Lutetium-177 prostate-specific membrane antigen-617 theranostics: New therapeutic hope in metastatic castrate-resistant prostate cancer?

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SUMMARY
Prostate-specific membrane antigen (PSMA) is a 750 amino acid Type II transmembrane glycoprotein normally expressed in the human prostate epithelium. Lutetium-177 (177 Lu) PSMA-617 (LuPSMA) is a radiolabeled molecule that binds to the enzymatic site of PSMA, enabling highly targeted delivery of beta radiation to PSMA avid cancer cells.

The recently published Phase II trial of long-term (median 31.4 months) outcome of 177LuPSMA treatment in 50 patients who progressed after standard therapy, and re-treatment in 15 patients, showed promising results in metastatic castrate-resistant prostate cancer (mCRPC). The inclusion criteria were biopsy-proven mCRPC patients with disease progression after standard therapies, patients unfit or refused for standard therapy and eastern cooperative oncology group (ECOG) performance status of ≤2. Disease progression was defined as a new radiographic lesion or a new site of pain in an area of radiographically evident disease, within prior 12 months of standard treatment (abiraterone or enzalutamide or both in 46, docetaxel in 42, cabazitaxel in 24, and docetaxel + enzalutamide/abiraterone + cabazitaxel in 39 patients). Patients with Hb <9.0 g/dL, neutrophil count <1500/mm³, platelet count <75,000/mm³, albumin ≤2.5 g/dL, estimated glomerular filtration rate (eGFR) <40 mL/min, prior radiotherapy (within 6 weeks), and uncontrolled comorbid illness were excluded from the study.

All patients underwent baseline contrast-enhanced computed tomography (CT) of the chest, abdomen, and pelvis, bone scan, 68Ga-PSMA-11 positron emission tomography (PET)/CT, and 18F-fluoro-deoxy-glucose (FDG) PET/CT. Patients with FDG-positive and PSMA-negative disease (discordant lesion) and SUVmax of tumor involvement of <1.5 times of SUVmean of the liver were excluded presuming poor response to treatment. Blood tests were performed at 2 and 4 weeks after each 6-weekly treatment, and if significant toxicities (Grade >1 hematological toxicity), full blood counts were repeated weekly until resolution. As per protocol, all patients had a 12-weekly clinical evaluation, eGFR, 68Ga-PSMA-11 PET/CT, 18F-FDG PET/CT, bone scan, and CT of the chest, abdomen-pelvis and prostate-specific antigen (PSA) was repeated more frequently.

LuPSMA was administered intravenously, starting from a dose of 6 GBq (about 150 mCi) and adjusted according to number of sites of the lesion, weight of the patient, and eGFR. All patients received a median of four cycles (1–4) of six weekly treatments. Primary endpoints were PSA response defined as a ≥50% PSA decline from baseline, toxicity according to common terminology criteria for adverse events v4.03, imaging responses (response evaluation criteria in solid tumors 1.1) and patient-reported quality of life (QoL).

PSA decline of ≥50% from baseline was seen in 64% (32) of patients (95% confidence interval [CI] 50%–77%), with an ≥80% decline seen in 44% (22) of patients (95% CI 3059%). At 3 months imaging, objective response (complete or partial) was seen in 56% (15/27), 42% (21/50), and 30% (15/30) of patients in CT, 68GaPSMAPET and FDG PET, respectively. The most common toxicity was Grade 1 xerostomia (58%) and Grade 1 nausea (40%) and vomiting (22%). Grade 3 toxicity was primarily hematological, including lymphopenia (32%), anemia (10%), thrombocytopenia (8%), and neutropenia (6%). Overall only one (2%) patient had Grade 4 toxicity (thrombocytopenia).

In secondary endpoints, global QoL (EORTC QLQ-C30) was improved after 2 cycles but stable at 3 months. Brief pain inventory severity and interference scores decreased at all-time points, including at the 3–month follow-up with a decrease of –1.2 (95% CI –1.5––1.9, \( P = 0.001 \)) and 1.0 (95% CI –0.2–0.18, \( P = 0.013 \)), respectively. Median overall survival (OS) was 13.3 months, OS and PSA progression-free survival (PFA) was significantly better in patients with PSA decline >50%, median 18.4 months versus 8.7 months, and 8.2 months versus 4.2 months, respectively.
On progression, thirty patients went on to receive further systemic therapy. In total, 15 (14 after the first relapse and one more after the second relapse) patients received further LuPSMA, and 21 patients had at least one line of other systemic therapy. Of 15 patients receiving further LuPSMA at first or second relapse after initial response to LuPSMA, 11 (73%) had a PSA decline ≥50%; and the median OS from the time of the study enrolment in these 15 patients who received re-treatment was 26.6 months, although, with lesser and lesser PFS duration.

The authors conclude that there are high therapeutic efficacy and low toxicity of 177 Lu-PSMA-617 radioligand therapy in men with mCRPC who have progressed after standard treatment. Interestingly, those relapsed after initial LuPSMA had a better outcome on subsequent LuPSMA therapy cycles than those who received a second- or third-line standard treatment.

**COMMENTS**

PSMA is overexpressed (100–1000 times) in up to 95% of prostate cancer, and the density of expression depends on Gleason score and castrate–resistant status, making it an effective target for radioligand therapy. 

\[ ^{177} \text{Lu} \] is a medium-energy \( \beta \) (490 KeV) and \( \gamma \) (208 KeV) emitter radioligand with a maximal tissue penetration of 1–2 mm, resulting in “crossfire” effect, i.e. can effectively target cells with low PSMA expression with minimal effect on a normal cell. \([2]\) Gamma (\( \gamma \)) radiation enables image acquisition and dosimetric calculation.

Until recently, radionuclide therapies in castrate-resistant prostate cancer (CRPC) were exclusively confined to bone pain palliation with \( \beta \) emitters strontium-89 (\( ^{89}\text{Sr} \)) and samarium-153 (\( ^{153}\text{Sm} \)), but these agents are primarily replaced by the \( \alpha \) emitter radium-223 (\( ^{223}\text{Ra} \)) which showed least myelosuppression and benefit in median OS of 3.6 months over placebo. \([3,4]\)

Indian investigators are not far off from these new areas of development and have done pioneering work in this field on safety, efficacy, toxicity, and QoL assessment following LuPSMA therapy; subsequently, they worked on individual dosimetry of LuPSMA. \([5]\) In a retrospective study of forty patients of mCRPC who failed on first-line treatment and received at least two cycles of \( ^{177}\text{Lu} \)PSMA radioligand therapy, 21 (52.5%) had a symptomatic and biochemical response and 16 (43%) responded on molecular imaging, without any Grade 3 or 4 toxicity. \([5]\) The most recent Phase II long-term outcome data on 90 patients in mCRPC with a median follow-up time of 28 months was published in January 2020\([6]\) and showed median OS of 14 months and PFS of 11.8 months, similar to the index study\([1]\) and with low toxicity.

Another Phase 2 study by Emmett et al. on progressive mCRPC showed ≥50% decline in PSA in 36% of patients of LuPSMA and the author concludes that PSMA PET/CT plays a vital role in predicting response after LuPSMA radioligand therapy. \([7]\) Considering the efficacy of LuPSMA radioligand therapy on visceral and bone metastasis and its promising result on PSA decline of ≥50%, it appears that LuPSMA therapy is going to stay for a long time to come and shall play a significant role in future in the treatment of metastatic CRPC.

**REFERENCES**

1. Violet J, Sandhu S, Iravani A, Ferdinandus J, Thang SP, Kong G, et al. Long term follow-up and outcomes of re-treatment in an expanded 50 patient single-center phase II prospective trial of lutetium-177 (\( ^{177}\text{Lu} \)PSMA-617 theranostics in metastatic castrate-resistant prostate cancer. J Nucl Med. 2019 Nov;51(11):1261-1266.
2. Ferdinandus J, Violet J, Sandhu S, Hofman MS. Prostate-specific membrane antigen theranostics: Therapy with lutetium-177. Curr Opin Urol 2018;28:197-204.
3. Parker C, Nilsson S, Heinrich D, Helle SI, O’Sullivan JM, Fosså SD, et al. Alpha emitter radium-223 and survival in metastatic prostate cancer. N Engl J Med. 2013;369:213-23.
4. Yadav MP, Ballal S, Sahoo RK, Dwivedi SN, Bal C. Radioligand therapy with \( ^{177}\text{Lu} \)-PSMA for metastatic castration-resistant prostate cancer: A systematic review and meta-analysis. AJR Am J Roentgenol 2019;213:275-85.
5. Suman S, Parghane RV, Joshi A, Prabhakar K, Bakshe G, Talole S, et al. Therapeutic efficacy, prognostic variables and clinical outcome of \( ^{177}\text{Lu} \)-PSMA-617 PRLT in progressive mCRPC following multiple lines of treatment: Prognostic implications of high FDG uptake on dual tracer PET-CT vis-à-vis Gleason score in such cohort. Br J Radiol 2019;92:20190380.
6. Yadav MP, Ballal S, Bal C, Sahoo RK, Damle NA, Tripathi M, et al. Efficacy and safety of \( ^{177}\text{Lu} \)-PSMA-617 radioligand therapy in metastatic castration-resistant prostate cancer patients. Clin Nucl Med 2020;45:19-31.
7. Emmett I, Crumbaker M, Ho B, Willowson K, Eu P, Ratnayake L, et al. Results of a prospective phase 2 pilot trial of \( ^{177}\text{Lu} \)-PSMA-617 PRLT in progressive mCRPC following multiple lines of treatment: Prognostic implications of high FDG uptake on dual tracer PET-CT vis-à-vis Gleason score in such cohort. Br J Radiol 2019;92:20190380.

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