

The Iranian Society of Nuclear Medicine practical guideline on radioligand therapy in metastatic castration-resistant prostate cancer using ^{177}Lu -PSMA

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ABSTRACT

Prostate-specific membrane antigen (PSMA) is a type II transmembrane protein, which is anchored in the cell membrane of prostate epithelial cells. It is highly expressed on prostate epithelial cells and strongly up-regulated in prostate cancer. Although, ^{177}Lu -PSMA has been recently introduced for radionuclide therapy of metastatic castration-resistant prostate cancer (mCRPC) with continuously increasing interest and use worldwide. This guideline is intended to assist nuclear medicine physicians in evaluating and managing patients with mCRPC for whom radioligand therapy (RLT) using ^{177}Lu -PSMA is a promising treatment option. In addition, more information could be provided by subsequent investigative studies in the field of RLT.

Key words: Prostatic neoplasms; Neoplasm metastasis; Radionuclide therapy; ^{177}Lu -PSMA; Radioligand therapy

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PURPOSE

The purpose of this guideline is to assist nuclear medicine physicians in evaluating, treating and managing patients who eligible for radioligand therapy (RLT) are using ^{177}Lu -PSMA ligands in metastatic castration-resistant prostate cancer (mCRPC).

BACKGROUND INFORMATION AND DEFINITIONS

Definitions

CRPC: CRPC is defined as castrate serum testosterone <50 ng/dl or 1.7 nmol/l plus one of the following types of progression [1]:

- *Biochemical progression:* Three consecutive rises in PSA 1 week apart, resulting in two 50% increases over the nadir, and PSA >2 ng/ml.
- *Radiologic progression:* The appearance of new lesions; either two or more new bone lesions on bone scan or a soft tissue lesion using the Response Evaluation Criteria in Solid Tumors.

PSMA: Prostate-specific membrane antigen (PSMA), also known as folate hydrolase I or glutamate carboxypeptidase II, is a type II transmembrane protein, which is anchored in the cell membrane of prostate epithelial cells. PSMA is highly expressed on prostate epithelial cells and strongly up-regulated in prostate cancer. The PSMA expression levels are directly correlated to androgen independence, metastasis, and prostate cancer progression [2]. Thus, PSMA is a promising molecular target for diagnosis and therapy of metastatic prostate cancer at present [3].

Lutetium-177 (^{177}Lu): ^{177}Lu is a β - and γ -emitting radionuclide with a physical half-life of 6.7 days. It has a maximum and mean β -particle energy of 0.498 MeV and 0.133 MeV, respectively. The maximum and mean soft-tissue penetration depth of ^{177}Lu is 1.7 mm and 0.23 mm, respectively. It has two main gamma emission lines: 113 keV (6% relative abundance) and 208 keV (11% relative abundance).

^{177}Lu -PSMA-617: ^{177}Lu -PSMA-617, a DOTA derivative of the Glu-urea-Lys motif, has been developed in the German Cancer Research Center (DKFZ) Heidelberg, Germany, for the treatment of patients with metastatic prostate cancer [4, 5].

RLT: Radioligand therapy in this context involves the systemic intravenous administration of a specific well-defined radiopharmaceutical composed of a β -emitting radionuclide chelated to a peptide for the purpose of delivering cytotoxic radiation to cancer cells.

Background

Most deaths related to prostate cancer are due to advanced disease, which results from any combination of lymphatic, blood, or contiguous local spread. Targeted radionuclide therapy is an attractive and quickly developing therapy option for many different cancers, such as lymphoma, melanoma, and neuroendocrine tumours [6-9]. After the rather unsuccessful therapy with 90Y-CYT-356 monoclonal antibody (mAb), which binds to the intracellular domain of PSMA [10], Phase 1 and 2 clinical trials utilising the PSMA mAb J591, radiolabelled with ^{177}Lu or 90Y, have shown promising results [11-14]; however, there were higher rates of haematological toxicity. Tagawa et al. [11] treated 47 patients with ^{177}Lu -PSMA mAb J591. They reported grade 4 thrombocytopenia in 46.8% (29.8% received platelet transfusions) and a total of 25.5% experienced grade 4 neutropenia. Monoclonal antibodies are large molecules and therefore show poor permeability in solid tumours. This characteristic along with slow clearance from the circulation is probably the cause of grade 4 haematotoxicity. Maresca et al. described the design and synthesis of a series of small molecule inhibitors of PSMA, instead of mAb [15]. First clinical experiences with PSMA-based radionuclide treatment using Iodine-131-labelled PSMA showed promising results with mild haematotoxicity and a PSA decrease $>50\%$ in 60% of all treated prostate cancer patients [16]. ^{131}I has a long half-life of 8.02 days and a maximum beta-particle range in soft tissue of 2.4 mm. Due to the gamma-emitting properties and long half-life, ^{131}I is less attractive from a radiation safety point of view. In contrast, ^{177}Lu has a half-life of 6.7 days and a lower beta-particle emission energy, meaning that there is a high probability of fewer side effects [17, 18].

In the first patient cohort of ten patients, the study groups of University Hospitals Bonn and Muenster in Germany reported a low side effects profile and also good response according to PSA changes in the mCRPC patients after one cycle of RLT with ^{177}Lu -PSMA-617 [19]. A PSA decline was reported in 70% of the patients, and more than 50% decline in 5 patients. The results of this preliminary study were confirmed by two multicentre retrospective studies, which showed a low haematotoxicity and nephrotoxicity profile of this therapy with a PSA decline more than 50% in up to 45% of patients [20, 21]. Ferdinandus et al. evaluated the predictive value of different pre-therapeutic parameters on therapy response, considering changes in PSA after the first cycle of RLT [22]. In this study, the multivariate analysis showed that patients with a high platelet count or a regular need for analgesics had a significantly worse response after the first RLT cycle, considering any PSA decline after 2 months.

When a PSA decline > 50% was considered, patients with a regular need for analgesics showed a worse response, however, other pre-therapeutic parameters including prior therapies and the amount of PSMA uptake in ⁶⁸Ga-PSMA PET imaging, measured by SUV max, had no impact on patient response [22]. Rahbar et al. showed in a multicenter analysis of 145 patients that the presence of visceral metastases and an alkaline phosphatase ≥ 220 U/L were negative predictors of therapy response [20]. The study group of Bonn evaluated the haematotoxicity and nephrotoxicity in patients who received at least three cycles of RLT [23, 24]. They studied 49 patients who were treated with three cycles of ¹⁷⁷Lu-PSMA-617 and reported anaemia, thrombocytopenia and leukopenia (common toxicity criteria; CTC 3°) during the observation period after the third cycle in only 4 (8.2%), 3 (6.1%) and 0 patients, respectively. No CTC 4° haematotoxicity was observed in the entire study population. More than 60% of patients did not show any haematotoxicity [24]. In this study, 20 patients (40.8%) received a median of 6 cycles of radionuclide therapy with ²²³Ra prior to ¹⁷⁷Lu-PSMA-617 therapy. There were no significant differences between the patients with a history of therapy with ²²³Ra and those without regarding leukopenia and thrombocytopenia. These results confirmed that performing repeated cycles of ¹⁷⁷Lu-PSMA-617 after radionuclide therapy using ²²³Ra seems to be safe with a very small probability of haematotoxicity [24]. Yordanova et al. studied 55 patients who received at least 3 cycles of RLT with ¹⁷⁷Lu-PSMA-617 and showed no grade 3 or 4 nephrotoxicity [23]. A significant negative effect on renal function was found for age (>65 y) ($p = 0.049$), hypertension ($p = 0.001$) and pre-existing kidney disease ($p = 0.001$). Rahbar et al. reported the overall survival benefit of RLT in comparison to a historical collective. They demonstrated that the estimated median survival was 29.4 weeks, which was significantly longer than the survival in the historical control group with 19.7 weeks (Hazard Ratio: 0.44 (95% confidence interval: 0.20-0.95); $P = 0.031$) [25]. According to Ahmadzadehfar et al. [26] it seems that patients with a favourable response and repeated therapies with ¹⁷⁷Lu-PSMA-617 have a significantly longer overall-survival in comparison to patients who showed no response to RLT according to PSA changes. According to Braeuer et al. an initial ALP level <220 U/L and a PSA decline measured two months after the first cycle were associated with a longer OS [27]. Delker et al. reported their dosimetry results with ¹⁷⁷Lu-PSMA-617 and calculated a mean absorbed dose/per cycle to the bone marrow, kidneys, liver, spleen and salivary glands of 0.012 Gy/GBq, 0.6 Gy/GBq, 0.1 Gy/GBq, 0.1 Gy/GBq and 1.4 Gy/GBq, respectively [28].

Regarding the different promising results, ¹⁷⁷Lu-PSMA-617 is a new and promising therapy option for

patients with mCRPC but has not yet reached clinical approval. It should therefore mostly be offered to patients as a salvage therapy.

The aim of this guideline is to provide a scientific and ethical platform for this useful treatment to initially pursue its application, preferably in academic centers in Iran under controlled investigational protocols.

REGULATORY ISSUES

RLT with ¹⁷⁷Lu-PSMA-617 -like other radionuclide therapies with an unsealed source- must be performed only by experienced Nuclear Medicine specialists. At the moment, in Iran, this therapy should only be undertaken by Nuclear Medicine specialists enrolled in an investigational protocol pursuant to a valid investigational radiopharmaceutical under the purview of a qualified institutional review board.

INDICATIONS AND CONTRAINDICATIONS

Indications

RLT with ¹⁷⁷Lu-PSMA-617 is indicated for the treatment of patients with mCRPC, who do not have any other approved therapy option planned by a multidisciplinary team. Candidate patients for RLT using ¹⁷⁷Lu-PSMA-617 should fulfil the following criteria:

- mCRPC with PSMA positive metastatic disease upon PSMA-PET or SPECT imaging.
 - There is no limitation regarding the number or site of metastases, i.e. bone or soft tissue metastases. Caution should be given to patients with diffuse bone marrow and brain metastasis.
- after initial hormone therapy (LH-RH agonists/antagonists) and
 - Progressive disease despite newly developed hormone therapies (Abiraterone/Enzalutamide) or these medications avoided by the patient.
 - Progressive disease despite chemotherapy (Docetaxel and Cabecitaxel) or the patient being unfit for chemotherapy or avoiding chemotherapy.
- Not suitable for ¹⁵³Sm-EDTMP or ²²³Ra-dichloride or other local available radiopharmaceuticals for bone-targeted therapies due to extra-osseous metastases or diffuse bone marrow metastases or avoided by the patient.
 - In patients without adequate response to bone-targeted therapies for pain palliation or exacerbation of pain even by such

therapy, an RLT with ¹⁷⁷Lu-PSMA-617 can be evaluated [24].

- Life expectancy longer than 4-6 months.
- Decision for salvage therapy at the institutional interdisciplinary tumour board.

In summary, mCRPC patients should undergo hormone therapy and chemotherapy as well as bone targeted therapy, if indicated. In the case of any contraindication for one of these therapies, it should be discussed and documented in an interdisciplinary tumour board.

Contraindications

- WBC $\leq 2 \times 10^3/\mu\text{l}$.
- Hb ≤ 8 g/dl.
 - In the case of symptomatic anaemia, a red-blood-cell transfusion should precede the therapy. RLT with ¹⁷⁷Lu-PSMA-617 may have a positive effect on bone marrow depression, causing the need for less blood to be transfused due to tumour regression in bone marrow [29]. It should be mentioned that pure anaemia without thrombocytopenia and leucopenia is not a contraindication for RLT.
- Platelets $\leq 75 \times 10^3/\mu\text{l}$.
- Creatinine > 2 mg/dl.
- Renal outflow obstruction.
- Previous chemotherapy or bone-targeted radionuclide therapy and extended external beam irradiation fields to the bone marrow (pelvis, spine), if performed during 4 weeks preceding the RLT.
- ECOG > 2 .

PREPARATION PRIOR TO RLT

- Prostate cancer proven by histopathology.
- Any PSMA-PET or SPECT imaging (as labelled with ⁶⁸Ga or ^{99m}Tc) to verify PSMA positive lesions.
 - In the case of liver or brain metastases, diagnostic imaging with CT or MRI should be performed to rule-out any PSMA negative metastases. If PSMA-negative liver or brain metastases exist, a multidisciplinary team should evaluate a combination therapy with other modalities (external beam radiation or local interventional therapies).
- Renal scintigraphy to evaluate renal function and rule out obstructive dysfunctions.
 - In the case of obstructive dysfunction, it should be treated first.

- The renal scintigraphy should be performed prior to the first cycle. Performing further renal scintigraphies prior to the next cycles is optional and depends on the renal function tests and the results of the first renal scintigraphy.

- Complete blood counts, renal function tests (creatinine and GFR), liver function tests, ALP, LDH, CRP and PSA should be examined prior to each cycle.

ADMINISTRATION

- Cooling the salivary glands, the patients receive ice packs over the parotid and submandibular glands from 30 min prior to and up to 4 hours after administration of ¹⁷⁷Lu-PSMA-617 to reduce the risk of salivary gland radiation injuries.
 - There is no evidence of whether cooling the salivary glands is an effective therapy for saving these glands from radiation; however, it is tolerable and not harmful for the patients.
- Using a urinary catheter in incontinent patients in the first 48 hours to avoid any contamination.
- Activity of 6 GBq (range: 5.5-6.5 GBq) ¹⁷⁷Lu-PSMA-617.
 - The amount of activity can be reduced to 4.0-5.0 GBq in the case of impaired renal function (e.g. Creatinine 1.5-2).
 - According to the preliminary results, an activity of 7.4 GBq can be administered safely; however, more data are required to increase the amount of activity.
- Injection of the activity intravenously as a slow bolus (over about 30 seconds) followed by 1000 ml Ringer or NaCl.
 - The patients should be encouraged to void as frequently as possible and drink about 2 litres of water daily.
 - In patients with dilated non-obstructive renal disease an administration of 40 mg Furosemide may be meaningful.
- 4 cycles of the RLT every 6-8 weeks.
 - In the case of continuously increasing PSA, after the first two cycles accompanied by worsening of the general condition, the indication of further RLTs should be re-evaluated.
 - In case of a decreasing PSA to < 1.0 ng/ml during the therapy cycles, a PSMA imaging could evaluate existence of small PSMA-positive metastases after

completion of RLT when post injection SPECT study is not enough informative.

- In case of a significant decline of platelets or leucocytes, the time interval between the 2 cycles can be prolonged.
- At least one whole body scan 24-48 hours post injection (preferably with SPECT(/CT)).

In patients with diffuse bone and bone marrow metastases as well as in patients with brain metastases a concomitant corticosteroid therapy (e.g. prednisolone 20 mg/daily) in the first two weeks after administration is advisable.

SIDE EFFECTS

Acute

According to the results of different published data, no severe adverse events immediately after injection have been reported to date [19, 25, 30-35]. The most common side effect in the first 48 hours after injection is mild nausea & vomiting (in up to 20% of patients) [20, 30, 31], which can be easily treated with Ondansetron. Fatigue is the most common complaint in patients after therapy, especially in the first 4 weeks (in up to 25%) [20, 30, 31].

Delayed side effects

Dry mouth was reported in up to 20% of cases and is transient and tolerable in the majority of patients [19, 25, 30, 36].

Renal toxicity

Dosimetry studies have shown that the most critical organs are the kidneys, with a maximum kidney radiation dose of 0.88 Gy/GBq for ¹⁷⁷Lu-PSMA-617 and 0.93 Gy/GBq for ¹⁷⁷Lu-PSMA-I&T [37, 38]. None of the current studies have reported any high grade nephrotoxicity (CTC grade 3, 4 or 5) [19, 20, 25, 30, 36, 39]. In a recently published study by Yordanova et al., the authors reported renal toxicity in 55 mCRPC patients who received at least 3 cycles of ¹⁷⁷Lu-PSMA-617. They observed increased creatinine levels of CTC 1° or 2° in 14 patients (25%) and increased GFR (grade 1/2) in 16 cases. None of the 55 patients experienced severe nephrotoxicity (grade 3/4) [23].

Bone marrow toxicity

Severe (grade 3 and 4) bone marrow toxicity is observed in less than 10% of patients in various publications [24, 40].

FOLLOW-UP

- PSMA-PET or SPECT imaging before the first and after the fourth cycle in the case of

continuously increasing PSA or PSA-decline to <1.0 ng/ml (as mentioned above), a PSMA-imaging is recommended for re-evaluating of further cycles).

- CBC and renal function test every 2-3 weeks; PSA could be monitored every 4 weeks.

THERAPY OF RECURRENT DISEASE

- If an increase in the level of PSA is documented after a good response following the first course of treatment (3 to 4 cycles of RLT), another course of therapy can be performed. For a second treatment course:

- The patient should be evaluated in a tumor board again.
- PSMA imaging is mandatory for documentation of PSMA positive metastases
- The aforementioned exclusion criteria should be considered.

FACILITY AND PERSONNEL

RLT with ¹⁷⁷Lu-PSMA-617 is still considered an investigational treatment and its implementation must comply with Iranian legislation and requirements, as well as with ethical principles regarding human studies. The decision to perform RLT should be taken by a multidisciplinary team, including all of the specialists involved in the care of patients with mCRPC. The treatment should take place in an approved nuclear medicine department and must be performed by an experienced Nuclear Medicine specialist. The Nuclear Medicine ward must have qualified personnel, appropriate radiation safety equipment and procedures for waste management and handling accidental contamination of the site or personnel. Isolation of patients in nuclear medicine department should be performed according to local radiation regulations for patient release after radionuclide therapy.

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