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Original investigation

Lu-177 PSMA I&T Therapy for Prostate Cancer; Treatment Response, Treatment Toxicity, and Survival Results

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ABSTRACT

Purpose: This study aims to evaluate the serum PSA response, Ga-68 PSMA PET/CT response, hematological/nephrological toxicity and survival results of patients with castration-resistant metastatic prostate cancer who are receiving Lu-177 PSMA therapy.

Methods: The data of 57 patients with a mean age of 68 years who were treated with Lu-177 PSMA I&T were retrospectively reviewed. Secondary toxicity to treatment was determined using the criteria of the Common Toxicity Criteria for Adverse Events v5.0. The Kaplan Meier method was used for survival and progression-free survival analysis.

Results: Forty percent of patients' serum PSA values' showed >25% regression after the first cycle of treatment. Serum PSA values were stable/regressed in 75% of the patients. While 2/57 patients showed grade 3 anemia, none showed grade 3 leukopenia or thrombocytopenia. One of 57 patient showed transient nephrotoxicity. Hematological and nephrological toxicity were not observed after treatment of eight cycles, and the serum PSA values of the patients were decreased by 97%. The mean survival time was 11.6 months in all patients, and 17.2 months in patients with serum PSA response. Progression-free survival was an average of 9.9 months.

Conclusion: Providing a stable or regressed disease via single cycle treatment in 75% of patients with progression despite the treatments improving survival is an indicator of the success of the therapy. The low rate of hematological and nephrological toxicity in patients (none of the patients that received eight cycles) suggests that the treatment is reliable. Survival was longer in patients with serum PSA response after treatment.

Keywords: PSMA, prostate cancer, radioligand therapy, mCRPC, theranostic, precision medicine

INTRODUCTION

Prostate cancer is the second most common type of cancer in males and it accounts for approximately 15% of all cancers worldwide (1). While the 5-year survival rate on localized prostate cancer is 100%, this rate decreases to 31% in the metastatic disease (2).

Prostate specific membrane antigen (PSMA) is a glutamate carboxypeptidase II enzyme which is glycoprotein structured and zinc-dependent. There are three parts of this glycoprotein; the intracellular part (19 amino acids), transmembrane part (24 amino acids), and extracellular part (707 amino acids). The enzyme is responsible for folate uptake, cell migration, proliferation, and survival (3). The detection of intensive PSMA expression in prostate cancer has made PSMA a therapeutic target in the treatment of prostate cancer.

Prostate cancer cells are sensitive to radiation. Radio-sensitivity is related to high metabolic rate, good nutrient intake, rate of cleavage, and rate of proliferation (4). PSMA expression in prostate cancer is positively associated with tumor stage and early recurrence. In radioligand treatment with Lu-177 PSMA I&T, the radioligand bonds to PSMA from the external side and internalizes into the cell by clathrin-mediated endocytosis (5).

This study aims to evaluate the serum PSA response, Ga-68 PSMA PET/CT response, hematological/nephrological toxicity and survival results of patients with castration-resistant metastatic prostate cancer who are receiving Lu-177 PSMA therapy.

MATERIALS and METHODS

Patient selection

This treatment was applied to patients with the diagnosis of prostate cancer and remain progression despite previously receiving at least one other survival-enhancing treatment (docetaxel, cabazitaxel, abiraterone, or enzalutamide). The consensus is built up with urologists and oncologists during the decision process of Lu-177 PSMA I&T treatment.

Patient characteristics

The data of 57 patients with a mean age of 68±8.5 (50–88) years who were treated with Lu-177 PSMA I&T were retrospectively reviewed (Table 1). Twelve patients had a prostatectomy, and ten patients had orchiectomy history. Eight patients received radiotherapy in the primary tumor area before the treatment. Twenty-eight patients received docetaxel treatment while 17 patients received both docetaxel and cabazitaxel treatment. Primary tumor in 46% of patients, bone metastasis in 88%, lymph node metastasis in 79%, lung metastasis in 16%, liver metastasis in 7%, adrenal gland metastasis in 7%, penile metastasis in 2% and peritoneal carcinomatosis in 2% was observed via Ga-68 PSMA PET/CT before treatment.

The treatment process was explained to all patients prior to the treatment by the Nuclear Medicine specialist, and the informed consent forms were obtained. The study was approved by the institutional ethics committee.

Patient preparation before treatment

All patients were evaluated with Ga-68 PSMA PET/CT before treatment. Hemogram, kidney function test, liver function test, electrolyte, LDH, ALP, and serum PSA values were analyzed. The renal function of all patients was evaluated by Tc-99 m MAG3 scintigraphy. Treatment was given to patients who showed PSMA expression in the Ga-68 PSMA PET/CT, no liver failure, no ureter obstruction, and no bone marrow depression.

Preparation and implementation of Lu-177 PSMA I&T

Lu-177 PSMA synthesis was performed in the synthesis unit. IV ondansetron was administered to patients to prevent nausea and vomiting at least 30 min before the treatment, and IV hydration was initiated. Lu-177 PSMA I&T was prepared within 100 cc of SF and given to patients by IV infusion over a period of 10–30 min. Following radioligand treatment, IV hydration was maintained for at least 2 h. Patients were warned to drink plenty of water and to empty their bladders. The patients were hospitalized overnight, and at the 24th h whole body planar images were taken. The patients were then discharged.

Follow-up after treatment

Biochemical and hemogram controls were performed at 15 day intervals after the treatment. The serum PSA value was examined approximately 8 weeks after each treatment. The treatment was repeated every 8–10 weeks.

PSA response to treatment was compared with baseline after each cycle and with serum PSA values after the previous treatment. Also, serum PSA levels and basal serum PSA levels at the end of treatment were compared in those patients who were receiving treatments of the same cycle number. A >25% reduction of PSA value was accepted as treatment response, >25% increase was considered progression and a change within ±25% was considered stable PSA.

Secondary toxicity to treatment was determined using the criteria of the Common Toxicity Criteria for Adverse Events (CTCAE) version 5.0. Patients were followed for 1–24 months after treatment.

Patients who received three or four treatments were evaluated by Ga-68 PSMA PET/CT after 12 weeks of treatment. A 30% reduction in the SUVmax value in Ga-68 PSMA PET/CT was defined as regression. None of these lesions were decreased in SUVmax value, even though an increase of 30% SUVmax value and observation of a new lesion is accepted as progression. A ±30% change in SUVmax value was accepted as stable disease. Due to the comparison of each lesion individually before and after the treatment; such cases with regression in some lesions while other some expressed progression or cases with new lesions which did not exist in previous imaging despite in the of regression his/her all other lesions were accepted as a mixed response.

Statistics

Data were evaluated using the IBM SPSS 22 (Armonk, NY) program. Mean, median and range were calculated for the various variables. The Kaplan Meier method was used for survival and progression-free survival analysis. Non-parametric test methods were used for survival analysis. A p-value of less than 0.05 was considered significant.

RESULTS

Characteristics of the patients are presented in Table 1. One-hundred-fifty-six cycles (1–8 cycles) of Lu-177 PSMA I&T treatment were applied to 57 prostate cancer patients who have an average Gleason score of 8 (range 6–10) (55 adenocarcinomas, one neuroendocrine differentiation prostate adenocarcinoma, and one large cell neuroendocrine prostate cancer with focal adenocarcinoma focus). The patients had an average age of 68 years. There were 63–70 days between treatments. The median PSA value was calculated as 77ng/mg before treatment, and the median PSA doubling time was 44 days. Eleven patients received one cycle of treatment. Any acute side effects, blood pressure changes, or fever were not observed during the treatment. The most common side effect during treatment was nausea.

One patient received five cycles of Lu-177 DOTATATE because of large cell neuroendocrine prostate cancer. Regression was observed after Lu-177 DOTATATE therapy. Lu-177 PSMA therapy

Table 1. Patient properties

Parameter	Value
Number of Patients	57
Age, median	68 (50–88) years
Gleason, median	8 (6–10)
PSA, median	77 (1.2–2710) ng/ml
PSA doubling time, median	44 (6–404) days
PSA progression, median	121 (16–351) days
Number of cycles	
1	11 patients (3.7–7.4 GBq)
2	14 patients (3.7–7.4 GBq)
3	20 patients (7.4 GBq)
4	6 patients (7.4 GBq)
5	6 patients (7.4 GBq)
Prostatectomy	12 patients (21%)
Orchiectomy	10 patients (18%)
Chemotherapy	
Docetaxel	28 patients (49%)
Docetaxel+Cabazitaxel	17 patients (30%)
Abiraterone	10 patients (18%)
Enzalutamide	3 patients (5%)
Local radiotherapy	8 (14%)
Primary tumor	26 (46%)
Bone metastasis	50 (88%)
Lymph node metastasis	45 (79%)
Lung metastasis	9 (16%)
Liver metastasis	4 (7%)
Adrenal metastasis	4 (7%)
Penile metastasis	1 (2%)
Peritoneal carcinomatosis	1 (2%)

was given after 11 months of treatment due to progression and PSA elevation. However, treatment was discontinued due to low PSMA uptake of the patient's lesions. Treatment could not be sustained because of 5 mortality occurred 76 (40–105) days later than the first treatment. Moreover, one patient withdrew from treatment after the initial treatment.

PSA Response to Treatment

The serum PSA responses, according to basal PSA value after each cycle, are given in Table 2. Serum PSA levels after treatment were missing in a few patients (Table 2). A >25% PSA decrease compared to baseline was observed in 20 of 50 (40%) patients after 8 weeks of one cycle of treatment, 22 of 39 (56%) patients after two cycles of treatment, 16 of 28 (57%) patients after three cycles of treatment, seven of ten (% 70) patients after four cycles of treatment, and two of three (67%) patients after five cycles treatment.

The PSA value after each cycle was compared to the PSA value after the previous cycle (Table 3); a >25% PSA decrease was observed in 40% of the patients after the first treatment, 2nd cycle after treatment in 49% of patients compared to the 1st cycle, 3rd cycle after treatment in 29% of patients compared to 2nd cycle, 4th cycle after treatment in 20% of patients compared to the 3rd cycle, after the 5th cycle, 67% of the patients compared to the 4th cycle.

A >25% decrease in PSA compared to baseline was observed in 20% of patients after one cycle of treatment, 38% after two cycles, 40% after three cycles, 50% after four cycles, and 50% after five cycles.

Only one patient received eight cycles of treatment. The pre-treatment serum PSA value of the patient was 1490 ng/ml, and this value decreased to 40 ng/ml after the eighth treatment.

PSA progression was observed in 33 (58%) patients (median 4 months) after the last treatment.

Table 2. Posttreatment serum PSA value compared to pretreatment

Cycle	Number of patients without PSA value after treatment (missing)	PSA decrease			Stabile PSA	PSA increase
		≥25%	≥50%	≥75%	±25%	≥25%
1	7	20 (40%)	12 (25%)	9 (18%)	18 (35%)	12 (25%)
2	7	22 (56%)	21 (54%)	14 (36%)	5 (13%)	12 (31%)
3	4	16 (57%)	11 (41%)	8 (30%)	4 (14%)	8 (29%)
4	2	7 (70%)	7 (70%)	6 (60%)	0 (0%)	3 (30%)
5	3	1 (50%)	1 (50%)	1 (50%)	0 (0%)	1 (50%)
8		1 (100%)	1 (100%)	1 (100%)	0 (0%)	0 (0%)

Table 3. Serum PSA response after each cycle compared to the previous cycle

Cycle	Number of patients without PSA value after treatment	PSA decrease			Stabile PSA	PSA increase
		≥25%	≥50%	≥75%	±25%	≥25%
1	6	20 (40%)	12 (24%)	9 (18%)	18 (36%)	12 (24%)
2	7	19 (49%)	12 (31%)	5 (13%)	8 (20%)	12 (31%)
3	5	8 (29%)	6 (21%)	0 (0%)	7 (25%)	13 (46%)
4	2	2 (20%)	1 (10%)	0 (0%)	1 (10%)	7 (70%)
5	3	2 (67%)	2 (67%)	0 (0%)	1 (33%)	0 (0%)

Table 4. PSA and PET/CT response to treatment of 9 patients who underwent Ga-68 PSMA PET/CT after 3 cycles of treatment

	Regression	Stabile disease	Progression	Mixed response
PSA decrease	3	0	0	2
Stabile PSA	0	0	0	1
PSA increase	0	0	3	0
Total	3 (33.3%)	0	3 (33.3%)	3 (33.3%)

Table 5. PSA and PET/CT response to treatment of 6 patients who underwent Ga-68 PSMA PET/CT after 4 cycles of treatment

	Regression	Stabile disease	Progression	Mixed response
PSA decrease	2	0	0	2
Stabile PSA	0	0	0	0
PSA increase	0	0	0	2
Total	2 (33%)	0	0	4 (67%)

PET/CT response to treatment

In 15 patients, Ga-68 PSMA PET/CT was performed after three or four cycles. Nine of these patients had three cycles (Table 4), and six of them had four cycles (Table 5). Both PET/CT regression and PSA decrease were observed in five (33%) patients. PET/CT and PSA progression were observed in three (20%) patients. Seven (47%) patients were evaluated as a mixed response on Ga-68 PSMA PET/CT. PSA was stable in one (14%) patients and observed as progressed in two (29%) patients. PSA regression was observed in four (27%) patients who had a mixed response.

Hematological toxicity

Hematological toxicity data can be seen in Table 6. Grade 3 anemia was observed in one of 50 patients after the first cycle; this was thought to be depending on disease progression because of the patient's PSA progression. Grade 3 anemia was observed after the second cycle of treatment in three of 39 patients. While two of these were related to disease progression, and one (3%) occurred secondary to Lu-177 PSMA therapy. Grade 3 anemia was observed in one of 28 patients after the third cycle and one of 10 patient after four cycles (because of the disease progression). Grade 3 anemia was not observed in any patient who received five cycles of treatment.

Grade 3 leukopenia and thrombocytopenia were not observed in any treated patient, and no hematological toxicity was observed in a patient who received eight cycles of 7.4 GBq of Lu-177 PSMA I&T.

Nephrological toxicity

Nephrological toxicity values can be seen in Table 6. The patient with chronic renal failure progressed to transient acute renal failure after the second cycle of Lu-177 PSMA I&T. Grade 3 creatinine elevation and low GFR were observed in this patient. The patient's treatment was not continued, but creatinine and GFR values improved during follow-up tests.

Two patients with grade 2 pre-treatment GFR value to determined secondary to treatment as Grade 3 after three cycles of treatment. One of these patients had a creatinine value of grade 2, while the other's was within the normal range.

There was no nephrological toxicity in any patient who received eight cycles of 7.4 GBq of Lu-177 PSMA I&T treatment.

Table 6. Hematological and nephrological toxicity on Lu-177 PSMA I&T treatment

Parameter	CTCAE Grade 1	CTCAE Grade 2	CTCAE Grade 3
Anemia			
Pre-treatment	25 (44%)	11 (19%)	2 (4%)
1. Cycle	26 (51%)	9 (18%)	1 (2%)
2. Cycle	17 (41%)	9 (21%)	3 (7%)
3. Cycle	5 (19%)	7 (27%)	1 (4%)
4. Cycle	1 (10%)	1 (10%)	1 (10%)
5. Cycle	1 (33%)	0 (0%)	0 (0%)
WBC			
Pre-treatment	4 (7%)	0 (0%)	0 (0%)
1. Cycle	3 (6%)	2 (4%)	0 (0%)
2. Cycle	2 (5%)	1 (2%)	0 (0%)
3. Cycle	0 (0%)	0 (0%)	0 (0%)
4. Cycle	0 (0%)	1 (10%)	0 (0%)
5. Cycle	1 (33%)	0 (0%)	0 (0%)
PLT			
Pre-treatment	7 (12%)	1 (2%)	0 (0%)
1. Cycle	6 (12%)	2 (4%)	0 (0%)
2. Cycle	1 (3%)	1 (3%)	0 (0%)
3. Cycle	4 (15%)	0 (%)	0 (0%)
4. Cycle	0 (0%)	0 (0%)	0 (0%)
5. Cycle	0 (0%)	0 (0%)	0 (0%)
Kreatinin			
Pre-treatment	4 (7%)	0 (0%)	0 (0%)
1. Cycle	2 (4%)	1 (2%)	0 (0%)
2. Cycle	2 (5%)	0 (0%)	1 (2%)
3. Cycle	1 (4%)	1 (4%)	0 (0%)
4. Cycle	0 (0%)	0 (0%)	0 (0%)
5. Cycle	0 (0%)	0 (0%)	0 (0%)
GFR			
Pre-treatment	18 (31%)	10 (18%)	0 (0%)
1. Cycle	17 (33%)	6 (12%)	0 (0%)
2. Cycle	12 (29%)	4 (9%)	1 (2%)
3. Cycle	9 (36%)	0 (0%)	2 (8%)
4. Cycle	2 (20%)	0 (0%)	0 (0%)
5. Cycle	0 (0%)	0 (0%)	0 (0%)

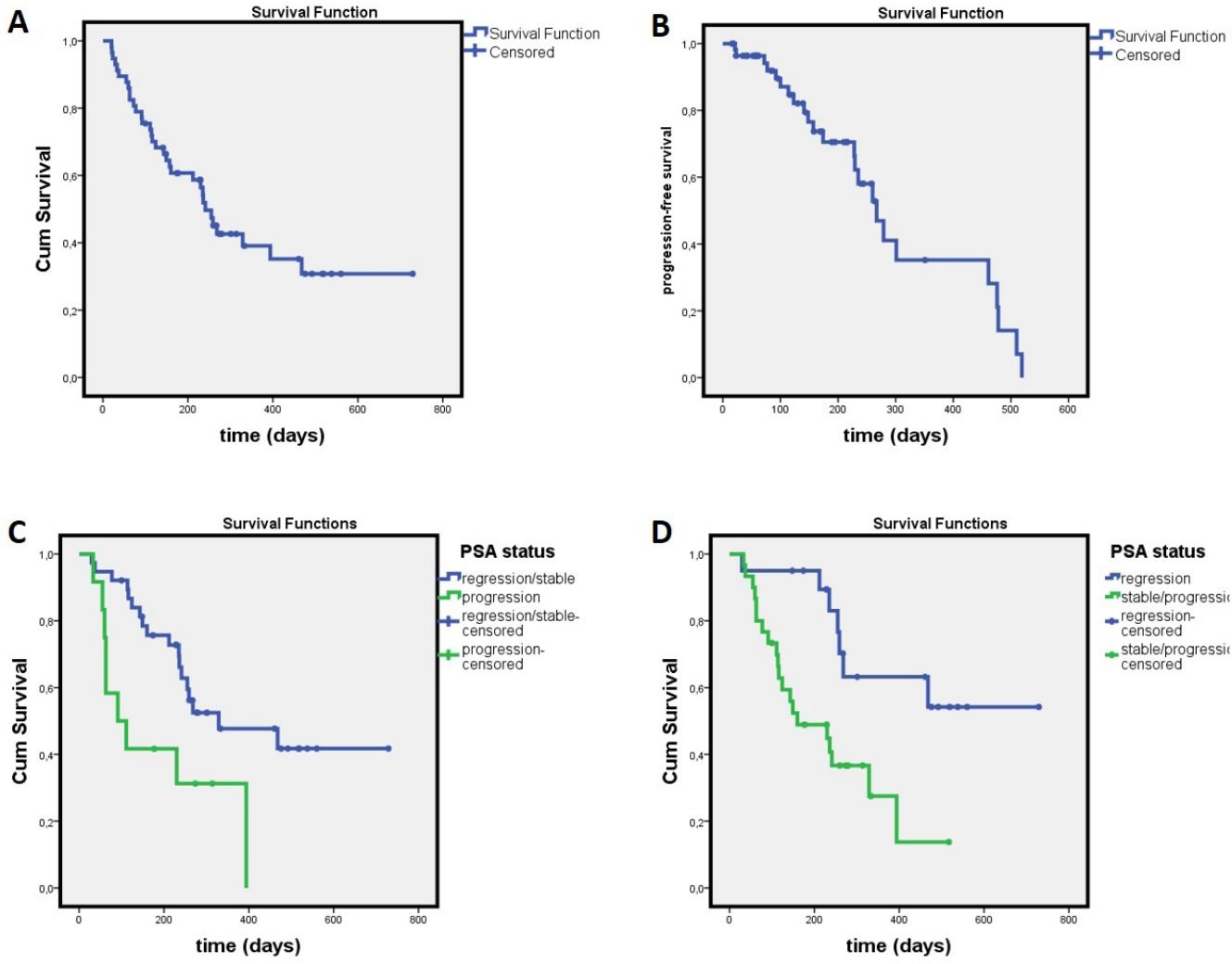

Figure 1. Survival tables after PSMA I&T treatment. Overall survival **(A)**, progression-free survival **(B)**, Kaplan Meier table which compares the stable/regressed and progressed PSA values after first treatment **(C)**, p=0.005. Kaplan Meier table which compares the stable/regressed and progressed PSA values after first treatment **(D)**, p=0.004.

Survival

The overall survival graphic can be seen in Figure 1. Thirty-three of 57 patients (58%) who were followed up for an average of 6.3 (1–24) months died after a median of 7.5 months from the first treatment. The mean survival was period after the Lu-177 PSMA I&T treatment was 11.6 months (median, 8 months). The mean progression-free survival was 9.9 months, (median, 8.9 months).

While the mean survival was 14.3 months (median, 11 months) in patients with stable/regressed serum PSA values after the first treatment, the mean survival of the patients with a progressed level of serum PSA was 6.2 months (median, 3 months) (p=0.005). The mean survival time was 17.2 months (median could not be calculated) in patients who have regressed serum PSA value, the mean of survival was 7.7 months (median, 5.3 months) in patients who have a stable/regressed serum PSA value (p=0.004).

DISCUSSION

None of the patients in this study received mitoxantrone treatment. Considering the treatments known to increase survival in prostate cancer, docetaxel provides a 3-month survival advantage compared to mitoxantrone. While the median survival on cabazitaxel was 15.1 months, this value is 12.7 months for mitoxantrone. The median survival with abiraterone was 15.8 months and was 11.2 months for the placebo. Enzalutamide provides a 4.8-month survival benefit. Ra-223 metastatic bone treatment provided a survival period of 14.9 months, while survival in the placebo group was 11.3 months. Sipuleucel T provides a 4.1-month survival benefit (6). In the treatment of metastatic prostate cancer, all of the above-cited drugs prolong survival by 3–4 months.

Radioligand treatments targeting PSMA in the treatment of castration-resistant metastatic prostate cancer have been used frequently in recent years, and the treatment success rate is

relatively high (7–9). The publications with Lu-177 are mostly based on Lu-177 PSMA-617. Therefore, there are relatively fewer data available for Lu-177 PSMA I&T. In this study, despite the previous treatment methods offered to patients with prostate cancer, regression was detected in 40% of patients (>25% increase in serum PSA) after first cycle of treatment. The serum PSA values were stable/regressed in 75% of the patients. A greater proportion of serum PSA values regressed as treatment number increased. When serum PSA values were compared to the previous cycle; the most significant decline was observed in the first two cycles. Decrease of the value of serum PSA ratio is determined in subsequent cycles.

When the treatment was evaluated with Ga-68 PSMA PET/CT, regression was observed in 33% of patients. Although the mixed response term is used in this study on Ga-68 PSMA PET/CT evaluation, even though it particularly didn't utilize in F-18 FDG PET/CT evaluation. According to our own experience; new lesions are observed during the treatment because of the short doubling time of the disease while regression of existed lesions during the treatment (showing Lu-177 PSMA I&T uptake) was observed on some patients. Although this situation is thought to be a progressive nature, there is actually a treatment response in patients with Lu-177 PSMA I&T uptake. Even, different types of response to PSA were observed in these patients. In this study, serum PSA response was observed in 57% of patients considered as a mixed response. If the only response to treatment with serum PSA was evaluated, it could be concluded that the disease was regressed in these patients.

While two of 57 patients showed grade 3 anemia depending on Lu-177 PSMA therapy, none of them showed grade 3 leukopenia or thrombocytopenia.

While one 57 patient showed transient nephrotoxicity, one of them showed grade 2 creatinine and grade 3 GFR nephrotoxicity, and one of them showed grade 3 GFR decrease without increase of creatinine.

To our knowledge, no other study has reported eight cycles of Lu-177 PSMA I&T treatment. In this study, hematological and nephrological toxicity were not observed after treatment of eight cycles, and the serum PSA value of patient was decreased by 97%.

In this study; the mean of survival was 11.6 months after treatment, and the mean survival time was 17.2 months in patients with a serum PSA response. Progression-free survival was an average of 9.9 months.

In the study of Baum et al. (10), stable/regressed serum PSA values were observed in approximately 87% of patients who received one to five cycles of Lu-177 PSMA I & T treatment. In our study, this rate was slightly lower as well as close to ours. This condition is thought to be secondary to the presence of widespread metastatic disease. In the literature, after one cycle Lu-177 PSMA 617 treatment, a PSA response of >25% was observed in 50–71% of patients (2, 11–15).

In the study of Baum et al. (10) performed by Lu-177 PSMA I&T, there was no hematological and nephrological toxicity observed in any patient. In the studies performed with Lu-177 PSMA-617 and I&T, 0–19% grade 3 anemia, 0–3% leukopenia, and 0–3% thrombocytopenia were observed (2, 10, 12–16). In our study, grade 3 anemia was observed in 4% of patients, and grade 3 leukopenia and thrombocytopenia were not observed. These results are consistent with the literature. In the literature, it is noteworthy that in the evaluation of hematological toxicity, the rates of toxicity were reported to be higher in the studies that did not include the comparison of hemogram data with disease progression (16).

There was no reported grade 3 nephrotoxicity on many studies conducted with Lu-177 PSMA I&T and 617 treatment, transient nephrotoxicity in one patient and additionally improvement of GFR values from two to three before and after the treatment was observed in two patients (2, 10, 12, 13, 15–17).

The mean survival after Lu-177 PSMA 617 treatment was 8.6 months in the study of Ahmadzadehfar et al. (18), 16 months in the study of Yadav et al. (15), 4.6 months in the study of Brauer et al. (16), and 4.2 months in the study of Rahbar et al. (19). The mean survival period varies considerably in the literature, and the data in our study is similar to other reports. Survival of patients with serum PSA response to first treatment was significantly better rather than those without sufficient PSA response, both in our study and the literature (16, 18).

Our progression-free survival data are similar to those reported by Kulkarni et al. (20), and Yadav et al. (15) (10.7 and 12 months, respectively).

CONCLUSION

Providing a stable or regressed disease via single cycle treatment in 75% of patients with progression despite the treatments improving survival is an indicator of the success of the therapy. The low rate of hematological and nephrological toxicity in patients (none of patients that received eight cycles) suggests that the treatment is reliable. Furthermore, the presence of a patient population with new lesion occurrence as well as serum PSA regression, we are of the opinion that evaluation to treatment response with Ga-68 PSMA PET/CT is essential. It was observed that survival was longer in patients with serum PSA response after treatment.

Ethics Committee Approval: İzmir Katip Çelebi University, Non-Interventional Clinical Studies Institutionel Review Board, 2019/198

Informed Consent: Our study is a retrospective study. However, informed consent was obtained from the patients during the treatment process.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - EA; Design - EA; Supervision - EA; Fundings - EA, BS; Materials - EA, BS, ED, RB, ÖÖ, GCK; Data Collection and/or Processing - EA, BS, ED, RB, ÖÖ, GCK; Analysis and/or Interpretation - EA; Literature Search - EA; Writing Manuscript - EA; Critical Review - EA, BS, ED, RB, ÖÖ, GCK

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