^{177}Lu-PSMA Therapy an Alternative Therapy for Metastatic Castrate Resistant Prostate Cancer with Suboptimal Response: Are we ready for it

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Abstract

Introduction: Lutetium-177-PSMA-617 (^{177}Lu-PSMA) is used as the last treatment option in metastatic castrate resistant prostate cancer (mCRPC). We present two cases of mCRPC with bone involvement to see the response of ^{177}Lu-PSMA as an alternative treatment option.

Case presentations: We present two cases, diagnosed as mCRPC with bone involvement, having suboptimal labelling and binding of the tracer and its effect on bone marrow. The two patients had 2-4 cycles of ^{177}Lu-PSMA with progressive disease despite chemotherapy and novel androgen therapy. The response of treatment was determined based on changes in radiological findings, biochemical and post-therapeutic scan. The last post therapy SPECT CT 99mTc-PSMA scans in both patients showed diffuse homogenous tracer distribution in the bone marrow with no suggestion of receptor avid disease. In both patients the PSA level decreased. Side effects seen were pancytopenia and mild increase in creatinine and urea.

Conclusion: The main benefit of ^{177}Lu-PSMA is to offer an alternative therapeutic option for patients with disease progression despite first line of treatment. We advocate the requirement of repeating the scan after every treatment session with ^{177}Lu-PSMA to ensure adequate radioisotope uptake and to assess for therapeutic response. A patient specific dosimetric approach should be applied before therapy to prevent organ toxicity.

Keywords: Nuclear medicine•Prostate specific antigen•Bone lesion•Androgen resistant•PSMA

Introduction

Prostate Cancer (PC) is one of the most prevalent cancers worldwide. Progression to androgen-independent status is the main cause of death in patients with prostate cancer [1]. Most deaths are related to metastatic disease, which results from any combination of blood, lymphatic, or local spread. Bone metastases, a major cause of morbidity and mortality in patients with metastatic castration-resistant prostate cancer (mCRPC), are associated with pain, pathological fractures, spinal cord compression, and decreased survival [2].

The prostate specific membrane antigen (PSMA) is a transmembrane protein that is over-expressed in advanced prostate cancer [3]. PSMA is highly expressed on prostate epithelial cells and strongly upregulated in prostate cancer. PSMA expression levels are directly correlated to androgen independence, metastasis, and progression [4]; thus, it is an attractive target for the diagnosis and therapy of metastasized prostate cancer.

A novel theragnostic drug, ^{177}Lu-PSMA, which is a DOTA-derivative of the Glu–urea–Lys motif, it is an example of PSMA-guided therapies, which together acts as a means of transporting destructive radiation to the tumor site without exposing the healthy cells [5,6].

We present a case series of two patients with mCRPC who underwent ^{177}Lu-PSMA therapy with suboptimal labelling and binding of the tracer with poor outcomes.

Case Presentation

Case 1

A 69 years old male patient was initially diagnosed with metastatic prostate cancer with bone involvement in 2017. He has a past history of Diabetes Mellitus, Hypertension and Cerebrovascular accident in 2015. His Eastern Cooperative Oncology Group (ECOG) performance status was 1. The initial prostate specific antigen (PSA) level during diagnosis was 854 mcg/L (normal range=<4.1 mcg/L). He received treatment with dual androgen blockades; Leuprolide, Bicalutamide and Zometa. He was then started on ^{177}LuPSMA therapy with a total of 4 cycles. After the first cycle his PSA level dropped to 36 mcg/L. Three months later, after the third cycle of therapy, the PSA was 8.6 mcg/L. Treatment was completed in May of 2018, with a PSA level within normal range.

In March of 2019, the patient presented significant low back pain and a PSA level of 130 mcg/L. Treatment with Zoladex, Abiraterone and Denosumab was initially commenced. Gallium-68 positron emission tomography/ computer tomography (68Ga-PET/CT) was performed, and it showed metastatic lesion within bone with increased intensity compared to a scan in July of 2018. 99mTechnetium-based Prostate-specific Membrane Antigen (99mTc-PSMA) whole-body scan with Single-photon emission computed tomography (SPECT-CT), showed widespread receptor avid bone disease. Diagnosis of metastatic castrate resistant prostate cancer with disease progression was made despite being on antiandrogen therapy. Treatment was changed to Abiraterone Acetate, Prednisolone, Zoladex for 3 months and Denosumab once a month. Therapy with ^{177}Lu-PSMA was recommended.

Prior to initial therapy, laboratory investigations demonstrated a PSA level of 214 mcg/L, a free PSA of 47.600 mcg/L (normal range= 0.084 -0.870 mcg/L) and PSA% of 22%. A complete blood count showed white blood cell (WBC) count was 6.7x109/L (normal range= 4.5-11 x109/L), hemoglobin (Hb) was 10.7 g/dl (normal range=12.6 -17 g/dl) and platelet count was 146 x109/L (normal range= 140-400 x109/L). A renal MAG3 (Mercaptuacetyltriglycine) nuclear scan for renal function demonstrated adequate renal function and a creatinine level 100 micromol/L (normal range= 62-106 micromol/L). Before radiotracer was started, patient was pre-hydrated well with IV fluids.

Post therapy 99mTc-PSMA with SPECT CT scan after the first cycle of ^{177}Lu-PSMA demonstrated multiple foci of increased tracer uptake throughout the bony skeleton. The most avid uptake was seen in the left orbital margin, L5, left sacroiliac (SI) joint, and left hip joint. Laboratory investigations post therapy revealed hypokalemia of 2.6 mmol/L (normal range= 3.2-5.6 mmol/L), rest were within baseline levels. The 99mTc-PSMA with SPECT CT scan after the second cycle of ^{177}Lu-PSMA, demonstrated good response to treatment. Laboratory values showed a drop in WBC of 3.6 x109/L and platelet count of 85 x109/L. Before commencement of the third cycle, PSA level was 181 mcg/L. After the third cycle the response assessment on post therapy scan could not be appreciated because of diffuse marrow uptake seen on the scan without delineating any focal receptor avid lesions seen on previous post therapy scans. Therapy with ^{177}Lu-PSMA showed a significant decrease in PSA levels, with 71% reduction (Figure 1).

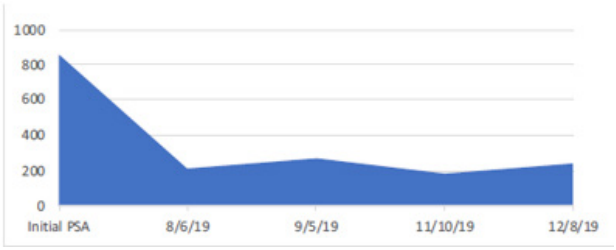

Figure 1. PSA levels of case 1 after 177Lu-PSMA therapy.

Each cycle of therapy was given one month apart. Infusion of ^{177}Lu-PSMA were given at dosage of 205 mCi (millicurie) at 1st and 2nd cycle, at 3rd cycle received 203.4 mCi and 208mCi at 4th cycle. No complications or side effects occured during therapy sessions. Clinically, the patient's symptoms were controlled with adequate pain relievers. At the end of the therapy there was a significant drop of 70%, 25% and 60% in platelet count, Hb & WBC, respectively (Figure 2). The PSA level at the end of the therapy was 241 mcg/L, free PSA of 28.900 mcg/L and PSA% of 12%. The last post therapy 99mTc-PSMA with SPECT CT scan showed diffuse homogenous tracer distribution seen in the bone marrow, suggestive of bone marrow uptake and no receptor avid disease (Figure 3A), comparing with the baseline scan (Figure 3B).

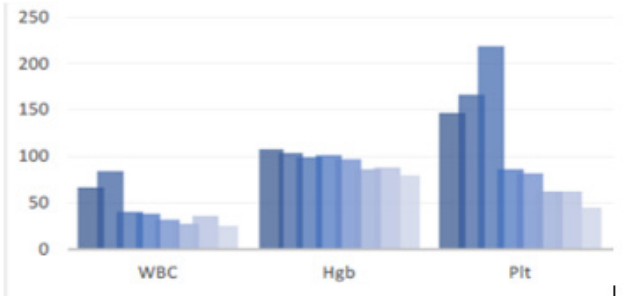

Figure 2. Trends of WBC, Haemoglobin and Platelets after 177Lu-PSMA therapy in case 1.

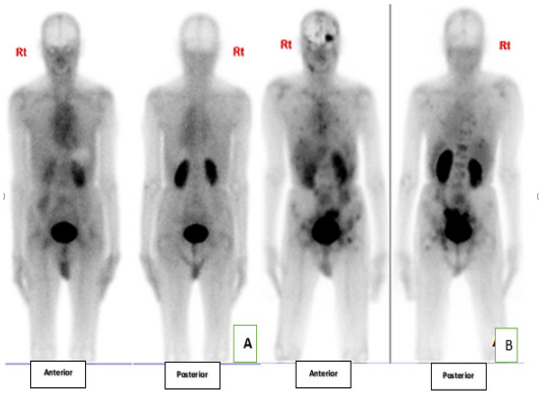

Figure 3. Last Post-therapy ^{177}LU-PSMA scan showing no receptor avid disease just bone marrow activity and 1st Post-therapy ^{177}LU-PSMA scan showing receptor avid disease involving the bony skeleton.

Case 2

A 46 years old male patient initially presented a year ago with significant left hip pain controlled with Morphine. Investigations revealed a PSA level of 752 mcg/L and imaging with CT and nuclear bone scan demonstrated widespread bone metastasis with foci seen throughout the cranium, spine, rib cage, upper and lower extremities, manubrium, sternum, and pelvic bones. Complete blood count revealed pancytopenia from bone marrow involvement. The diagnosis of metastatic prostate cancer was made despite no biopsy at that time as he was severely ill and symptomatic from the bone metastases. He was given Leuprorelin and Abiraterone/Prednisolone. He also received radiotherapy for symptomatic T7, L5 vertebral bodies and left hip metastatic lesions. He responded to the treatment and his PSA level dropped to 6.1 mcg/L after 2 months of initial diagnosis. The patient was on Morphine for his low back pain and was able to walk with an ECOG performance status of 0.

After 6 months of initial management completion, the patient presented with significant severe bilateral leg pain up to mid-calf with limited mobility. His PSA level rose up to 34.8 mcg/L and imaging with CT demonstrated progression of extensive bone metastasis with newly developed compression fractures of T7 and L5 vertebral bodies. There was slight retro bulging of the L5 vertebral body, which resulted in mild cord compression. The SPECT CT bone scan revealed significant increase in the number of sites of osteoblastic activities in the axial and appendicular skeleton; throughout the spine, bilateral ribs, proximal humeri, frontal bone, scapulae, sternum, pelvis, right proximal femur. The patient was started on chemotherapy with Docetaxel and Prednisolone.

The PSA levels progressed up to 189 mcg/L, and The patient was planned for ^{177}Lu-PSMA therapy. The 99mTc-PSMA with SPECT CT scan revealed widespread PSMA receptor avid disease in the axial and proximal appendicular skeleton. Complete blood count before therapy showed WBC 8.7 x109/L, Hb 10.5 g/dl and platelet 176 x109/L. Renal function was normal with a creatinine level of 60 micromol/L and adequate function without outflow obstruction seen in renal MAG3 nuclear scan. Chemotherapy was stopped due to progression of disease after a total of 5 cycles. The patient completed 2 cycles of ^{177}Lu-PSMA with response seen in 99mTc-PSMA with SPECT CT post therapy scan. Infusion of ^{177}Lu-PSMA were given at dosage 207 mCi at 1st and 2nd cycle. The PSA level had a reduction of 92% (Figure 4). After the 2nd therapy cycle The patient developed myelosuppression with pancytopenia and required admission for transfusion (Figure 5). The post therapy 99mTc-PSMA with SPECT CT scan showed diffuse homogenous tracer distribution in the bone marrow with no suggestive of bone marrow uptake and no receptor avid disease (Figure 6A), as compared to the baseline scan (Figure 6B). Therapy was stopped as patient developed severe sepsis requiring admission under intensive care.

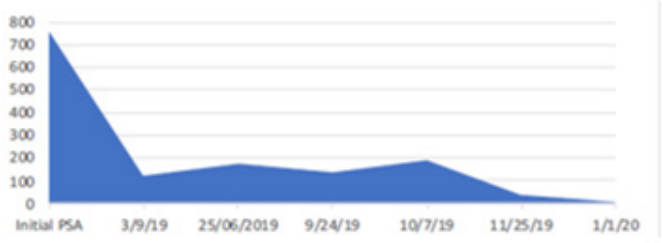

Figure 4. PSA levels of case 2 after ^{177}Lu-PSMA therapy.

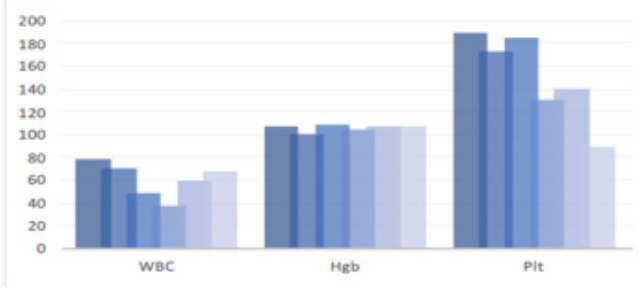

Figure 5. Trends of WBC, Haemoglobin and Platelets after ^{177}Lu-PSMA therapy in case 2.

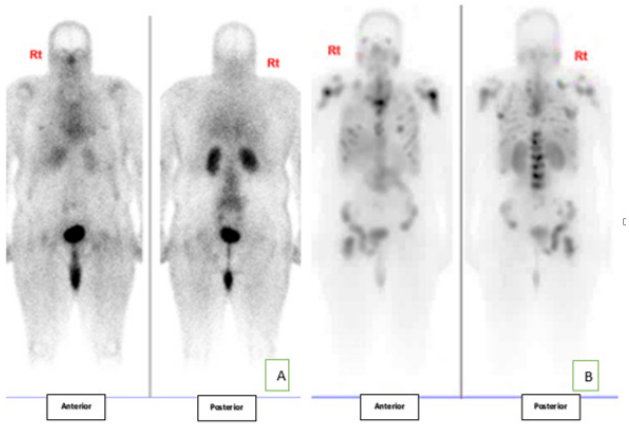

Figure 6. Last Post therapy ^{177}LU-PSMA scan showing no receptor avid disease just bone marrow activity and Trends of WBC, Haemoglobin and Platelets after ^{177}Lu-PSMA therapy in case 21st Postherapy ^{177}LU-PSMA scan showing receptor avid disease involving the bony skeleton.

Discussion

We report two cases of metastatic prostate cancer with bone involvement that were pre-treated with chemotherapy and anti-hormonal therapy with initial good response and stable disease on imaging. However after one year, PSA levels increased with progression to mCRPC. Both patients underwent ^{177}Lu-PSMA therapy with suboptimal response. The last post therapy 99mTc-PSMA with SPECT CT scans in both patients showed diffuse homogenous tracer distribution in the bone marrow with no suggestion of receptor avid disease. All of which raises the question of suboptimal uptake of radioisotope targeting the tumor cells, therefore narrowing the therapeutic window. The only reason we could contribute to this was suboptimal labelling and poor binding of the tracer. The reasons for poor labelling are still unclear, as they may be related to the peptide/buffer tagging to the ^{177}Lu, the transportation conditions that may affect the labelling efficiency, and/or the solutions used for the quality control that can mislead to pass quality control (QC) results. We attribute bone marrow suppression to free ^{177}Lu, although the QC was more than 95% for both ^{177}Lu-PSMA therapy doses. Further studies are required to confirm the cause of pancytopaenia in these two patients.

Wright GL et al, have demonstrated that while PSMA is expressed at low levels in normal human prostate epithelium, it is overexpressed up to 1000 times higher in almost all prostate cancer cells than in normal prostate cells [7]. It was observed that the density of expression of this transmembrane receptor on prostate cancer cells further increases depending on hormone-resistant prostate cancers [8].

PSMA is not entirely prostate specific and is expressed in cells of small intestine, proximal renal tubules and salivary glands [8]. Although the expression of PSMA on these cells is significantly reduced when compared to prostate cancer cells, there is a radiation dose that can be delivered to these target organs [8]. This has an impact on the benefit/risk profile and determination of the safe dose of radiotherapy that can be delivered without causing significant radiation damage to non-target organs. This is an important consideration for our patient as it is possible that PSMA-targeted therapy will be affecting other tissues that are positive for PMSA receptors especially the kidney. In fact, patients with mild or moderate renal impairment may be at greater risk of toxicity. Therefore, it is suggested to perform more frequent assessments of renal function in patients with mild to moderate renal impairment.

Emmett L et al reported that ^{177}Lu-PSMA has gained popularity as the therapeutic radionuclide of choice due to its physical properties [8]. ^{177}Lu-PSMA is a low-energy β-particle emitter which limits the distance β-particles can travel through tissue. The shorter β-range of ^{177}Lu-PSMA provides better irradiation of small tumors, compared to longer β-particles. The γ-emission from ^{177}Lu allows for ex vivo imaging and consequently the collection of information pertaining to tumor localization and size, which has the advantage of follow-up of ^{177}Lu-PSMA therapy. It has relatively long physical half-life of 6.73 days, which allows for the delivery of high activity ^{177}Lu-PSMA to prostate cancer cells [8]. ^{177}Lu-PSMA can easily be administered without significant symptoms at the time of injection. The main safety issues are standard radiation safety precautions, that are inherent in all intravenously injected, and renal excreted radionuclide therapies [8].

In the TROPIC, phase III clinical trial, there was reduction in PSA levels from 30% to 70%, which is highly comparable to the PSA response rates achieved by chemotherapy agents used in mCRPC, like Cabazitaxel and Docetaxel [10]. Baum RP et al, included 56 men; 80% of all men had reduction of PSA levels after therapy [11]. Patients were receiving up to five treatments of ^{177}Lu-PSMA at 6-weekly intervals with possible survival benefits. This study found that with a follow-up period of 28 months, there was a survival of 78.6%. Median progression-free survival was 13.7 months [11]. Tagawa ST et al, published the results of a Phase II clinical trial that demonstrated ^{177}Lu-PSMA resulted in declines in PSA among patients with mCRPC [12]. In a follow-up analysis, they reported a better response, including increased survival, but with higher toxicity with increased dose [12]. Additionally, a large decline in circulating tumor cells (CTCs), which is an important biomarker for the follow up treatment of advanced prostate cancer [13].

In 33% of those men treated to date show progressive disease despite treatment [8]. These are likely due to a variety of factors. One important factor is the tumor cells uniformly express a high density of the PSMA receptor in the targeted tissue. Because of heterogeneity of PSMA receptor activity within the tumor population, this may mean that some will not respond to treatment with ^{177}Lu-PSMA, which will manifest as disease progression, and in a rising of the PSA levels [8]. Bone metastases appeared to respond less compared to visceral or lymph node disease to treatment with ^{177}Lu-PSMA [11].

Overall, toxicities related to ^{177}Lu-PSMA therapy has been of low grade and manageable with close monitoring. Hematological toxicity is the most commonly reported serious side effect related to ^{177}Lu-PSMA therapy that also deserves a close monitoring and the follow-up of local specific clinical practices guidelines. Ferdinandus J et al, reported the identification of low platelet levels and the need for pain relief, as the most significant predictors of poor response to ^{177}Lu-PSMA [14]. In men with significant bone metastases, up to 10-25% of men had mild to moderate reduction in hemoglobin or platelets that should be clinically manageable [8]. Because of the longer particle range of ^{177}Lu-PSMA, compared to alpha emitters such as radium 223, it is likely that ^{177}Lu-PSMA will have a higher radiation dose to surrounding marrow in men with extensive metastatic bone disease, than alpha emitter treatment options [15]. Another concern was about renal toxicity due to the mechanism of excretion which is an anticipated long-term complication [16]. Safety & efficacy of targeted radionuclide therapies can be improved with patient-specific dosimetry, which can act as an early indicator of organ toxicity [8].

All currently published studies about ^{177}Lu-PSMA therapy in metastatic prostate cancer are retrospective, mostly single arm, and involve a variety of treatment regimens, both in terms of dosage (ranging from 3.5 to 8.0 Gbq/injection of ^{177}Lu-PSMA) and the dose frequency administered (ranges from a single injection up to 4-6 injections 6 weeks apart) [8,17]. Younger, healthier and less aggressive PC had better outcomes [17]. Currently there are no long-term prospective Randomized Controlled Trials (RCTs) available for the evaluation of PSMA-targeted radioligand therapy on survival benefits compared with approved standard therapies for advanced prostate cancer such as Abiraterone, Enzalutamide, radium-223-dichloride, Docetaxel or Cabazitaxel.

Conclusion

The ^{177}Lu-PSMA therapy for progressive mCRPC is safe, effective, well-tolerated, and has a considerable effect on PSA levels. The main objective of the therapy is to minimize toxicity in patients whose disease had progressed despite all standard treatments. The factors contributing to our therapy, related side-effects and outcomes of treatment are suboptimal and our experience in our cohort of patients remains unanswered. Therefore, a patient specific dosimetric approach should be applied before therapy to prevent organ toxicity.

Authors Contribution

Author 1; Contributed in case presentation and writing of manuscript

Author 2; Contributed in manuscript writing and structured manuscript

according to journal format

Author 3; Contributed in preparation of the case and provided images

Author 4; Contributed in editing the manuscript and provided images

Author 5; Contributed in prepared the case

Author 6; Contributed in preparing the case

Author 7; Contributed in preparing the case

Author 8; Contributed in preparing the case

Author 9; Contributed in editing and proofreading the manuscript

Author 10; Contributed in preparing the case and in editing the manuscript

Author 11; Contributed in preparing the case, editing the manuscript and provided images

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