

Editorial, Theranostics.

Theranostics in Prostate Cancer.

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ABSTRACT:

Metastatic castration resistant prostate cancer (mCRPC) is a highly mortal disease, requiring safe and effective therapeutic agents to improve the patient outcome. Prostate-specific membrane antigen (PSMA) is over expressed in many prostate cancer cells, and act as target for molecular imaging (MI) and radionuclide therapy (RNT). The introduction of Gallium-68 (68Ga) PSMA- PET/CT in 2012 has changed the management of prostate cancer. In addition to its importance in identifying PSMA expression for selection of patients suitable for PSMA RNT, PSMA- PET/CT showed superior diagnostic accuracy to combined CT and bone scan. Lutetium-177 (177Lu) PSMA-617 is the most investigated PSMA radio ligand for RNT in prostate

cancer, it is a radiolabelled small molecule, binds with high affinity to PSMA, enabling beta-particles emissions with short tissue penetration depth (mean range of 0.7 mm and maximum range of 2.1 mm in soft tissue). Since 2014 multiple studies showed a highly impressive therapeutic efficacy and safety of ¹⁷⁷Lu-PSMA RNT. The evidence achieved by these studies paved the way to ongoing randomized clinical trials, and currently this therapy is being applied and clinically accepted in many centers worldwide. The aim of this article is to share the practical aspect of PSMA Theranostics for prostate cancer, including patient selection, therapy protocol and follow-up.

INTRODUCTION:

Prostate cancer is the second most common cancer among men and one of the leading cause of cancer death, after lung cancer ⁽¹⁾.

Its biological behavior differs according to the disease stage. Although localized disease may be cured with surgery or radiotherapy, distant metastatic disease may develop in many patients. Androgen deprivation therapy (ADT) with or without docetaxel is recommended as a first-line treatment of distant metastatic prostate cancer ⁽²⁾,

however eventually most of the patients progress and develop metastatic castration resistant prostate cancer (mCRPC). Enzalutamide and Abiraterone, are anti-androgen agents that have been approved for mCRPC; However, they carry serious side effects, such as cardiac morbidity ⁽²⁾. Other treatment options of mCRPC include; cabazitaxel, sipuleucel-T, and in bone metastases, Radium-223 dichloride ⁽³⁾.

Prostatic specific membrane antigen (PSMA), is a type II transmembrane glycoprotein, that is highly expressed in most prostate cancer, it act as a target for molecular imaging (MI) and radionuclide therapy (RNT) in the sense of a theranostic approach ⁽⁴⁾. PSMA PET/CT provide higher diagnostic accuracy than conventional imaging in prostate cancer ⁽⁵⁾, in addition to its importance to assess PSMA expression for selection of patients for PSMA

RNT (6-8). Although ⁶⁸Ga-PSMA PET/CT has been used in the majority of the studies, other ligands such as ¹⁸F-DCFBC, ¹⁸F-DCFPyL and ¹⁸F-PSMA-1007 have emerged for PSMA PET/CT imaging ⁽⁹⁻¹¹⁾.

PSMA theronostic with PSMA- small molecules or targeted antibodies, conjugated to either alpha or beta-particle emitting radioisotopes, have shown highly promising therapeutic efficacy in prostate cancer. PSMA-targeted small molecules have the advantage of the rapid internalization and blood pool clearance, compared to PSMA-targeted antibody ⁽¹²⁾.

Although alpha-particle emitters have higher energy than beta-particle emitters, they show non-specific binding to normal tissue and carry more toxicity to salivary gland and kidneys ⁽¹³⁾. The therapeutic radionuclide of choice is the beta-particle emitters, Lutetium-177 (¹⁷⁷Lu); it has a short tissue penetration depth and lower abundance of gamma emissions.

¹⁷⁷Lu-DOTA-PSMA-617 (¹⁷⁷Lu-PSMA-617) and ¹⁷⁷Lu—DOTAGA-PSMA-I&T (¹⁷⁷Lu-PSMA-I&T) are the most commonly used PSMA-targeted small molecule-based RNT ⁽⁶⁾. Several studies using ¹⁷⁷Lu-PSMA-617 in Europe and Australia, showed significant results with decrease in PSA and minimal toxicity ^(7, 8, 14-18).

Currently there are randomized clinical trials on the efficacy of PSMA RNT, including; the VISION trial, NCT03511664 (it's an international, prospective multicentre, randomized phase 3 trial opened in May 2018) and TheraP trial, NCT03392428 (it's a multicentre randomized trial in Australia) (19, 20).

Patient Selection:

A multidisciplinary uro-oncology team, including a medical oncologist, radiation oncologist, and urology surgeon as well as nuclear medicine physician is recommended for selection of prostate cancer patients suitable for PSMA RNT. Castration resistant prostate cancer with progressive disease and rising PSA level as recommended by the Prostate Cancer Trials Working Group 3 (PCWG 3) criteria, in addition adequate bone marrow, renal and liver function are pre-requisites (21). Presence of sufficient PSMA expression remains the gatekeeper for patient selection, while the threshold of PSMA uptake on PSMA PET/CT below which PSMA RNT is less likely to be effective is still not clear. Eligibility of PSMA RNT in the VISION trial required ^{68}Ga -PSMA-11 uptake above normal liver activity, the TheraP trial required certain SUV threshold ($\text{SUV max} \geq 20$ at a site of disease and $\text{SUV max} > 10$ at

sites of measurable disease ($\geq 10\text{mm}$), and Lu PSMA trial mandated ^{68}Ga -PSMA-11 uptake of 1.5 times above normal liver uptake (7, 19, 20). There is evidence of cellular and molecular heterogeneity in prostate cancer, and this may explain the non-uniform therapeutic response. The importance of dual tracer MI has been highlighted in Lu PSMA study, where all patients underwent ^{68}Ga -PSMA-11 and ^{18}F -FDG PET/CT for screening, 11% of the screened patient were excluded due to presence of FDG avid sites that lack PSMA avidity (7). Interestingly, the excluded group had poor outcome and shorter overall survival (22).

Administration of ^{177}Lu -PSMA:

PSMA-RNT should be given by well-trained nuclear medicine team. Before administration the patient is informed of the benefit and risks of this treatment as well as provided with radiation safety instruction. In Australia, oral hydration with 1.5 L of water is recommended on the day of therapy, intravenous hydration is an alternative if there is non-compliance with adequate oral hydration, ^{177}Lu -PSMA-617 is administered by slow intravenous injection over 2–10 min (23).

In Europe, some centers infuse ^{177}Lu -PSMA-617 at a slower rate and use routine intravenous fluid for hydration after ⁽¹⁷⁾.

The patient stays under observation and then released after meeting the threshold of discharge according to national radiation protection regulations.

One time point post-therapy imaging at 24-48 hours, including whole body planar acquisition and SPECT/CT provides sufficient information regarding presence of targetable PSMA-expressing disease and can be used to monitor response in subsequent cycles. The optimal number of cycles required is still to be determined; it varies according to the response, toxicity, and disease burden. Studies showed variation with 2–6 cycles of ^{177}Lu -PSMA RNT at a minimum 6 weeks interval between cycles and radioactivity in the range of 2–9.3 GBq ^(6, 7, 14, 16, 17 and 24).

Follow-up and response assessment:

A combination of clinical, biochemical and radiographic assessment is required. Blood tests, including complete blood count and serum creatinine or clearance tests should be performed 2-4 weeks after treatment. Biochemical response assessment with tumor marker PSA should be tested in 4-week intervals, results of studies for mCRPC patients who were treated with ^{177}Lu -PSMA

RNT and achieved $\geq 50\%$ PSA decline were associated with significantly longer duration of response and longer overall survival compared to $< 50\%$ decline ^(8, 25, 26).

MI assessment using PSMA PET/CT and FDG PET/CT provides information regarding disease heterogeneity and mixed responses, in addition to its superiority to CT, especially for evaluating bone metastases ^(23, 27).

Most mCRPC patients are subject to relapse, re-treatment with ^{177}Lu -PSMA RNT can be considered, particularly in patients with good initial response.

Side effect:

The salivary gland has been shown to receive the highest absorbed dose, causing mild to moderate xerostomia, different ideas have been adopted by some centers aiming to reduce this side effect, including local cooling and sialagogues ^(17, 28).

Hepatotoxicity is a common side effect. In Lu PSMA study post-treatment grade 3–4 anemia, thrombocytopenia, and neutropenia were found in 10%, 10%, and 6% of the patients, respectively ⁽⁷⁾.

In German multicenter study post-treatment grade 3–4 anemia, thrombocytopenia, and leukopenia, occurred at lower rate, 10%, 4%, and 3%, respectively ⁽¹⁷⁾.

Renal toxicity is less common side effect.

Yordanova et al, reported no grade 3-4 post-treatment nephrotoxicity on 55 patients (29).

Hofman et al, reported 10% short term renal toxicity (7).

Pain, nausea and vomiting have been reported. In TheraP trial, patients are

prescribed a 3-day course of dexamethasone and antiemetic (20).

Future direction:

Consideration of PSMA RNT at earlier stage of prostate cancer. Efficacy and safety of combining beta and alpha particle emitter as well as combining PSMA RNT with other treatment modalities.

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