EDITORIAL

Radionuclide Targeted Therapy, Theranostics, and Precision Medicine in the Era of Hybrid Imaging: An Important Pillar in Cancer Care

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Cancer is one of the leading causes of death worldwide due to non-communicable diseases. In 2020, the World Health Organization reported that there were approximately 48,000 new cancer cases per year in Malaysia, the majority of which were breast cancers, followed by colorectal and lung cancers (1). Among Malaysian men, the top three cancers were lung, colorectal and prostate cancers, whereas Malaysian women succumbed mostly to breast cancer, followed by colorectal and ovarian cancers (1). The alarming rise in cancer cases makes oncology services ever more pertinent, involving a spectrum of work that translates from bench side to bedside. Hence making synergistic works by the scientists and clinicians available for cancer care.

Broadly, cancer care is comprised of five main pillars of treatment options, namely surgery, radiotherapy, chemotherapy, molecular targeted therapy, and immunotherapy (Figure 1). The first three pillars are the cornerstones of cancer treatment. Surgery involves the excision of the tumour mass in order to ultimately achieve a cure or at least avail a better disease control. Nevertheless, surgery may not always achieve its curative aim, particularly in instances when the cancer has spread to involve critical organs or metastasized to distant sites in the body. Consequently, the other two pillars, i.e., systemic chemotherapy with or without external beam radiotherapy (DXT) or internal beam DXT via brachytherapy; are administered for disease control. As cancer care evolves in this era of personalised medicine and hybrid imaging, molecular targeted therapy, targeted radionuclide therapy (TRT), and immunotherapy have been introduced as part of the anticancer armamentarium.

TRT is generally provided by nuclear medicine (NM) facilities. In Malaysia, there are various NM facilities in both government and private sectors that offer TRT services (2). There are several general NM centres in

Figure 1: The five pillars of cancer care for selection of treatment mode

Malaysia that offer radioiodine therapy for the treatment of thyroid cancers. The largest government facility that provides state-of-the-art TRT is Institut Kanser Negara (IKN) at Putrajaya. Among the services provided at IKN include TRT treatment for thyroid cancers, neuroendocrine tumours (NETs), metastatic castrate-resistant prostate cancer (mCRPC), and liver metastases. There are also several private medical centres in the Klang Valley that offer similar TRT services. Moreover, many more centres including academic centres are planned in the near future to cater for the increasing demand for TRT services in Malaysia. TRT, being a type of precision medicine in oncology, enables the

information regarding the patient's genetics, protein information, and epigenetics, i.e. environmental influence on the genes to be analysed in order to aid in the prevention, diagnosis, treatment planning and monitoring of cancers (3). Precision medicine using TRT is designed to use carrier molecules tagged to radionuclides that emit particulate radiation to signal the diseases at a molecular level. This is followed by using a molecule tagged to the same or similar radionuclide, which emits higher energy of ionizing radiation that can selectively destroy specific cancer cells. This process gave rise to the term theranostics, a form of treatment that combines image-guided therapy for diagnosing and treating cancers.

Theranostics involving TRT provides a non-invasive and real-time analysis of cellular activity and tumour metabolism via signalling of biomarkers tagged to radioactive materials, followed by delivering cytotoxic levels of particulate radiation using similar molecular signalling pathways. Historically, TRT was started with radioiodine therapy for thyroid cancer treatment in the 1940's. Slowly, this evolved to include TRT for the treatment of NETs, mCRPCs, and liver metastasis. Furthermore, the rapid technological innovations in the field of hybrid imaging have paved to way forward for better image-guided diagnostics. As a results, imaging biomarkers such as 18F-Fluorodeoxyglucose (18F-FDG) that signals the glucose metabolism of cancer cells, as well as other newer radiopharmaceuticals have been developed to aid in image-guided therapy using hybrid imaging modalities such as positron emission tomography/ computed tomography (PET/CT) scans.

The basic principles of using TRT in oncology involves understanding the radiobiology of the interactions of radionuclide treatment agents with cancer cells, studying the radiochemistry and pharmacokinetics of the radiopharmaceuticals, assessment of dosimetry to minimise ionizing radiation effects to critical organs, and setting-up of proper clinical protocols for ensuring appropriate patient selection, correct delivery of treatment, and monitoring of treatment outcomes (Figure 2). This can be illustrated in the management of NETs. Specifically, Ki-67 staining of gastrointestinal neuroendocrine tumours (GI-NET) cells is important for tumour grading and is an accurate method for the assessment of the biological aggressiveness of the tumour. NET with Ki-67 of < 3% is considered as Grade 1, Ki-67 ≥ 3 and ≤ 20% as Grade 2, and Ki-67 > 20% as Grade 3. The lower grade tumours demonstrate excellent signalling using Ga68-DOTA peptide PET/CT scans and patients are stratified according to receive peptide receptor radionuclide therapy, which is a form of TRT. The higher-grade GI-NETs are more aggressive and become less differentiated compared to the primary cell line. These dedifferentiated tumours are best signalled using 18F-FDG biomarkers via image-guided assessment using PET/CT scans, and generally

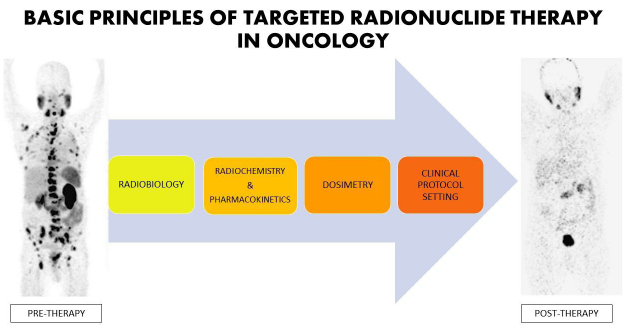

Figure 2: Illustration of the basic principles of targeted radionuclide therapy using image-guided management to detect cancer, in this case a metastatic neuroendocrine tumour on pre-therapy Ga68-DOTA peptide scan signalling the somatostatin receptors on the cancer cells. Subsequently, post-therapy scan demonstrated excellent disease control after administration of targeted radionuclide therapy using peptide receptor radionuclide therapy.

demonstrate discordant results with Ga68-DOTA peptide scans, often favouring the selection of systemic chemotherapy over TRT (4).

Similarly, selection for TRT among mCRPC patients involves the assessment of image-guided theranostics by signalling the prostate specific membrane antigen (PSMA) that acts as a biomarker of the disease. Quantitatively assessment using Ga68-PSMA PET/CT scans can define the metabolically activate tumour volume, which then can be used to determine the radiation dose to be delivered when administering the beta particle-emitting radionuclide, i.e., Lutetium177-PSMA-671 (177Lu-PSMA-617). Identification of these checkpoints enables better definition of tumour biology and helps determine the correct type of treatment that can be tailored to best benefit the patients with mCRPC (5).

In summary, the field of oncology is undergoing rapid change spurred by technological advancements in image-guided cancer management availed by hybrid imaging. Fusion of functional data with anatomical images provides the foundation for developing novel radiopharmaceuticals in delivering TRT services. Justification of improved overall survival and reduced drug toxicity may well put TRT as a frontline treatment of choice for selected cancers in the near future.

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