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Early experience of rechallenge ^{177}Lu-PSMA radioligand therapy after an initial good response in patients with advanced prostate cancer

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ABSTRACT

Aim: To retrospectively evaluate the feasibility of rechallenge ^{177}Lu-Prostate-specific membrane antigen (^{177}Lu-PSMA) radioligandtherapy (RLT).

Material&Methods: Rechallenge RLT was defined as subsequent treatment with ^{177}Lu-PSMA after initial exposure with excellent response followed by progression. Biochemical, radiographic, clinical antitumor response and adverse events were analysed. Prostate-specific antigen progression-free survival (PSA-PFS) and overall survival (OS) were calculated.

Results: Eight patients underwent a median of 2 (range:1-4) cycles of ^{177}Lu-PSMA-I&T rechallenge. Maximum PSA-decrease of 50% was achieved in 3 (37.5%) of patients. Radiographic response was favorable in 3 patients, whilst 4 exhibited progressive disease. Eastern-Cooperative-Oncology-Group (ECOG) Performance-Status was stable during therapy in all patients. No grade 4 toxicity was noticed and grade 3 toxicity occurred in 3 (37.5%) patients. The median PSA-PFS and OS were 3.2 (95%CI:2.6-3.7) and 14.0 (95%CI:6.2-21.8) months, respectively.

Conclusion: In a small patient cohort with initial excellent response ^{177}Lu-PSMA rechallenge is still active, with lower efficacy and increased toxicity levels.

Keywords: PSMA, ^{177}Lu-PSMA, rechallenge, radioligand therapy, prostate cancer

INTRODUCTION

Metastatic castration-resistant prostate cancer (mCRPC) is the lethal phenotype of the disease. Despite several new agents having been approved, more than 250.000 men still die of prostate cancer worldwide each year (*1*). In recent years, prostate-specific membrane antigen (PSMA) became an attractive target for both diagnosis and treatment of prostate cancer (*2*). The application of PSMA-ligands labelled with radionuclide ^{177}Lu has demonstrated encouraging efficacy and good safety profile for ^{177}Lu-PSMA radioligand therapy (RLT) (*3,4*). Rechallenge of docetaxel in patients with mCRPC who initially responded to docetaxel chemotherapy regimen was described as a potential treatment option after docetaxel-free interval. Available data indicate reasonable antitumor response at moderate toxicity (*5,6*).

So far, data for rechallenge of ^{177}Lu-PSMA RLT in patients after prior effective treatment followed by progressive disease after ^{177}Lu-PSMA-free interval has not been published. Therefore, we aimed to retrospectively assess the efficacy and safety profile of ^{177}Lu-PSMA rechallenge in this specific patient cohort.

MATERIAL AND METHODS

All patients who underwent ^{177}Lu-PSMA-I&T RLT in a rechallenge setting at our institution between October 2014 and February 2018 were extracted. The rationale to consider initial ^{177}Lu-PSMA-I&T accomplished and inclusion criteria for ^{177}Lu-PSMA rechallenge are detailed in Supplement (*3,7*). Rechallenge treatment was applied every 6-8 weeks including a ^{68}Ga-PSMA-11 PET/CT every two cycles. All patients signed a written informed consent and were treated under a compassionate use. The institutional review board approved the analysis (reference 115/18S).

Non-hematological and hematological adverse events (AEs) were graded according to Common Terminology Criteria for Adverse Events v5.0. Biochemical response was determined using Prostate-

specific antigen (PSA) decline ≥30%, ≥50%, and ≥90% during initial and rechallenge treatment. For radiographic response ^{68}Ga-PSMA-11 PET/CTs were assessed as described recently (*8*). Clinical response was assessed by Eastern Cooperative Oncology Group (ECOG) Performance-Status and changes in bone pain from the Brief-Pain-Inventory. Overall survival (OS) and PSA progression-free survival (PSA-PFS) were calculated according to guidelines of the Prostate Cancer Trials Clinical Working Group 3 (*9*).

PSA-PFS and OS were determined using the Kaplan-Meier curve method with corresponding 95% confidence intervals (95%CI). Statistical analyses were performed using IBM SPSS Statistics v22.0 (IBM Corp., Armonk, USA).

RESULTS

Eight patients with ^{177}Lu-PSMA-I&T RLT in a rechallenge setting were analyzed. One patient even underwent a third course of treatment. Details on patient characteristics including mCRPC pretreatment regimes, number of cycles and tumor sites are given in Supplement and Table 1.

Safety Profile

Specific non-hematological and hematological parameters for all patients at baseline and after ^{177}Lu-PSMA-I&T rechallenge are presented in Supplemental Table 1 and Figure 1. Adverse events graded according to Common Terminology Criteria for Adverse Events v5.0 are shown in Table 2. No grade 4 AEs were noticed. Grade 3 AEs occurred in three (37.5%) patients, two of them with thrombocytopenia and one with anemia. Grade 1 increase in creatinine serum was observed in one (12.5%) patient. Grade 1 xerostomia was noticed in two (25%) patients. Note, that nearly all patients with grade 2 or grade 3 toxicities have presented with grade 1 toxicity at the start of ^{177}Lu-PSMA-I&T rechallenge.

Antitumor Response

Biochemical. At initial treatment with ^{177}Lu-PSMA-I&T, all patients achieved a maximum PSA-decline of at least 50% of whom 75% (6 of 8) had at least a 90% PSA-decline. During ^{177}Lu-PSMA-I&T rechallenge, a maximum PSA-decline of at least 30%, 50%, and 90% was achieved in 75.0% of patients (6 of 8), 37.5% (3 of 8), and 12.5% (1 of 8), respectively. Table 1 presents intraindividual PSA-responses and PSA-levels at baseline and after ^{177}Lu-PSMA-I&T, both at initial and rechallenge treatment. Figure 2 shows the waterfall plot of maximum PSA-responses at rechallenge treatment.

Radiographic. Radiographic antitumor response was assessed in seven patients. One patient did not undergo the follow-up ^{68}Ga-PSMA-11 PET/CT due to progressive disease and deterioration of the general condition. According to adapted PERCIST 1.0 (*10*), three patients had a partial response, whilst four patients exhibited progressive disease due to new lesions.

Clinical. At baseline, an ECOG score of 0, 1 and 2 was present in one (12.8%), six (75%) and one (12.8%) patients, respectively. ECOG Performance-Status remained stable in all patients during the course of rechallenge treatment. At baseline, six patients had pain related to bone metastases. Of these, two (33%) reported complete resolution of pain, one (16%) had partial remission, two (32%) reported no changes and one (16%) patient reported worsening bone pain.

Time on Treatment and Survival Curve Analyses

Swimmer plot (Fig. 3) displays intraindividual mCRPC therapies duration and maximum PSA response at ^{177}Lu-PSMA-I&T rechallenge. Treatment was discontinued in four patients due to AEs (3x thrombopenia, 1x renal function impairment) and in three patients due to biochemical or radiographic progression. In one patient ^{177}Lu-PSMA rechallenge was halted after four cycles due to exceptional response

and restarted the thirds course after an additional ^{177}Lu-PSMA-free interval. One case example is displayed in Supplemental Figure 1.

Median OS was 23.1 (95%CI: 19.5-26.7) months after first initiation of ^{177}Lu-PSMA-I&T and 14.0 (95%CI: 6.2-21.8) months after initiation of rechallenge treatment. Three patients (37.5%) were alive at last follow-up. The median PSA-PFS was 12.4 (95%CI: 10.4-14.3) months from the beginning of the initial ^{177}Lu-PSMA-I&T RLT and 3.2 (95%CI: 2.6-3.7) months from the beginning of rechallenge treatment.

DISCUSSION

To our knowledge, this is the first report assessing efficacy and safety profile of ^{177}Lu-PSMA rechallenge in patients with mCRPC. Exposing a patient to the same oncological treatment, which was effective during primary application is an increasingly used concept, e.g. for docetaxel (*5,6*).

In our selected group of patients with excellent response to initial ^{177}Lu-PSMA-I&T, the median PSA-PFS at first therapy course was 12.4 (95%CI: 10.4-14.3) vs. 3.3 (95%CI: 2.6-3.7) months at treatment rechallenge and also much shorter compared to an unselected cohort of patients at initial ^{177}Lu-PSMA-I&T treatment (median PSA-PFS 5.8 (95%CI: 1.2-10.5) months (*3*)). Only 37.5% of patients achieved 50% PSA-decline during rechallenge. In a similar setting involving patients who had an initial good response to docetaxel, a 50% PSA-decline was reported in 28-40% of patients at rechallenge treatment (*5,6*). These results outline rechallenge treatment offers antitumor activity, but to a lower extent comparing to initial treatment.

The benefits of ^{177}Lu-PSMA rechallenge have to be weighed against the risk of cumulative toxicity. All three patients with grade 3 AEs exhibited impaired lab results prior to ^{177}Lu-PSMA rechallenge (Fig. 1). Furthermore, both patients with grade 3 thrombopenia had substantial tumor progression during rechallenge treatment. Therefore, discriminating bone marrow failure etiology (progression vs. treatment-related) is difficult.

There are no guidelines for the optimum number of cycles of ^{177}Lu-PSMA in patients who show good response. Currently, in our institution, the initial treatment with ^{177}Lu-PSMA is typically discontinued after a maximum number of six cycles. Usually, patients who undergo RLT are heavily pretreated with other mCRPC therapies including second-line androgen receptor target treatments or taxane-based regimens. In our study, patients underwent a mean of four (range: 2-8) mCRPC pretreatments lines. Chemotherapy with Cabazitaxel and radiopharmaceutical Radium-223-dichloride are two common therapeutic choices after initial ^{177}Lu-PSMA RLT discontinuation. When compared, the median OS were 14.5 (95%CI: 13.5-15.3), 14.5 (95%CI: 13.5-15.3) and 14.0 (95%CI: 6.2-21.8) months for 3-weekly 25mg/m^2 Cabazitaxel, Radium-223 and our small cohort of ^{177}Lu-PSMA-I&T rechallenge, respectively (*11,12*). However, with only eight patients in our analysis, caution is warranted for comparison with survival data of other treatments. Notably, in a recent abstract describing ^{177}Lu-PSMA-617 in a rechallenge setting 75% of patients achieved any PSA-decrease at acceptable toxicity level (*13*).

Our analysis has limitations. First, we report only a small cohort of eight patients. Consequently, our results have to be interpreted with caution and further analyses (e.g. predictor factors) were not possible. However, ^{177}Lu-PSMA RLT has been introduced only recently and the number of patients with an excellent response is limited. Second, due to a missing established system to evaluate response on PSMA PET, we adopted PERCIST 1.0 as described (*8*). The validation of PERCIST for non-FDG application is still under discussion.

CONCLUSION

Our results in a small patient cohort with initial excellent response during ^{177}Lu-PSMA RLT indicate that this treatment is still active in a rechallenge setting, but with lower efficacy and increased toxicity levels. The present study proposes ^{177}Lu-PSMA rechallenge as a potential therapeutic option in this palliative setting with a lack of alternatives. Its benefits have to be weighed against the risk of cumulative toxicity.

Further prospective studies including larger patient cohorts are warranted to investigate the clinical outcome for mCRPC patients undergoing ^{177}Lu-PSMA rechallenge.

CONFLICT OF INTEREST

No potential conflicts of interest relevant to this article exist.

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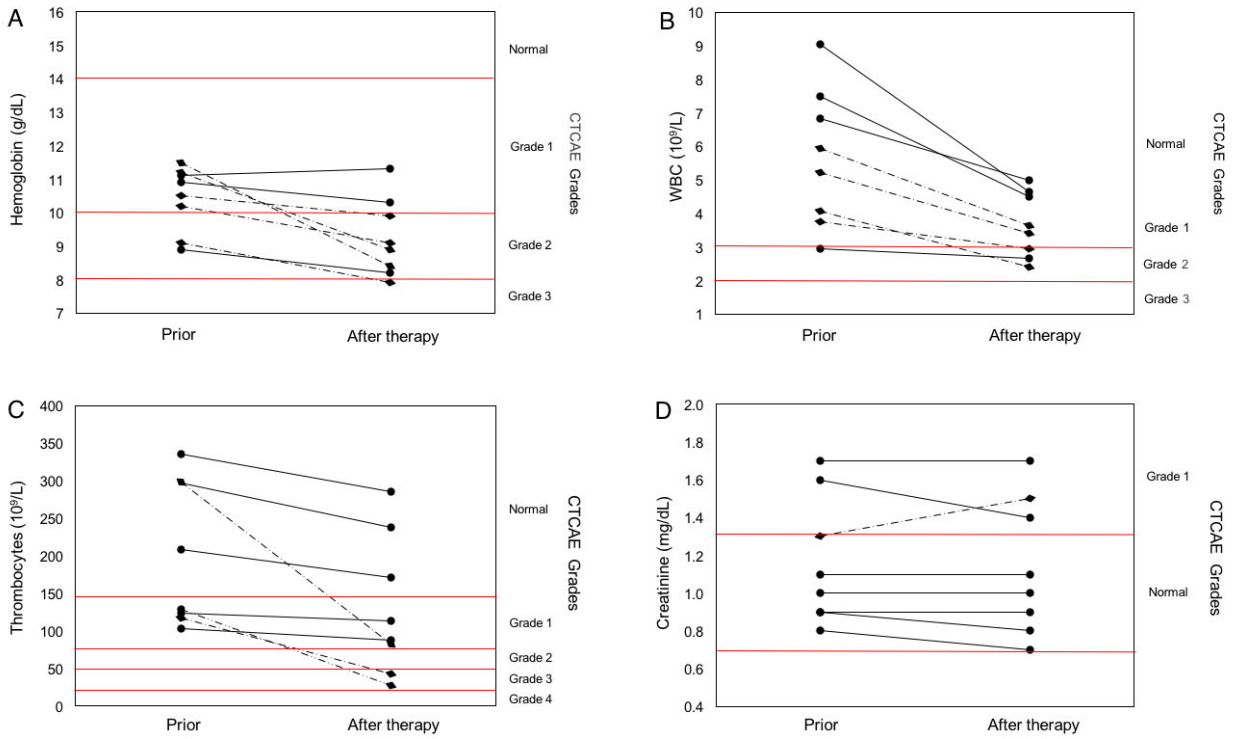

Fig. 1. Comparison of the hematological lab results Hb (A), WBC (B) Thrombocytes (C) and Creatinine (D) values prior and after ^{177}Lu-PSMA-I&T rechallenge

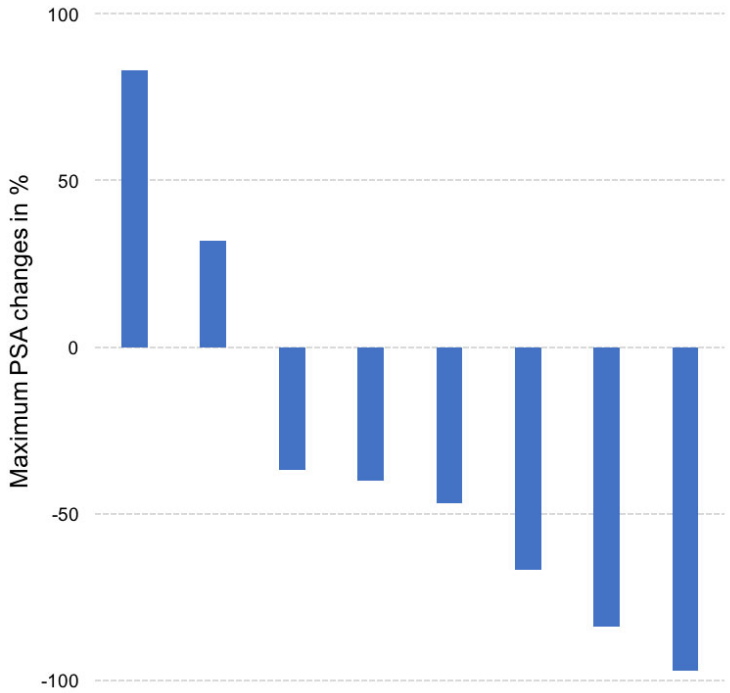

Fig. 2. Waterfall plot of maximum PSA responses during ^{177}Lu-PSMA-I&T rechallenge as compared to baseline levels.

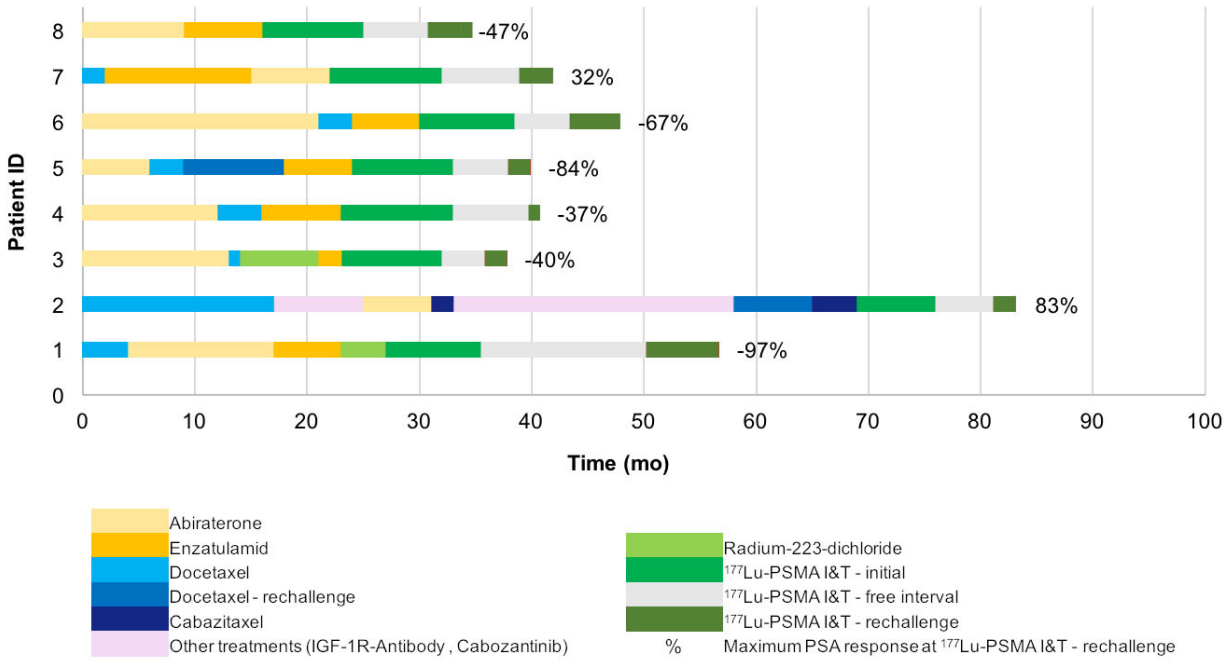

Fig. 3. Swimmer plot demonstrating mCRPC treatments time duration and the maximum PSA responses at ^{177}Lu-PSMA-I&T rechallenge

Table 1. Patients characteristics

ID	Primary diagnosis				Prior treatments			^{177}Lu-PSMA-I&T Initial treatment				^{177}Lu-PSMA-I&T Free-interval		^{177}Lu-PSMA-I&T Rechallenge								
						mCRPC therapies										Sites of metastases						
	Date	iPSA	GS	Mets.	Primary therapy (RP/RT)	Drugs	Lines	Baseline PSA (ng/mL)	No. of cycles	Post-therapy PSA (ng/mL)	Max. PSA Resp.	Time (m)	Other therapies	Age	ECOG score	Bone	LN	Visceral	Baseline PSA (ng/mL)	No. of cycles	Max. PSA Resp.	PSMA PET/CT Resp.†	Therapy discontinuation
1	2008	40	9	LN	+/+	Docetaxel Abiraterone Enzalutamide Radium 223	4	605	4	<0.03	-100%	14.7	ADT	72	0	+	+	-	5	4	-97%	PR	Therapy break after excellent response
2	2001	6	9	-	+/+	Docetaxel‡ Cabazitaxel Abiraterone Others*	8	97	4	16	-78%	5.1	ADT	67	1	+	+	Lungs	54	2	83%	-	Tumor progress
3	2002	24	6	Bones	-/-	Docetaxel Abiraterone Enzalutamide Radium 223	4	1193	4	18	-98%	3.8	ADT	73	1	+	-	-	66	2	-40%	PR	Toxicity
4	2012	26	7a	LN Bones	-/+	Docetaxel Abiraterone Enzalutamide	3	227	6	5	-96%	6.7	ADT	75	1	+	+	Adrenal glands	50	1	-37%	PD	Toxicity
5	2004	29	9	LN	+/+	Docetaxel‡ Abiraterone Enzalutamide	4	176	6	1	-98%	4.9	ADT	70	1	+	-	-	51	2	-84%	PR	Toxicity
6	2008	7	9	-	+/+	Docetaxel Abiraterone Enzalutamide	3	950	6	35	-94%	4.9	ADT	62	2	+	+	-	2328	3	-67%	PD	Tumor progress
7	2005	72	9	LN	+/+	Docetaxel Abiraterone Enzalutamide	3	63	6	8	-87%	6.9	ADT	75	1	+	+	-	34	2	32%	PD	Tumor progress
8	2006	14	7b	-	+/+	Abiraterone Enzalutamide	2	124	6	3	-97%	5.7	ADT	77	1	-	+	-	110	2	-47%	PD	Toxicity

* IGF-1R-Antibody (NCT00313781), Cabozantinib (COMET-1-Trial, NCT01605227)
† PR = Partial Response, PD = Progressive Disease
‡patients underwent initial docetaxel and docetaxel rechallenge

Abbreviations: iPSA = initial PSA; GS = Gleason Score; Mets. = metastases; LN = lymph nodes; RP = radical prostatectomy; RT = local radiotherapy; ADT = continuous-androgen-deprivation-therapy

Table 2. Adverse events at ^{177}Lu-PSMA-I&T rechallenge graded according to Common Terminology Criteria for Adverse Events v5.0

	Grade 1	Grade 2	Grade 3	Grade 4
Anemia		4	1	
Leucopenia	2	2		
Thrombopenia	1		2	
Renal function impairment	1			
Xerostomia	2			