has attracted many patients from other countries such as China, the USA, Malaysia, Taiwan and Indonesia. Many of our 120 sessions of treatment yearly are foreign patients who are here specifically seeking PRRT expertise.

Our workflow and protocol in SGH/DNMMI are quite concordant with recommendations by current international guidelines [7, 8]. All patients must have ^{68}Ga-SSA PET/CT scan with 18F-fluorodeoxyglucose PET/CT optional for pre-PRRT evaluation. Patients are admitted for infusion following amino acids cocktail infusion for renal protection. Post-therapy scan including targeted SPECT/CT is done at 24 h for purpose of localization and dosimetry.

With experience accumulated in the past 7 years from hundreds of patients, SGH/DNMMI is now providing training in PRRT for colleagues from other hospitals in the region and is carrying out multicentre clinical research in the field. Our expert physicians share their experiences and insights into international or regional conferences (Fig. 3) and peer-reviewed journals [9]. Further advanced treatments including PRRT plus chemotherapy (PRCRT), alpha emitter PRRT with actinium-225 is currently being planned to benefit patients who do not respond well to conventional PRRT alone.

Yttrium-90 Selective Internal Radiation Therapy

The use of radionuclides for SIRT has seen tremendous growth in the recent years. We have used both resin (SIR-Spheres) and glass microspheres (TheraSphere). In the past,

Fig. 1 SGH delegation on study tour in Europe 2011

Fig. 2 1st PRRT in Singapore general hospital, March 2012

Fig. 3 SGH/DNMMI doctors Taipei Veterans General Hospital oncologist and grateful patients in Taiwan NET symposium, 2017

we have also used Iodine-131 lipoidal and Rhenium-188 lipiodol as part of an IAEA-sponsored multicentre study.

Our department has been a strong advocate that a pre-procedure Tc-99 m macroaggregated albumin scan has uses beyond that of a conventional liver lung shunt scan; namely that of a radiation simulation study. A team of dedicated technologists and doctors come together drawing regions of interest on the SPECT/CT images of the liver and lungs and perform dosimetry based on MIRD for the tumours and normal organ tissues. We have published widely on our partition modelling for Y-90 SIRT and our dosimetry worksheets are freely available online to peers and colleagues who wish to adopt or understand more on this topic [10].

Our institution has also participated in multinational trials under the Asia-Pacific Hepatocellular Carcinoma (AHCC) Trials Group resulting in the pivotal SIRveNIB study which was presented at the 2017 American Society Clinical Oncology Annual Meeting and published in the March 2018 volume of The Journal of Clinical Oncology. Other research topics we have been involved in include Y-90 PET for SIRT [11–13] and determining remnant Y-90 activity post radioembolization [14].

Our work in Y-90 SIRT spans over a decade of clinical experience and our centre treats close to 150 cases yearly. Our caseload comprises primarily the hypervascular hepatocellular carcinomas and to a lesser extent other tumours such as cholangiocarcinoma or colorectal tumour metastases. With the expertise from our interventional radiology colleagues, we employ the latest techniques using intra-arterial computed tomography during angiography to super-selectively target tumours [15] or even perform radiation segmentectomy/lobectomy for better outcomes. Our local experience mirrors the published literature with common side effects such as post-embolisation phenomenon and rarely radiation pneumonitis or radiation-induced liver disease. Our patient selection process is usually in a multidisciplinary setting. The patients are usually admitted inpatient for the procedure under the care of the primary liver surgeon or medical oncologist.

Radium-223

Radium-223 dichloride (Ra-223) is a predominantly alpha-emitting radiopharmaceutical, developed by Algeta ASA and Bayer AG, for the treatment of patients with bone metastases. Previously, the department used strontium-89 chloride and samarium-153-EDTMP for bone metastases pain palliation. We also studied the use of rhenium-188 HMDP for bone pain. Ra-223 has potentially more advantageous radiation characteristics with a physical half-life of 11.4 days.

The department started using Ra-223 (previously known as Alpharadin and now marketed as Xofigo) in the phase III double-blind randomised ALSYMPCA trial in 2008, and subsequently, in the ERA 223 trial in 2014, as a phase III randomised, double-blind, placebo-controlled trial in combination with abiraterone acetate and prednisolone in the treatment of asymptomatic or mildly symptomatic chemotherapy-naïve subjects with bone predominant metastatic castration-resistant prostate cancer. Other clinical studies that the department was involved in is the radium-223 dichloride Asian population study in the treatment of CRPC patient with bone metastasis in 2013 and in the treatment of bone metastases in breast cancer in 2015. Following regulatory approval and obtaining satisfactory logistical arrangements, the department became the first centre in the region to offer Ra-223 dichloride as a clinical service in 2014.

Our experience is that it is a relatively easily prepared radiopharmaceutical with ease of administration in an outpatient setting. We typically hold consultations with the patient prior to the first injection to discuss indications, side-effects, radiation safety precautions and schedule of cycles. The side effects that we encountered are similar to those described in the literature with abdominal discomfort, diarrhoea, nausea and drop in blood counts. There is symptomatic improvement in many patients with drop in serum alkaline phosphatase and occasionally PSA levels.

Prostate-Specific Membrane Antigen Radioligand Therapy

Prostate cancer is the third most common cancer in men in Singapore [16].

Prostate-specific membrane antigen radioligand PET (PSMA PET) was introduced in Singapore General Hospital in August 2015 using 68Ga-PSMA-11. Retrospective review of our initial results are largely in line with published data and affirm the high sensitivity of

PSMA PET for the evaluation of biochemical recurrence of prostate cancer, even at low PSA values [17]. The use of PSMA PET in the primary staging of prostate cancer also identified a significant number of lymph node and bone metastases, especially in patients with intermediate to high risk (PSA > 10 and Gleason score > 7). Approximately, 70% of metastatic nodes detected on PSMA PET would have been missed on routine pelvic CT/MRI.

For metastatic castration-resistant disease, many patients eventually relapse following chemotherapy, second-generation hormonal treatment and other systemic therapies. The median survival for metastatic castration-resistant prostate cancer remains short [18] and the most advanced treatment options today only offer several months of survival benefit each [19–22].

Because of this, lutetium-177 prostate-specific membrane antigen radioligand therapy (177Lu-PSMA RLT) has received increasing attention over the past few years. Several retrospective studies have reported favourable biochemical and imaging responses as well as significant pain relief in the patients treated with 177Lu-PSMA RLT [23–30]. A prospective study by Hofman et al. further confirms the high response rates and low toxicity of this treatment [31]. More recently, Yordanova et al. showed that re-challenged PSMA therapy is safe and the majority of the retreated patients have a longer median overall survival compared to those who received only baseline PSMA RLT [32].

PSMA RLT was commenced in Singapore in May 2018. Singapore General Hospital is currently the sole site in Singapore delivering this treatment to our local as well as overseas patients from the region. As of December 2018, we have treated 33 patients and delivered 83 treatment cycles.

Our selection criteria for treatment and our treatment protocol is largely based on those published in the Lancet Oncology paper [31]. However, due to the limited availability of PSMA-617 worldwide, we have opted for PSMA I&T as our precursor for treatment (prepared via Scintomics). These two precursors are believed to be comparable and recent study by Heck et al. have also shown that Lu-177 PSMA I&T is safe and efficacious [33].

Our patients receive up to four cycles of 177Lu-PSMA treatment in the outpatient setting in 6 to 8-week intervals. Following each cycle, the patient will have post-therapy scans (including SPECT/CT at 24 h) and blood test monitoring at 2 and 4 weeks post-treatment. The patients will be restaged 3 months following their last cycle of treatment.

Our early experience has shown promising treatment responses in some patients and overall, our patients have tolerated the treatment fairly well. As the majority of our patients are still receiving ongoing treatment and have not had their restaging scans as yet, the full results of our PSMA RLT experience will be separately reported at a later date.

Conclusion

Radionuclide theranostics has seen tremendous growth and we hope to be able to grow alongside to continue to serve the patients in Singapore and in the region.

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Compliance with Ethical Standards

Conflict of Interest Hian Liang Huang, Aaron Kian Ti Tong, Sue Ping Thang, Sean Xuexian Yan, Winnie Wing Chuen Lam, Kelvin Siu Hoong Loke, Charlene Yu Lin Tang, Lenith Tai Jit Cheng, Gideon Su Kai Ooi, Han Chung Low, Butch Maulion Magsombol, Wei Ying Tham, Charles Xian Yang Goh, Colin Jingxian Tan, Yiu Ming Khor, Sumbul Zaheer, Pushan Bharadwaj, Wanying Xie and David Chee Eng Ng declare no conflict of interest.

Ethical Statement Ethical approval is not required for this work.

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