Journal of Nuclear Medicine, published on April 7, 2016 as doi:10.2967/jnumed.116.173757

Response and tolerability of a single dose of ^{177}Lu-PSMA-DKFZ-617 in patients with metastatic castration-resistant prostate cancer: a multicenter retrospective analysis

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Short title: ^{177}Lu-PSMA therapy and advanced mCRPC

Keywords: mCRPC, prostate cancer, Lu-PSMA, Radioligand therapy

Word count: 3543

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Abstract

Background:

Radiolabelled prostate specific membrane antigen (PSMA) ligands represent a true theranostics concept for diagnosis and therapy of relapsed and metastatic prostate cancer patients. The aim of this study was to evaluate response and tolerability of a single dose of ^{177}Lutetium-PSMA-617 (Lu-PSMA) in a large cohort of patients with metastatic castration resistant prostate cancer (mCRPC).

Methods:

The data of 82 consecutive patients (median age: 73 years, range: 43-87) with metastatic castration resistant prostate cancer who received a single dose of Lu-PSMA (mean: 5.9±0.5 GBq) were retrospectively analyzed. Data was collected at baseline and 8 weeks after therapy. ^{68}Ga-PSMA-11 PET/CT was performed in all patients to verify sufficient PSMA expression. Bone, lymph node, liver and lung metastases were present in 99%, 65%, 17% and 11% of the patients, respectively. Tolerability and response were evaluated using hematologic parameters, renal scintigraphy, clinical data and prostate specific antigen (PSA) value at baseline and 8 weeks after therapy application.

Results:

A total of six patients died and two patients dropped out not willing to continue therapy and follow-up. Complete dataset of 74 patients were available for analysis. 47 (64%) of the patients showed a PSA-Decline, of these 23 (31%) had a PSA decline > 50%, 35 (47%) had a stable disease with a PSA decline from <50% to an increase <25% and 17 (23%) showed a progressive disease with a PSA increase >25%. There were no significant changes indicative of toxicity in hemoglobin, white blood cells, creatinine and tubular extraction rates. There was a significant but mild decrease of platelets with a median value still within the normal range.

Conclusion:

This retrospective multicenter analysis suggests that radioligand therapy with Lu-PSMA is safe, well tolerated and shows considerable response in PSA values. Therefore, it offers an additional

therapeutic option for patients with mCRPC. This data may justify further prospective randomized studies to evaluate and prove the clinical benefit in survival and quality of life.

Introduction

Prostate specific membrane antigen (PSMA) is a promising target in diagnostics and therapy of metastatic prostate cancer (PCa). In the last few years there is increasing evidence that PSMA imaging is valuable for diagnosis of recurrent and metastatic prostate cancer and more recently in preoperative staging of biopsy proven prostate cancer patients to rule out distant metastases and evaluate the extent of intraprostatic disease *(1-5)*.

With regard to the high PSMA expression on prostate cancer cells, especially increasing in high grade metastatic disease and castration resistant PCa, PSMA as therapeutic target has been an issue during the past decade *(6-8)*. First therapy attempts using the ^{90}Y-labelled monoclonal antibody CYT-356, which binds to the intracellular component of PSMA, did not have favorable results *(6)*. Further study using ^{177}Lu labelled monoclonal antibody J591 showed promising results in a Phase II trial treating patients with progressive castration resistant prostate cancer *(7)*. Introduced by the German Cancer Research Center in Heidelberg PSMA-617 is a true theranostic agent in imaging and therapy of PCa *(9)*. In a first cohort of 10 patients a single dose of ^{177}Lu-PSMA-617 (Lu-PSMA) showed a low toxicity profile and respectable response in prostate specific antigen (PSA) level *(8)*.

The aim of this retrospective study was to evaluate response and toxicity of this novel therapeutic option for PCa patients after a single dose of Lu-PSMA in a large cohort of metastatic castration resistant Prostate cancer (mCRPC) patients treated with Lu-PSMA as salvage therapy.

Material and Methods

Patient population

Data of 82 consecutive patients (median age: 73 years, range: 43-87) with mCRPC were analysed after treatment with a single dose of Lu-PSMA at the departments of Nuclear Medicine of University Hospitals of Bonn, Muenster, Cologne and Aachen between December 2014 and November 2015. Patients were analyzed retrospectively according to response and tolerability after a single dose of Lu-PSMA. Mean administered activity was 5.9±0.5 GBq of Lu-PSMA. Radioligand therapy (RLT) with Lu-PSMA was performed as “Compassionate Use” according to German Medicinal Drugs Act, AMG §13 2b. The decision to offer this treatment was made by the local interdisciplinary institutional tumor board. Prerequisite for salvage therapy was the absence of other therapeutic options: progressive despite first line or second line chemotherapy

(Docetaxel and Cabecitaxel) or patient not suitable for chemotherapy as well as not suitable for Ra-223-dichloride and patients should be pretreated with at least one of the new generation hormone therapy drugs (Abiraterone or Enzalutamide). All patients gave their written consent after a detailed informative description of therapy and possible risk and side effects. Retrospective analysis was performed according to institutional ethical guidelines. A separate informed consent was waived.

Patient preparation

^{68}Ga-PSMA-11 PET/CT was performed prior therapy to demonstrate PSMA positive metastatic disease and adequate PSMA expression in tumor lesions. Detailed procedures for ^{68}Ga-PSMA-11 PET/CT have been described earlier *(3,5)*.

Blood samples were drawn at the day of therapy before tracer administration and 8 weeks after injection. The PSA, alkaline phosphatase (ALP), parameters of hematological, renal and liver status were determined at this time points and are analyzed here. Additional blood samples were drawn by the family doctor (general practitioner) during the eight weeks (data not presented here according incomplete nature of the data).

Renal scintigraphy was preformed prior therapy planning to rule out obstructive disease and evaluate renal function. This procedure was performed in accordance to clinical standards and has been described in detail before *(10,11)*. In case of obstructive disease patients were referred to the local urologist in order to eliminate the obstruction as far as possible.

Preparation of ^{177}Lu-PSMA-617

PSMA-617 precursor was obtained from ABX GmbH (Radeberg, Germany). ^{177}Lutetium was obtained from ITG (Garching, Germany) and IDB (Holland). The in house production and labelling of Lu-PSMA was conducted in accordance to The German Medicinal Drugs Act, AMG §13 2b. Detailed labelling procedures have been described before *(8)*.

Therapy administration

To reduce Lu-PSMA uptake in salivary gland cooling the glands using cool packs was started 30 minutes prior therapy injection and was continued up to 4 hours after injection.

Nearly 6 GBq of Lu-PSMA (mean: 5.9±0.5 GBq) were injected intravenously as a slow bolus injection within 30 to 60 seconds followed by at least 1000 ml Ringer or isotonic NaCl solution. Immediately 10 minutes after therapy administration and 24 as well as 48 hours after therapy whole body scintigraphic imaging was performed to document Lu-PSMA uptake and retention in tumor lesions. Images showed high Lu-PSMA uptake within the metastatic lesions concordant to pretherapeutic performed ^{68}Ga-PSMA-PET images (Figure 1).

Evaluation of response and toxicity

PSA was considered as the main factor of response. Although the changes in PSA were not confirmed with a second measurement, as requested by the prostate cancer working group 2 criteria (PCWG2) *(12)*, we used those recommendations as guidance for response evaluation. A PSA decline ≥ 50% was considered as response; between PSA decline < 50% and PSA increase < 25% was considered as stable disease and a PSA increase > 25% was considered as progressive disease. Therapy induced changes in ALP was also analyzed.
The Eastern Collaborative Oncology Group (ECOG) performance status was documented at baseline and 8 weeks after therapy. Toxicity according side effects and hematologic changes were documented according to common toxicity criteria for adverse events (CTCAE version 4.0).

Statistical analysis

SPSS Statistics 23 (IBM Inc., Armonk, NY, USA) was used for analysis. The descriptive statistics are reported as the medians and ranges as far as applicable. Wilcoxon's signed rank test was performed to determine the significance of the differences between median values. A *P* value <0.05 was considered as significant.

Results

A total of 6 patients died because of extensive disease and 2 patients dropped out not wishing to be referred for further evaluation and therapy. Data of 74 patients were available for analysis. Patient's characteristics at baseline including extent of metastatic disease and prior therapies are

given in table 1. The majority of patients (99%) had bone metastases. 84% of those showed a high compromised and disseminated multifocal bone metastases.
Eighty-one patients were formally castration resistant and received anti androgen therapy prior Lu-PSMA. Only one patient did not receive anti androgen therapy because of having non hormone active neuro endocrine prostate cancer and very low PSA value at baseline.
72% of the patients had an initial ECOG Score of 0-1, 25.6% an ECOG of 2 and 2.4% an ECOG of 3. There was no significant change in ECOG Score after 8 weeks, in 2 patients an improvement and in 4 patients a worsening of 1 score point was reported. Among the patients who died during the 8 weeks period initial ECOG was 1 or 2. Out of these patients 3 patients died 4 weeks after therapy, 1 died 5 and 2 died 10 and 11 weeks after the RLT. All patients presented extensive metastatic disease including diffuse bone metastases and had a history of multimodal therapies. To our knowledge there was no association between the performed Lu-PSMA therapy and death in these patients.

Response

Forty-Seven (64%) of the patients showed any PSA-Decline, of these 23 (31%) had a PSA decline > 50%. 35 patients (47%) had a stable disease with a PSA decline from <50% to an increase of <25% (Figure 2). Progressive disease with a PSA increase >25% occurred in 17 patients (23%). According to these results 58 patients (78 %) may have a benefit from the RLT with Lu-PSMA. Serum median ALP showed a minor decrease from 179 (range 38-1607) to 159 (range 37-1299, p = n.s.).

Toxicity

Results according CTC criteria are given in table 2. Serious adverse events during therapy administration and hospitalization did not occur.
There were no significant changes in median values of Hb, WBC, Creatinine and liver parameters. A significant decrease in platelets was observed after 8 weeks compared to baseline, although still within normal range. 10 patients received erythrocyte concentrate prior RLT due to extent of skeletal metastases. Only two patients still needed erythrocyte transfusion after RLT. Renal parameters creatinine (median: 0.86 vs. 0.85) and tubular extraction rate (median: 218 vs. 214) did not change significantly.

Xerostomia was reported by 4 patients (4.8%) prior RLT due to previous chemotherapy. After RLT a mild xerostomia Grade I was reported by 7 patients, in 3 of them only as short time complaints. Permanent RLT related xerostomia did not occur.
Diarrhea did not occur in any patient. Nausea at baseline was reported by 8 patients related to prior therapies and to their general condition. 8 weeks after RLT mild nausea was reported only in one patient (1.4%).

Discussion

Targeted RLT is a favorable and elegant method for selective and individualized therapy of different kinds of tumors with fewer side effects due to lower uptake in uninvolved tissue. Glutamate Carboxypeptidase II - these days frequently called PSMA - is a membrane bound metallopeptidase with highest expressions in prostate cancer tissue *(13)*. Therefore, PSMA is an ideal target for RLT.
In the present study we evaluated tolerability and response of a single administered dose of ^{177}Lu-PSMA-617 in a larger cohort of patients in a multicenter setting.

Using the monoclonal antibody J591 targeting the extracellular component of PSMA, Tagawa et al. *(7)* could show a PSA decline ≥50% and any PSA decline in 10.6% and 59.6% after a single dose of ^{177}Lu labelled J591 in a phase II study. These results were in line with a prior phase I study by Bander et al. showing similar results with a PSA decline ≥50% in 11% of the patients treated with the same radioligand *(14)*. In contrast to these results the present study demonstrates a PSA decline ≥50% and any PSA decline in 31% and 64% of patients treated with a single dose of 6 GBq of ^{177}Lu PSMA-617. According to our response-criteria, described above, 47% of the patients experienced a stable disease. According to these results 78% of the patients may have benefited from the RLT with Lu-PSMA. Further studies evaluating response according PCWG criteria have to confirm these data.
In a first case series of 10 patients *(8)* we could demonstrate a PSA decline ≥50% and ≥30% in 50% and 70% of the patients and a low toxicity profile after a single dose of Lu-PSMA.
A prior study by Zechmann et al. using a ^{131}Iodine labelled PSMA ligand showed a PSA decline ≥ 50% in more than 60% of patients *(15)*.

More recently Baum et al. *(16)* presented results of a single center study of 56 patients receiving different number of therapy cycles of ^{177}Lu labelled PSMA-I&T. They showed a valuable response with PSA decline ≥50% in 58.9% and progressive disease in 12.8% in an inhomogeneous group of patients treated with up to 5 therapy cycles. The authors presented only the overall results after different treatments and did not mention therapy effects after different cycles compared to baseline. The other limitation of their study which is already mentioned by the authors is the absence of pre-therapeutic patient selection criteria. In the presenting study a homogeneous group of patients with very advanced metastatic disease were treated according our selection criteria in case of salvage therapy of patients pretreated or not suitable for established therapeutic options for mCRPC.

All these publications showed respectable but variable response rates. The variation of response may be due to different ß-energies of ^{131}Iodine and ^{177}Lutetium and especially patient selection such as extent of metastatic disease and prior treatments.

In phase II therapy study using ^{177}Lu labelled monoclonal antibody J591 all patients showed a reversible thrombocytopenia and grade 4 thrombocytopenia occurred in 46.8 % of the patients *(7)*. In the present study no grade 4 and 5 thrombocytopenia were observed. A grade 3 thrombocytopenia occurred in only one patient (Table 2). There was no relevant toxicity according to hematologic parameters. There was a mild but significant decline in median platelets count, but with a median value still within the normal range. Further studies are needed to evaluate these results according several RLT and hematological changes.
Data according tolerability and hematologic toxicity presented here support prior impression of published data *(8,15,16)* showing low toxicity profile and a high tolerability in patients with advanced metastatic disease.

According to available dosimetry data after RLT with Lu-PSMA *(17)*, salivary glands and kidneys show high uptake but not critical absorbed doses. Therefore, low affection of the salivary glands and renal function is expected. Our study confirms results of prior studies *(8, 16)* showing no permanent xerostomia and no nephrotoxicity related to RLT.

The major limitation of this study is its retrospective design. Further prospective randomized trials are needed to evaluate response in earlier stage of metastatic prostate cancer as an additional therapy or competitor to approved available therapies such as abiraterone or enzalutamide. In addition future studies have to evaluate variables affecting or predicting response prior RLT with Lu-PSMA.

Conclusion

This retrospective multicenter analysis suggests that radioligand therapy with Lu-PSMA is safe, well tolerated and shows considerable response in PSA values in patients with advanced mCRPC. Further studies are needed to evaluate response and toxicity after several therapy cycles and to determine the optimal number of therapy cycles not only in case of salvage therapy, but also as an additional therapy in earlier stages of metastatic castration resistant prostate cancer.

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Acknowledgment

The authors thank the radiochemistry groups at all involved Departments of Nuclear Medicine for highly reliable production of ^{177}Lu-PSMA-617 and ^{68}Ga-PSMA-11.

Disclosure

The Authors declare they have no conflicts of interest concerning the subject and materials presented in this manuscript.

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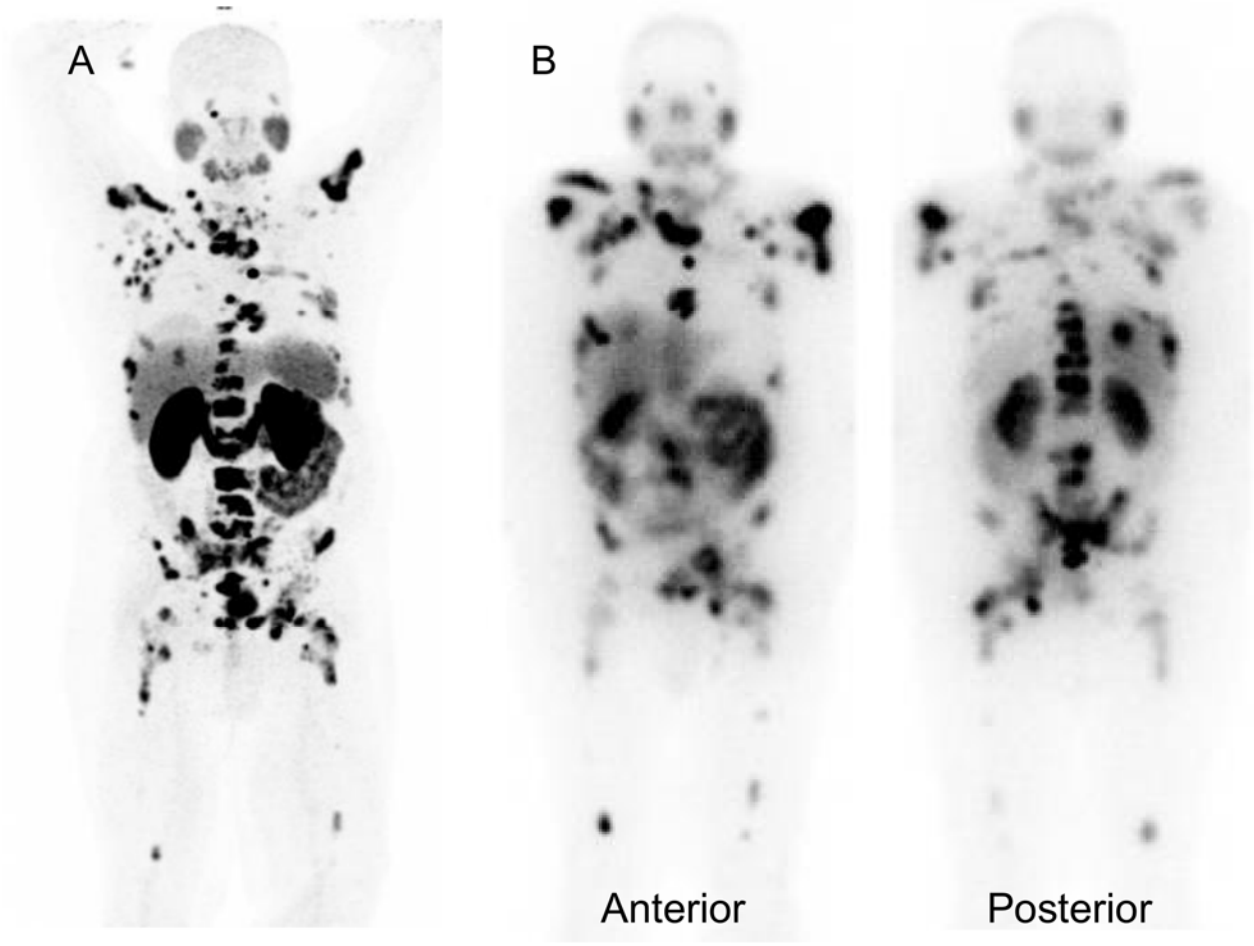

Figure 1. Maximum intensity projection of ^{68}Ga-PSMA-PET (A) shows multiple bone and lymph node metastases. Posttherapeutic planar scintigraphic images (B) showing high ^{177}Lu-PSMA uptake within corresponding lesions to PET images.

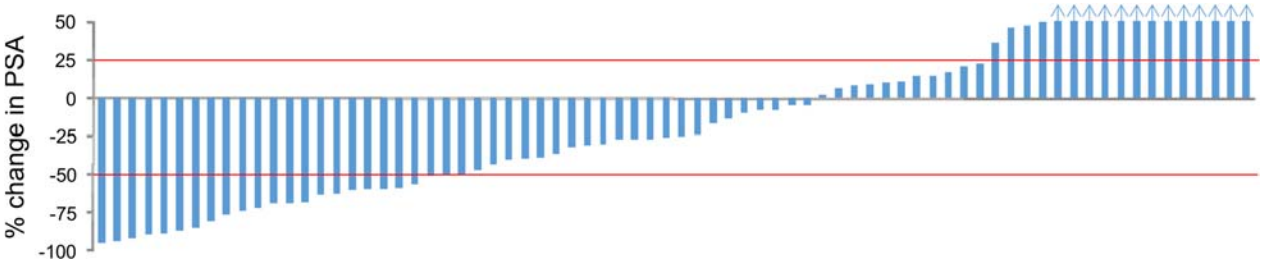

Figure 2. Waterfall curve showing percentage change in PSA values. In case of PSA progression ≥50% the maximum value is scaled to 50. Blue arrows represent patients with PSA increase ≥ 50%.

Table 1. Patient Characteristics at Baseline

	Patients	
Characteristics	**N**	**%**
Age, years		
Median	73	
Range	43 - 87	
PSA, ng/dl		
Median	342	
Range	5-5910	
Hemoglobin, g/L		
Median	10.6	
Range	6-15	
WBC X 10^3/dl		
Median	4.9	
Range	3.3-12.4	
Platelets X 10^3/dl		
Median	251	
Range	62-557	
Creatinine		
Median	0.86	
Range	0.3-1.4	
Alkaline phosphatase, U/L		
Median	179	
Range	38-1607	
Sites of Metastases		
Bone	81	99
LN	65	79
Liver	17	21
Lung	9	11
Brain	1	1
Prior therapy		
Prostatectomy	45	55
RTx prostate region	38	46
Hormonal	81	99
Docetaxel	52	63
Cabacitaxel	11	13
Abiraterone	69	84
Enzalutamide	66	80
Ra-223	19	23
RTx to Bone	31	38

LN: lymph node, RTx: radiation therapy

Table2. Adverse Events according common toxicity criteria (version 4.0)

	Baseline				after RLT			
	CTC 0° (%)	**CTC 1° (%)**	**CTC 2° (%)**	**CTC 3° (%)**	**CTC 0°(%)**	**CTC 1° (%)**	**CTC 2° (%)**	**CTC 3° (%)**
WBC	74 (90.2)	6 (7.3)	2 (2.4)	0 (0)	62 (84)	8 (10.8)	4 (5.4)	0 (0)
Hb	26 (31.7)	40 (48.8)	11 (13.4)	5 (6.1)	47 (63.5)	16 (21.6)	10 (13.5)	1 (1.4)
Plt	67 (81.7)	11 (13.4)	3 (3.7)	1 (1.2)	57 (77)	15 (20.2)	1 (1.4)	1 (1.4)
Crea	81 (98.8)	1 (1.2)	0 (0)	0 (0)	70 (94.5)	4 (5.5)	0 (0)	0 (0)
Nausea	74 (90.2)	8 (9.8)	0 (0)	0 (0)	73 (98.6)	1 (1.4)	0 (0)	0 (0)
Diarrhea	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Xerostomia	78 (95.1)	3 (3.6)	1 (1.2)	0 (0)	67 (90.6)	7 (9.4)	0 (0)	0 (0)

There were no treatment associated grade 4 or 5 toxicities.

WBC: white blood cells, Hb: hemoglobin, Plt: platelets, crea: serum creatinine