Factors predicting the early biochemical response to [^{177}Lu]Lu-PSMA therapy in patients with metastatic castration resistant prostate cancer

Original Article

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ABSTRACT

Introduction: Targeted radionuclide therapy with [^{177}Lu]Lu-prostate-specific membrane antigen (PSMA) has shown promising results for the treatment of castration-resistant prostate cancer (mCRPC). Nevertheless, a proportion of patients do not respond to this therapy. Here, we aimed to evaluate the prognostic significance of the pretreatment pathologic and laboratory factors for the prediction of biochemical response to the first cycle of [^{177}Lu]Lu-PSMA therapy.

Methods: In this retrospective study, mCRPC patients, referred for [^{177}Lu]Lu-PSMA therapy, were included. We retrieved the data of patients, undergone [^{177}Lu]Lu-PSMA, from March 2019 to March 2021. Multiple baseline pathologic and laboratory parameters were extracted and correlated with the response to the first cycle. The prostate-specific antigen (PSA) level was evaluated six weeks after [^{177}Lu]Lu-PSMA therapy for the biochemical response.

Results: Forty-three patients with a mean age of 69.8±10.2 were included. Bone and visceral metastases were present in 81.4% and 14.0% of the patients, respectively. Except for two, all patients had received hormone- and chemotherapy. The mean PSA level was 189.9±259.0 at baseline. Following one cycle of [^{177}Lu]Lu-PSMA, "≥ 10% PSA response" and "≥ 50% PSA response" were seen in 81.4% and 44.2% of the patients, respectively. Patients with higher baseline PSA more frequently had ≥ 10% PSA response (p= 0.004). Also, the reduction in the PSA level correlated with baseline PSA (p=0.013, r=0.375).

Conclusion: [^{177}Lu]Lu-PSMA therapy results in the biochemical response in a considerable number of patients after one cycle. In nearly half of patients, PSA declines more than 50%. Higher baseline PSA is correlated with the level of PSA response.

Key words: Castration-resistant prostate cancer; [^{177}Lu]Lu-PSMA; Radioligand therapy; Biochemical response

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INTRODUCTION

Prostate cancer is the second common cancer and the fifth cause of cancer-related death among men, worldwide [1]. It is estimated that 1.4 million men are diagnosed with this type of cancer in 2020 [1]. Metastatic castration-resistant prostate cancer (mCRPC) is a subgroup of patients showing progressive disease despite hormonal therapy [2]. When the patient reaches this stage of the disease, the median overall survival (OS) is approximately 14 months [3].

Radioligand therapy (RLT) is a subset of precision medicine [4]. The key feature for successful treatment relies on the overexpression of the cell surface receptor, prostate-specific membrane antigen (PSMA) [5]. In this regard, RLT with [^{177}Lu]Lu-PSMA has revealed promising results [5].

The phase III VISION trial showed that [^{177}Lu]Lu-PSMA increases OS and progression-free survival (PFS) compared to the best supportive/best standard care [6]. Despite favorable results, some patients do not respond to [^{177}Lu]Lu-PSMA RLT [7]. Multiple clinical and paraclinical parameters have been investigated to find the prognostic factors, among which the PSA decline of any amount after the first cycle of the therapy was found as a predictor of OS in a meta-analysis [8]. However, the results are discordant for most of the other factors evaluated in different studies [7]. Here, we aimed to evaluate the prognostic significance of the pretreatment pathologic and laboratory factors in the prediction of biochemical response to the first cycle of [^{177}Lu]Lu-PSMA RLT.

METHODS

This retrospective study was performed on pathologically proven mCRPC patients who have been referred for [^{177}Lu]Lu-PSMA RLT in the Nuclear Medicine departments of Dr. Shariati and Khatamolanbia hospitals. We retrieved the data of patients undergone [^{177}Lu]Lu-PSMA from March 2019 to March 2021. The inclusion criteria were 1) available histopathologic data confirming the diagnosis of prostate cancer, 2) tumor progression in spite of receiving available standard treatments, 3) PSMA-expressing metastases confirmed on the pre-treatment [^{68}Ga]Ga-PSMA positron emission tomography/computed tomography (PET/CT), and 4) the absence of PSMA-non-avid liver metastasis.

Multiple factors, including baseline pathologic and laboratory parameters were extracted and correlated with the response to the first cycle. The PSA level was evaluated six weeks after therapy for the assessment of biochemical recurrence. At least ≥ 10% and ≥ 50% reduction in PSA level were considered as the target for the response. In addition, the percentage of decline in PSA (the amount of PSA reduction/baseline PSA) was correlated with different pre-treatment factors.

Statistical analysis

Statistical analysis was conducted using SPSS 23.0, IBM. All variables were analyzed by the Kolmogorov Smirnov test to evaluate the normal distribution. Numeric data are presented as mean ± standard deviation (SD; for data with normal distribution) or median with interquartile range (IQR; for data without normal distribution). The relation between PSA response and different variables were analyzed using independent T-test, U-Mann Whitney or Chi2 tests. The bivariate correlation test was employed to assess the correlation between the percentage of reduction in PSA level and different factors. A P-value of less than 0.05 was considered significant.

RESULTS

Forty-three patients with a mean age of 69.8 ± 10.2 years (ranged: 47-89) and median Gleason score of 8 (IQR: 7-8) were included. Baseline demographics and clinical characteristics, as well as prior treatments of patients and sites of involvement, are shown in Table 1.

Time interval from the first diagnosis to [^{177}Lu]Lu-PSMA RLT ranged from less than a year to 14 years (median: 2, IQR: 2-4 years). The majority of the patients (81.4%) had evidence of metastatic bone involvement .

PSA value before [^{177}Lu]Lu-PSMA RLT ranged from 0.25 to 1264 ng/mL (189.9 ± 259 ng/mL; IQR: 28.8-200.0). Other baseline laboratory parameters are outlined in Table 2.

The first administered dose ranged from 130 to 200 mCi (median: 164, IQR: 154-180 mCi). PSA values after the first cycle ranged from 1.3 to 753.0 (median: 47.0; IQR: 12.3-102.0). Following one cycle of [^{177}Lu]Lu-PSMA "≥ 10% PSA response" and "≥ 50% PSA response" were seen in 81.4% and 44.2% of the patients, respectively. Also, the paired sample T-test showed a significant decline following the first cycle of [^{177}Lu]Lu-PSMA RLT (mean difference: 102.6 ng/mL [95% CI: 53.1-152], p-value <0.001; Table 3). An example of post-therapy image is shown in Figure 1.

The independent T-test showed a relation between higher baseline PSA and ≥ 10% PSA decrease (p=0.004). Also, there was a significant correlation between baseline PSA and the amount of PSA decline after the first cycle (p<0.001, r=0.842), which also remained significant after normalizing the amount of PSA decline to the baseline value (p=0.013, r=0.375). No relation was depicted between other parameters and ≥ 10% or ≥ 50% response to therapy (Table 4).

Table 1: Baseline demographics and characteristics.

Characteristic		(%) Number	
Tissue diagnosis	-Biopsy	(72.1) 31	
	-Prostatectomy	(27.9) 12	
Previous therapies	-Radiation therapy	(55.8) 24	
	-Hormonal therapy	(100) 43	
	-Chemotherapy	(95.3) 41	
	-Brachytherapy	(2.3) 1	
De novo metastasis	Yes	(58.1) 25	
	No	(41.9) 18	
Gleason score	7	(48.8) 21	
	8	(34.9) 15	
	9	(14) 6	
	10	(2.3) 1	
Sites of involvement on the baseline [^{68}Ga]Ga-PSMA PET/CT	-Prostate bed	(4.6) 2	
	-Bladder	(2.3) 1	
	-Lymph nodes	(30.2) 13	
		Abdominopelvic	(18.6) 8
		Not otherwise specified	(11.6) 5
	-Bone	(81.4) 35	
		Oligometastatic bone	(14) 6
		Widespread	(67.4) 29
	-Lung	(6.9) 3	
	-Liver	(4.6) 2	
	-Pleura	(2.3) 1	

Table 2: Summary of baseline laboratory parameters.

Parameter	Range	Mean ± SD
Prostate-specific antigen	0.25-1264	189.9 ± 259
Alkaline phosphatase (IU/L)	3-2548	470.1 ± 510.1
Lactate dehydrogenase (U/L)	3-2476	484.2 ± 366.3
Hemoglobin (g/dL)	9-15	12.0 ± 1.6
Platelet counts (×10^3/µL)	123-412	242.1 ± 73.1
White blood cell counts (×10^3/µL)	3.4-15.4	6.5 ± 2.4

Table 3: Summary of PSA response following radioligand therapy.

Type of PSA response	Number (%)
Any* decline	35 (81.4)
≥ 50% decline	19 (44.2)
Mean decline	-14% (-99.3 to +700)
PSA progression **	7 (16.3)
Stable PSA **	1 (2.3)

* Any PSA decline in the literature review indicate any decrease; however, in our research we consider it as a 10% decrease at least which is the found difference between the two PSA values in the least responder patient.
** According to the PCWG3 criteria which considers >25% increase as PSA progression and <25% progression as stable [6].
PCWG3: Prostate Cancer Working Group 3; PSA: prostate-specific antigen

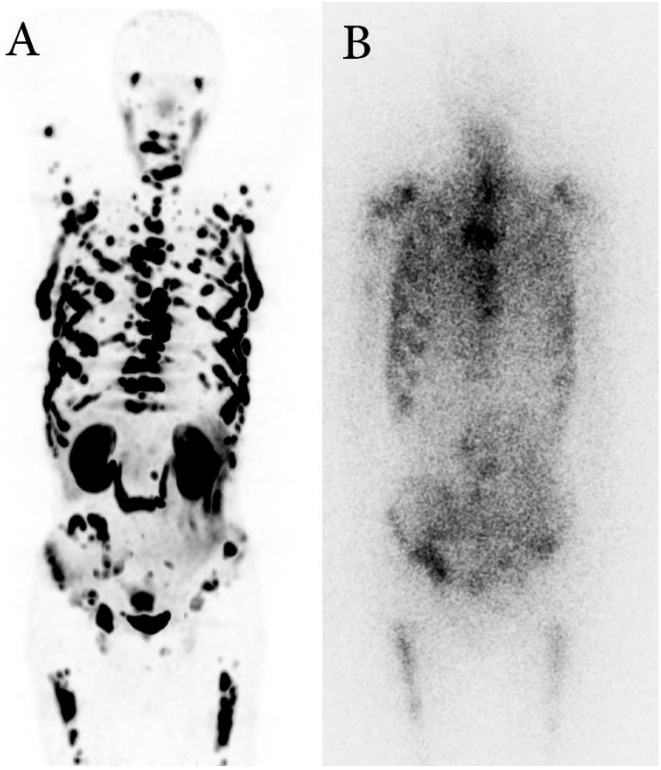

Fig 1. A 65-year-old man with a history of de novo metastatic prostate cancer (Gleason score = 9). He had refractory bone pain in the pelvic region. The [^{68}Ga]Ga-prostate-specific membrane antigen positron emission tomography ([^{68}Ga]Ga-PSMA PET) shows widespread bone metastases (A). Prostate-specific antigen level (PSA) was 14 ng/mL before [^{177}Lu]Lu-PSMA therapy, which declined to 3.65 ng/mL after the first cycle. Post-treatment [^{177}Lu]Lu-PSMA whole body scan reveals good targeting of the [^{177}Lu]Lu-PSMA in the metastatic lesions (B).

DISCUSSION

The management of mCRPC is still a challenge despite advances in the treatment of prostate cancer. [^{177}Lu]Lu-PSMA RLT has shown encouraging results. It increases OS in patients that have progressive disease receiving standard of care [7]. However, some patients do not respond to this therapy. Multiple factors have been evaluated to predict the ultimate outcome [8], among which any PSA response after the first cycle of the therapy has shown to be a robust predictor of OS [9]. In this study, we assessed the baseline pathological and paraclinical parameters to predict the PSA response after the first cycle of [^{177}Lu]Lu-PSMA RLT. We found that 81.4% and 44.2% of the patients had ≥ 10% PSA response and ≥ 50% PSA response, respectively, which is in line with the findings of other studies showing any response rate of approximately 60-80% [10, 11] and ≥ 50% response rate of approximately 30-50% [11-13].

We found that the patients with higher baseline PSA more frequently show ≥ 10% PSA response (p=0.004). Also, there was a relation between PSA decline and baseline PSA (p<0.001, r=0.842; PSA decline percentage: p=0.013, r=0.375). The results regarding the predictive value of the baseline PSA are contradictory in different studies. Although some authors have demonstrated that patients with higher OS have a lower baseline PSA 15-16, others have found no significant association between baseline PSA and survival parameters 17-20. We did not correlate the baseline PSA with OS. However, we found that higher baseline PSA is associated with ≥ 10% response after the first cycle. In a study on patients with a high disease burden, it has been shown that more than half of patients experience a significant decrease in PSA level following [^{177}Lu]Lu-PSMA RLT [14]. Higher PSA levels indicate a higher disease burden and worse outcome; however, considering our results, it can be postulated that patients with the higher baseline PSA may benefit more from [^{177}Lu]Lu-PSMA RLT. On the other hand, not all metastatic patients have increased PSA levels. There are cases with progressive or metastatic disease despite low or undetectable PSA levels [15]. Some of these patients may have atypical pathologic subtypes that may neither produce PSA nor express enough PSMA for effective RLT. Hence, it can be hypothesized that patients with low PSA but progressive mCRPC may respond less to [^{177}Lu]Lu-PSMA RLT. The value of [^{177}Lu]Lu-PSMA RLT in this setting warrants further investigations.

Table 4. The results regarding the relation between different factors and PSA response.

	%10 ≤ Response			%50 ≤ Response			Normalized PSA (PSA decline/baseline PSA)	
			P-value			P-value	P-value	Correlation (r)
Age (year)	Mean ± SD	Yes: 70.97±10.35 No: 64.50±8.35	0.108	Mean ± SD	Yes: 72.42±10.52 No: 67.67±9.72	0.132	0.373	0.139
Gleason score	Median	Yes: 8.0 No: 7.5	0.198	Median	Yes: 8.0 No: 7.5	0.543	0.611	0.080
PSA before RLT (ng/mL)	Median (IQR)	Yes: 101.0 (56.0-275.0) No: 23.0 (2.05-66.5)	0.004	Median (IQR)	Yes: 145.0 (42.0-400.0) No: 69.7 (27.3-186.7)	0.171	0.013	0.375
ALP (IU/L)	Median (IQR)	Yes: 295.0 (200.0-680.0) No: 228.0 (208.0-301.5)	0.236	Median (IQR)	Yes: 222.0 (194.0-432.0) No: 294.0 (211.2-663.5)	0.328	0.889	0.022
Hb (g/dL)	Mean ± SD	Yes: 12.04±1.59 No: 11.87±1.49	0.791	Mean ± SD	Yes:12.20±1.64 No: 11.85±1.50	0.483	0.898	0.020
Plt (×10^3/µL)	Mean ± SD	Yes: 236±73 No: 267±74	0.291	Mean ± SD	Yes: 246±68 No: 239±78	0.764	0.218	0.192
WBC (×10^3/µL)	Median (IQR)	Yes: 6000 (5300-6800) No: 5800 (4375-8825)	0.938	Median (IQR)	Yes: 6000 (5270-6600) No: 5985 (5100-8225)	0.845	0.405	0.130
De novo metastasis	Percent (number)	Yes: 43% (15/35) No: 50% (4/8)	0.507	Percent (number)	Yes: 63.2% (12/19) No: 50% (12/24)	0.388	0.885	0.023
Radiotherapy	Percent (number)	Yes: 54.3% (19/35) No: 62.5% (5/8)	0.671	Percent (number)	Yes: 47.4% (9/19) No: 62.5% (15/24)	0.321	0.310	0.158
Visceral metastasis	Percent (number)	Yes: 14.3 (5/35) No: 12.5% (1/8)	0.692	Percent (number)	Yes: 15.8% (3/19) No: 12.5% (3/24)	0.541	0.605	0.081
Bone Metastasis	Percent (number)	Yes: 82.9% (29/35) No: 75.0% (6/8)	0.467	Percent (number)	Yes: 78.9% (15/19) No: 83.3% (20/24)	0.507	0.854	0.029
Lymph node metastasis	Percent (number)	Yes: 28.6% (10/35) No: 37.5% (3/8)	0.620	Percent (number)	Yes: 26.3% (5/19) No: 33.3% (8/24)	0.619	0.466	0.114

Highlighting that the present study is the first reporting results of RLT in mCRPC patients from Tehran, the present study was hampered by several limitations. First, since this treatment is a novel option in our country, the sample size was small. In addition, it is reported that 20-50% of cases undergoing RLT may show delayed PSA responses (i.e. PSA response in the second or third cycles) [16, 17]. Therefore, providing data regarding further cycles could be helpful. However, to the best of our knowledge, no study has yet evaluated the usefulness of this so-called "delayed PSA responder" subgroup and compared its prognosis with stable or progressive PSA subgroups. We could not include the data of multiple treatment cycles since the number of patients received more than 3 cycles were still very limited. Moreover, we did not have the long-term outcome of patients to evaluate the survival parameters. Also, there might be a selection bias that is patients with end-stage and very poor outcomes were referred for this therapy.

However, in the setting of the primary disease, this relation loses its significance in patients with PSA > 100 ng/mL [18]. Also, it has been shown that the PSA reduction after treatment is a significant indicator of survival [19]. However, there are patients with radiologic evidence of distant metastasis and a lower level of increased PSA [20].

Limitations

There are limitations to our study. First, although we performed a two-center study, the number of patients is small. It is because this treatment was rather new in our country, and a few numbers of patients were referred for [^{177}Lu]Lu-PSMA RLT. Second, we only included the data of the first cycle. Again, since this treatment was new, only a few patients had undergone more than one cycle. Third, we did not have the data for pain scores and the clinical impact of this treatment. Forth, when we initiated this study, most of the patients had received only one cycle of therapy; therefore, the data about the outcome and survival parameters were not available.

CONCLUSION

In conclusion, [^{177}Lu]Lu-PSMA RLT reduces PSA in more than 80% of the patients after one cycle. The higher baseline PSA values are associated with better PSA response. The value of [^{177}Lu]Lu-PSMA RLT in patients with progressive disease and low PSA levels warrants further investigations. No other pre-therapeutic parameter was found to be associated with better PSA response.

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