The Outcome and Safety of Re-challenge Lutetium-177 PSMA (^{177}Lu-PSMA) Therapy with Low-Dose Docetaxel as a Radiosensitizer—a Promising Combination in Metastatic Castrate-Resistant Prostate Cancer

Masha Maharaj[1,*], Lucille Heslop[2], Trisha Govender[1], Nisaar Korowlay[3], Aviral Singh[4], Partha Choudhary[5], Mike Sathekge[6]

[1]Department of Nuclear Medicine, Imaging and Therapy Centres of Excellence, Durban, KwaZulu Natal, South Africa

[2]Durban Oncology Centre, West Ridge, Durban, South Africa

[3]Division of Nuclear Medicine, Tygerberg Hospital, Stellenbosch University, Stellenbosch, South Africa

[4]Theranostics Center for Molecular Radiotherapy and Molecular Imaging (PET/CT) ENETS Center of Excellence, Zentralklinik Bad Berka GmbH, Bad Berka, Germany

[5]Department of Nuclear Medicine, Rajiv Gandhi Cancer Institute and Research Centre, New Delhi, India

[6]Department of Nuclear Medicine, University of Pretoria & Steve Biko Academic Hospital, Pretoria, South Africa

*Correspondence to Masha Maharaj.

Email addresses

Masha Maharaj drmasha@yahoo.co.uk

Lucille Heslop mludgate@mweb.co.za

Trisha Govender trisha.govender.tg@gmail.com

Nisaar Korowlay nak@sun.ac.za

Aviral Singh aviral.singh@yahoo.com

Partha Choudhary pschoudhary@hotmail.com

Mike Sathekge mike.sathekge@up.ac.za

Abstract

Prostate-specific membrane antigen (PSMA)-directed radioligand therapy (PSMA-RLT) with lutetium-177 (^{177}Lu-PSMA) has been used in metastatic castrate-resistant prostate cancer (mCRPC), and retrospective data have shown this therapy to be favourably safe with attractive clinical responses. Re-challenge ^{177}Lu-PSMA therapy in early responders has been shown to be safe and effective. We report the use of low-dose Taxol-based chemotherapy (modified dose 25 mg/m^2 weekly × 6 weeks) as a radiosensitizer with re-challenge ^{177}Lu-PSMA therapy (4 cycles). In a period of 3 years, the patient underwent a total of 8 cycles of ^{177}Lu-PSMA with a cumulative dose of 51.8 GBq. All therapies were uneventful and well tolerated. There was a good response to re-challenge ^{177}Lu-PSMA therapy and low-dose docetaxel (Taxol-^{177}Lu-PSMA) with no recorded tumour resistance.

Keywords: ^{177}Lu; PSMA; Prostate cancer; Docetaxel; Radiosensitizer; Re-challenge

Introduction

Prostate-specific membrane antigen direct radioligand therapy (PSMA-RLT) with lutetium-177 (^{177}Lu-PSMA) is currently undergoing clinical validation in patients with metastatic castrate-resistant prostate cancer (mCRPC). Retrospective data acquired from multiple centres have concurred with the partial results from a prospective study (phase II clinical trial). The studies have reported high response rates and low toxicity with tangible clinical responses in pain and performance status [1,2,3,4,5]. In this case report, we explore the efficacy of a radiosensitizer and re-challenge ^{177}Lu-PSMA therapy in a patient with delayed progression post initial ^{177}Lu-PSMA therapy.

Case Report

A 70-year-old male with metastatic castrate-resistant prostate cancer and increasing prostate-specific antigen (PSA = 53.44) presented for further therapy. Previous therapies included brachytherapy (2008) and hormonal therapy (2009–2017). The hormonal therapy regimen was goserelin and abiraterone followed by goserelin and enzalutamide.

^{68} Ga-PSMA PET/CT scans were performed for therapy planning and monitoring. Imaging protocol was with injection 3–5 mCi of ^{68} Ga-PSMA including Lasix 40 mg intravenous stat, followed by whole body scanning at 40 min post injection. The image quantification was done with SUV (g/ml with reference to lean body mass) using Q-Clear Technology-enhanced measurements. Baseline PET/CT (Fig. 1a) showed multiple PSMA-avid bone lesions with an SUVmax of 22.71 (SUVmax @T12). A single discrete lesion seen in segment 6 of the liver was seen with no corresponding CT changes (SUVmax 8.39, reference liver = SUVmax of 4.34). The patient was referred by his oncologist for ^{177}Lu-PSMA therapy.

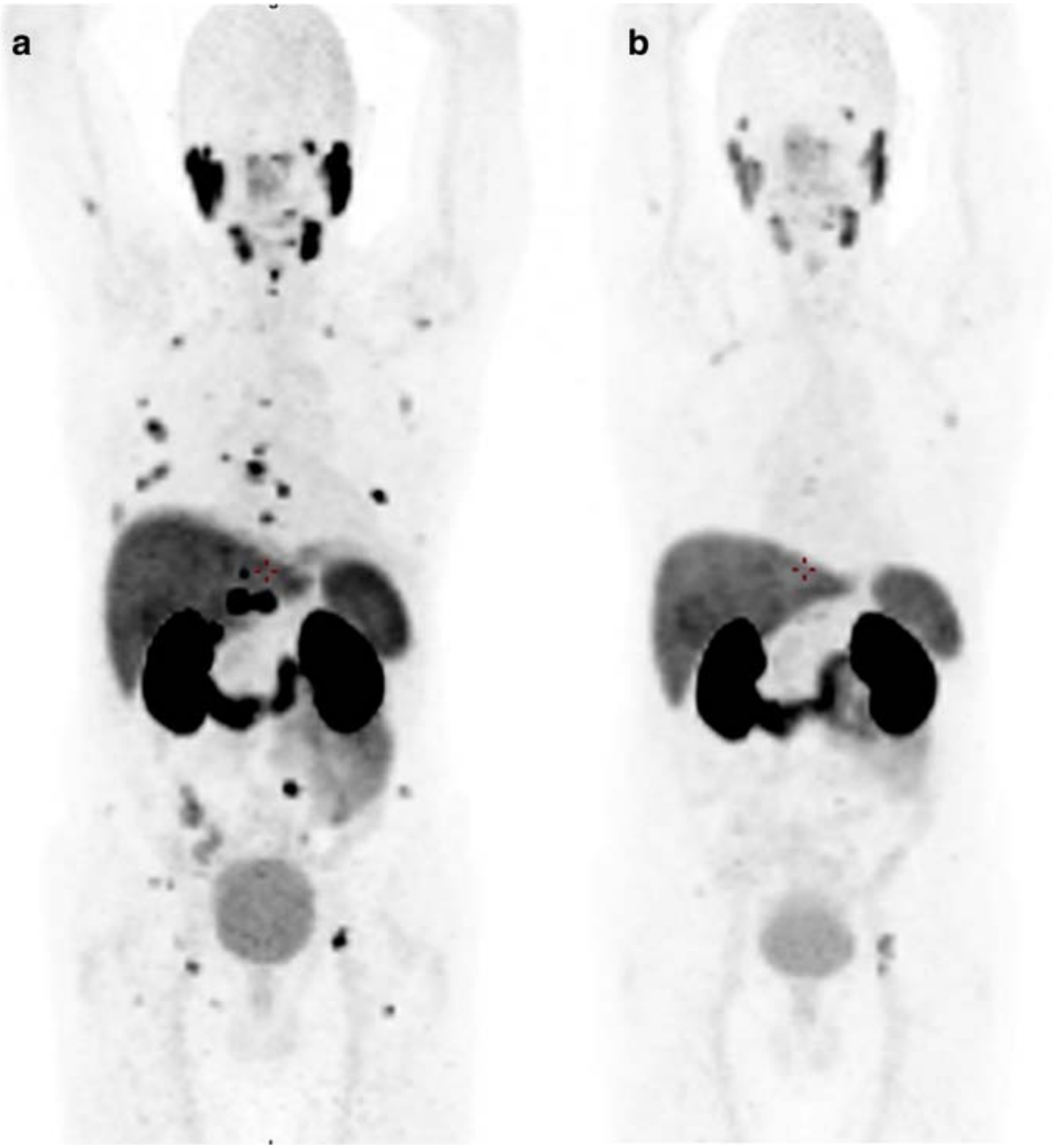

Figure 1. a Baseline ^{68} Ga-PSMA PET/CT. The scan showed multiple PSMA-avid bone lesions with an SUVmax of 22.71. A single discrete lesion seen in segment 6 of the liver showed increased uptake with no corresponding CT changes (SUVmax 8.39, compared to the reference liver activity with an SUVmax of 4.34). PSA = 53.44. **b** ^{68} Ga-PSMA PET/CT done at 12 months post baseline scan. Patient had completed 4 cycles of ^{177}Lu-PSMA therapy. When compared to the previous study, there was a significant improvement in the uptake and distribution of metastasis. The foci seen previously in the liver was not seen post therapy. Residual disease was seen in ~13 out of the previous ~49 lesions. SUVmax 6.59. PSA = 2.81

The patient received 4 cycles of ^{177}Lu-PSMA therapy with a dose of 200 mCi per cycle. The patient continued enzalutamide therapy while receiving the initial 4 cycles of ^{177}Lu-PSMA. The intervals between cycles were 6–8 weeks; however, the 4th cycle was delayed by 8–12 weeks due to travel-related technical difficulties. A follow-up ^{68} Ga-PSMA PET/CT was done at 3 months post initial 4 cycles of treatment (Fig. 1b). The scan showed significant response in the uptake and distribution of the PSMA-avid metastases. The discrete focus seen previously in the liver was not seen on the post therapy scan. Approximately 36 out of 49 (~70%) of the previously detected lesions had resolved (Fig. 1b).

At 6 months post initial treatment, the PSA level began to rise (PSA = 94.67), and a follow-up scan showed an increased number and distribution of PSMA-avid metastases compared to those on the previous scan, with an SUVmax of 16.58. No soft tissue lesions were observed (Fig. 2a).

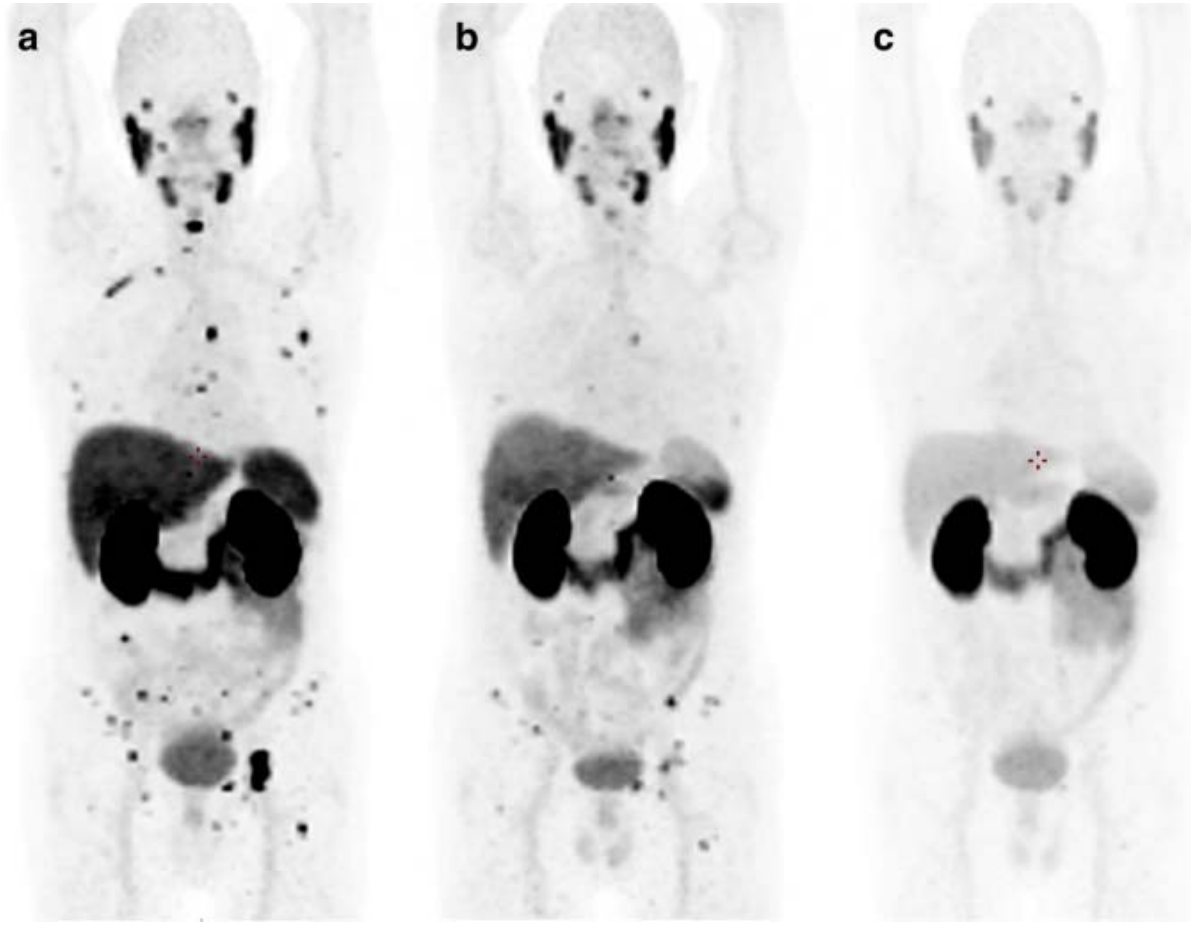

Figure 2. a ^{68} Ga-PSMA PET/CT scan done at 6 months post ^{177}Lu-PSMA therapy showed multiple avid bone lesions which are more intense, increased in number and distribution. SUVmax 16.58. PSA = 94.67. **b** ^{68} Ga-PSMA PET/CT scan post 2 cycles re-challenge ^{177}Lu-PSMA combined with low-dose Taxotere showed significant improvement with multiple PSMA-avid bony lesions completely resolved on the current study. SUVmax 9.04. PSA = 3.56. **c** ^{68} Ga-PSMA PET/CT scan 3 months post second set of 2 cycles re-challenge ^{177}Lu-PSMA with low-dose Taxotere showed a near complete response. Residual activity was seen in 3 lesions. SUVmax 1.81. No new bone or soft tissue lesions were seen. PSA = 9.74 at time of scan. PSA = 4.46 a month after scan showing a remarkable continued decline in PSA

After a discussion with a multidisciplinary team, it was decided that a re-challenge of ^{177}Lu-PSMA therapy would be combined with a low-dose chemotherapy agent as a radiosensitizer. Informed consent was obtained from the patient. The post treatment regimen with two cycles (average dose of 150 mCi × 6 weekly) of re-challenge ^{177}Lu-PSMA therapy and low-dose docetaxel (modified dose of 25 mg/m^2 weekly × 6 weeks) demonstrated a good response (Fig. 2b). Two further cycles (average dose of 150 mCi × 6 weekly) of ^{177}Lu-PSMA and low-dose docetaxel (modified dose of 25 mg/m^2 weekly × 6 weeks) were administered, with complete and continued good response in most of the PSMA-avid lesions. No soft tissue lesions were observed. ^{68} Ga-PSMA PET/CT imaging was performed 3 months post last cycle (Fig. 2c). The scan showed a remarkable improvement in number, size, and intensity of lesions. Residual activity was seen in the left iliac crest, left acetabulum and left proximal femur, SUVmax 1.81. The PSA level taken prior to scan (Fig. 2c) was 9.74; this was repeated 1 month post scan and showed a decline to 4.46.

At 3 months after the first 2 cycles of re-challenge of ^{177}Lu-PSMA therapy and low-dose docetaxel (Taxol-^{177}Lu-PSMA), the patient manifested symptomatic transient iron deficiency anaemia. The patient responded to a single dose of iron dextran, oral iron supplementation and dietary intake. The iron dextran was re-administered prophylactically after the second 2 cycles of re-challenge Taxol-^{177}Lu-PSMA therapy. No new lesions or resistant lesions were recorded during re-challenge therapy or during the 8-month follow-up period. The patient experienced continued optimal performance with no change in daily routine. The patient remained haematologically stable. There was no decline in renal function. No salivary gland dysfunction was noted. No pain was recorded during or post treatment. We noted at the follow-up ^{68} Ga-PSMA PET/CT scan post 3rd and 4th cycle re-challenge therapy, the PSA level was elevated at 9.74 despite the remarkable improvement seen visually on the scan. A follow-up PSA showed a continued downward trend supporting the image findings and consistent with a delayed biochemical response. The oncologist continued maintenance therapy with 3 monthly injections of goserelin (LHRH) and bondronate (Table 1).

Table 1. Biochemistry baseline pre DL, 3 months post 1st and 2nd DL cycle, 3 months post 3rd and 4th DL cycle, 8 months post complete DL treatment

Test (reference value)	Baseline pre DL therapy	3 months post 1st and 2nd cycle DL therapy	3 months post 3rd and 4th cycle DL therapy	8 months post complete DL therapy
Haemoglobin (13.0–17.0 g/dL)	12.9	10.6	12.3	12.4
White blood cell count (3.92–9.88 10 9/L)	7.15	7.90	8.99	4.74
Platelet (150–450 10 9/L)	255	232	254	207
Urea (<8.4 mmol/L)	5.3	6.4	6.0	6.7
Creatinine (64–104 umol/L)	71	80	72	100
Alkaline phosphatase (40–130 U/L)	71	58	50	55
Gamma GT (<60 U/L)	17	20	17	20
ALT (<50 U/L)	<5	10	6	10
AST (<38 U/L)	15	21	13	30
Total protein (60–83 G/L)	60	54	55	60
Iron (11.6–31.3 umol/L)		4.3		14.9
Ferritin (30–400 G/L)		534		
Transferrin (2.0–3.6 G/L)		1.8		
% Saturation (20–50%)		10		

*DL, Taxol-^{177}Lu-PSMA

Discussion

In 1853, the surgeon J. Adams described and reported the first case of prostate cancer as "a very rare disease"; 164 years later, according to the NCR 2016, men have a 1 in 9 lifetime risk of developing prostate cancer (the rate continues to increase as diagnosis improves and the average age of the population increases) [6]. In 2018, there were over 3 million men living in the USA with prostate cancer, and the overall risk of an individual male dying from prostate cancer was 1 in 39 or approximately 2.6% [7]. Prostate cancer is biologically and clinically heterogeneous, making imaging evaluations, follow-up and management challenging [8]. mCRPC is defined as the progression of disease despite androgen depletion therapy (ADT). The patient may present with clinical, biochemical or imaging progression.

PSMA is expressed in most prostate cancers. PSMA expression is higher in primary prostate tumours and metastatic lesions compared with benign tissue and is positively associated with tumour grade and stage. Because of its high expression in malignant prostate tissue, PSMA has been used in immunoscintigraphy to monitor metastatic disease and as a target antigen for immunotherapy. PSMA-RLT with ^{177}Lu-PSMA has been used in mCRPC, and retrospective data have shown the therapy to be favourably safe with attractive clinical responses [1,2,3, 9].

Re-challenge ^{177}Lu-PSMA therapy in previous good responders has been proven to be safe and effective [4, 5]. Low-dose docetaxel radiosensitization with radiotherapy in patients with prostate cancer and other cancers has been described in several articles [10,11,12]. In 2009, Kelly et al. presented a study using ^{177}Lu-hu3S193 and low titrated doses of docetaxel, showing significantly improved efficacy [13]. In 2020, Batra et al. combined ^{177}Lu-J591, a prostate-specific monoclonal antibody, with titrated doses of docetaxel/prednisone and recorded notable efficacy [14]. Several studies have shown that radiosensitizers enhance the effect of therapy and can improve the overall response to therapy with other lutetium-based therapies [15,16,17]. A radiosensitizer is an agent that makes tumour cells more sensitive to radiation therapy. It is generally known that the tumour response decreases after repeat courses of antitumour regimens due to a slow development of resistance, as described by Gafita et al. [18]. The benefit of the combination a Taxol-based drug and ^{177}Lu-PSMA may account for the absence of resistance to therapy and enhanced therapeutic efficacy in our patient.

The authors in this case report discuss the use of low-dose Taxol-based chemotherapy as a radiosensitizer with re-challenge ^{177}Lu-PSMA. To the best of our knowledge, this is the first case report where a Taxol-based agent and ^{177}Lu-PSMA have been used in combination for mCRPC to achieve a favourable outcome and maintained an excellent performance status with no recorded tumour resistance.

Ethics declarations

Conflict of Interest

Masha Maharaj, Lucille Heslop, Trisha Govender, Nisaar Korowlay, Aviral Singh, Partha Choudhary and Mike Sathekge declare no conflict of interest.

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