Predictors of Response to Radioligand Therapy of Metastatic Castrate-Resistant Prostate Cancer with ^{177}Lu-PSMA-617

Justin Ferdinandus[1], Elisabeth Eppard[1], Florian C. Gaertner[1], Stefan Kürpig[1], Rolf Fimmers[2], Anna Yordanova[1], Stefan Hauser[3], Georg Feldmann[4], Markus Essler[1], and Hojjat Ahmadzadehfar[1]

[1]Department of Nuclear Medicine, University Hospital Bonn, Bonn, Germany; [2]Institute for Medical Biometry, Informatics and Epidemiology, University of Bonn, Bonn, Germany; [3]Department of Urology, University Hospital Bonn, Bonn, Germany; and [4]Department of Internal Medicine, MED III, University Hospital Bonn, Bonn, Germany

Radioligand therapy (RLT) with ^{177}Lu-PSMA-617 (PSMA is prostate-specific membrane antigen) is a novel targeted therapy for metastatic prostate cancer. In this study, we evaluated the effect of different pretherapeutic parameters on the therapeutic response measured by prostate-specific antigen (PSA) 2 mo after RLT. **Methods:** RLT was performed in 40 hormone-refractory patients with distant metastases and progressive disease (mean age, 71.4 y). ^{68}Ga-PSMA-11 PET/CT was performed in all patients 1–2 wk before RLT. All patients were treated with a mean of 6 GBq. The SUV$_{max}$ of tumor lesions was determined using region-of-interest analysis. Complete blood counts, renal and liver function assessments, previous therapies, pain medication, and SUVs were included in the analysis. PSA was assessed 2 mo after RLT. **Results:** In the univariate analysis, younger age, higher levels of γ-glutamyl transferase, lower pretherapeutic hemoglobin, a higher Gleason score, a higher number of platelets, higher C-reactive protein, regular need for pain medication, and higher lactate dehydrogenase had a negative impact on the therapeutic response; however, the multivariate analysis revealed that the most significant independent factors were the number of platelets and regular need for pain medication. The response was independent of the amount of PSMA uptake as well as previous therapies and other measured factors. **Conclusion:** A PSA decline of more than 50% was observed significantly more in patients without a regular need for analgesics.

Key Words: PSMA; ^{177}Lu; prostate cancer; radioligand therapy; PSA; treatment response

Prostate-specific membrane antigen (PSMA) is an attractive target for the diagnosis and therapy of metastasized prostate cancer (PC) (1,2). All of the recently published papers about radioligand therapy (RLT) with ^{177}Lu-PSMA-617 have indicated that this therapy is safe and has a low toxicity profile (3–8). The first results showed a positive effect on the prolongation of overall survival as well (6). Although, at the moment, RLT is performed for hormone-refractory patients in an advanced stage of disease with continuously increasing prostate-specific antigen (PSA), a decline in

PSA has been detected in about 60%–70% of patients (3–8). However, it is still unclear as to whether any of the pretherapeutic parameters, such as the level of PSMA expression in ^{68}Ga-PSMA-11 PET or prior therapies, may affect the treatment response according to PSA changes. In the current study, we retrospectively evaluated the effect of different pretherapeutic parameters and prior therapies on the therapeutic response measured by PSA 2 mo after the first cycle of RLT.

MATERIALS AND METHODS

Patients

Forty consecutive hormone-refractory PC patients with distant metastases and progressive disease according to the PSA level were treated with ^{177}Lu-PSMA-617. The data regarding the treatment response and toxicity as well as treatment tolerability of the included patients in this study have been published together with the data from 3 other centers as a multicenter study (7). The prior therapies are listed in Table 1. All patients had an extensive metastatic disease, which is demonstrated in Table 1. PSMA PET was performed for all patients 1–2 wk before therapy to evaluate the PSMA expression status of the metastases. The local ethics committee approved this retrospective study, and all subjects signed a written informed consent form.

Treatment Planning

^{68}Ga-PSMA-11 PET/CT. ^{68}Ga-PSMA-11 was applied via slow intravenous injection (30–60 s) using a weight-adapted dose of 2 MBq/kg of body weight in a total volume of 5–10 mL (diluted with 0.9% sterile sodium chloride solution), followed by 20 mL of sterile 0.9% sodium chloride. The average injected dose was 140 MBq. PET/CT was performed on a Biograph 2 PET/CT scanner (Siemens Medical Solutions). PET emission data were acquired from the pelvis to the head using 6–8 bed positions (3-dimensional mode); the emission time was 4 min per bed position. PET images were reconstructed iteratively. After reconstruction, images were smoothed by a 5-mm gaussian filter. Attenuation correction was performed using CT data. The SUV$_{max}$ was determined by a region of interest applied in the transaxial attenuation-corrected PET slice with the highest PSMA uptake. The SUV$_{max}$ was recorded for up to 5 bone and lymph node metastases as well as for liver and spleen for the calculation of target/nontarget. Thus, the following parameters were calculated: mean SUV$_{max}$ of the bone lesions (SUV$_{max}$Bn = SUV$_{max}$Bn$_1$ + …..SUV$_{max}$Bn$_x$/x), mean SUV$_{max}$ of the lymph node metastases (SUV$_{max}$Ln = SUV$_{max}$Ln$_1$ + …..SUV$_{max}$Ln$_x$/x), SUV$_{max}$Bn/SUV$_{max}$Liver, SUV$_{max}$Bn/SUV$_{max}$spleen, SUV$_{max}$Ln/SUV$_{max}$liver, SUV$_{max}$Ln/SUV$_{max}$spleen.

Laboratory Tests

One day before therapy, the hematologic and renal status, liver function tests, tumor marker PSA, alkaline phosphatase, and blood biochemistry were evaluated in all patients (Tables 2 and 3).

TABLE 1
Patient Characteristics

Characteristic	No. of patients	History (*n*)	Ongoing (*n*)	No history (*n*)	Extent
Gleason score					
6	4 (10)				
7	3 (7.5)				
8	11 (27.5)				
9	14 (35)				
10	5 (12.5)				
Unknown	3 (7.5)				
Prior and ongoing therapies					
Prostatectomy		21 (52.5)		19 (47.5)	
Abiraterone*†		18 (45)	9 (22.5)	13 (32.5)	
Enzalutamide*†		10 (25)	15 (37.5)	15 (37.5)	
Chemotherapy		21 (52.5)		19 (47.5)	
Bisphosphonate or RANKL inhibitor		3 (7.5)	29 (72.5)	8 (20)	
^{223}Ra		14 (35)		26 (65)	
Regular need for analgesics			15 (37.5)		
Extent of disease in 40 patients, detected by ^{68}Ga-PSMA PET/CT					
Local recurrence	17 (42.5)				
Bone met	40 (100)				<6 met in 3 pts (7.5)
					6–20 met in 2 pts (5)
					>20 met in 29 pts (72.5)
					Diffuse met in 6 pts (15)
Lymph node met	33 (82.5)				Ileal and abd in 14 pts (45.5)
					Thor in 2 pts (6)
					Ileal to thor in 16 pts (48.5)
Liver met	8 (20)				Singular met in 2 pts
					Multiple met in 6 pts
Lung met	3 (7.5)				Singular met in 2 pts
					Multiple met in 1 pt

*Five patients took neither abiretarone nor enzalutamide, and 3 patients took bicalutamide.

†All patients who were taking enzalutamide or abiraterone had increasing PSA under these medications.

RANKL = receptor activator of nuclear factor κ-B ligand; met = metastases; pts = patients; abd = abdominal; thor = thoracic.

Data in parentheses are percentages.

RLT

PSMA ligand (PSMA-617) was obtained from ABX GmbH. The preparation of ^{177}Lu-PSMA-617 was explained in detail in a previous publication (*3*).

The treatment solution was administered by slow intravenous injection over 1 min followed by 1,000 mL of NaCl or Ringer's. All patients were discharged 48 h after therapy according to the rules of the Federal Office for Radiation Protection in Germany (BfS).

Tumor Response Evaluation

The tumor marker PSA was used as the main marker for the response evaluation. We classified the changes in PSA level as a decrease of more than 50% and any decline. Any increase in PSA was considered as disease progression.

Evaluated Parameters for Evaluation of Predictive Factors of Response

All of the patients' parameters and laboratory tests are shown in Tables 1–4, including the extent of bone and lymph node metastases, the existence of liver metastases, age, the need for pain medication, the Eastern Cooperative Oncology Group (ECOG) score, SUV, $SUV_{max}Bn$, $SUV_{max}Ln$, $SUV_{max}BN/liver$, $SUV_{max}BN/spleen$, $SUV_{max}Ln/liver$; $SUV_{max}Ln/spleen$, injected dose of ^{177}Lu-PSMA-617, and injected dose/kg of body weight.

Statistical Analysis

The baseline characteristics of the study were analyzed with regard to their correlation to quantitative PSA changes. For this, a linear regression was used. Two qualitative assessments of PSA decline (any PSA decline and PSA decline > 50%) were analyzed with uni- and

TABLE 2
Blood, Renal, and Hepatic Parameters Before First Cycle

Parameter	Minimum	Maximum	Mean	Median
Blood parameters				
WBCs (G/L) (norm, 3.6–10.5)	2.7	12.2	6.4	6.3
Hb (g/dL) (norm, 12.5–17.2)	6.0*	14.5	10.9	11.0
Plt (G/L) (norm, 160–370)	62	557	278.9	262.5
Renal parameters				
Creatinine (mg/dL) (norm, 0.6–1.3)	0.53	2.54	0.95	0.9
GFR (mL/min) (norm, > 70)	50	>70†		
Liver function tests				
Bilirubin total (mg/dL) (norm, 0.2–1.0)	0.21	1.20	0.41	0.40
ALT (U/L) (norm, <50)	8	67	18.9	16.5
AST(U/L) (norm, <50)	10	302	37.5	24
GGT (U/L) (norm, <55)	17	425	67.6	40
Albumin (g/L) (norm, 35–52)	25.8	46.9	37.6	37.6

*Seven patients had received blood transfusion before therapy because of grade 3 tumor anemia 10–180 d before ^{177}Lu-PSMA therapy (median, 21 d); 1 of the patients had another blood transfusion 1 d before therapy because of an Hb of 6 g/dL.

†Thirty-two patients (80%) had a GFR greater than 70 mL/min.

WBCs = white blood cells; Hb = hemoglobin; Plt = platelets; GFR = glomerular fraction rate; ALT = alanine transaminase; AST = aspartate transaminase; GGT = γ-glutamyl transferase.

multivariate logistic regression. Multivariate models were derived by stepwise regression analysis primarily including parameters selected depending on the results of the unifactoral logistic regression.

RESULTS

Forty cycles of ^{177}Lu-PSMA-617 were performed in 40 consecutive hormone-refractory patients with a mean age of 71.4 y (age range, 43–87 y). Each patient received a mean of 6.0 GBq (range, 4.1–7.1 GBq; median, 6.1 GBq) of ^{177}Lu-PSMA-617. According to the patient's weight, each patient received a mean activity of 78.5 MBq/kg of body weight. The mean and median time between diagnosis of PC and RLT was 6.9 and 5.5 y (range, 0.8–20 y), respectively. The median Gleason score was 9 (range, 6–10). The extent of disease in these patients and their prior and ongoing therapies are shown in Table 1. The mean and median PSA levels before therapy were 495.1 and 325.5 ng/mL (range, 4.73–2,360 ng/mL), respectively (Table 3).

Twenty-six patients exhibited good ECOG scores (0 or 1). Thirteen patients exhibited an ECOG score of 2, and 1 an ECOG score of 3. The blood and renal parameters before the first cycle are shown in Table 2. Seven patients had received blood transfusion before therapy because of grade 3 tumor anemia 10–180 d before ^{177}Lu-PSMA-617 therapy (median, 21 d). The tumor parameters are listed in Table 3. The SUVs of bone and lymph node metastases are shown in Table 4. Eight weeks after RLT, 27 of 40 patients (67.5%) experienced a PSA decline, of whom 13 showed a PSA decline of more than 50% (32.5%). Thirteen patients showed progressive disease according to an increasing PSA level (Supplemental Fig. 1; supplemental materials are available at http://jnm.snmjournals.org).

Impact of Pretherapeutic Parameters on Percentage PSA Changes

The linear regression analysis of different parameters showed that a higher platelets count, high C-reactive protein (CRP) level, younger age, higher Gleason score, and a regular need for pain medication have a negative impact on the PSA response according

TABLE 3
Tumor Parameters

Parameter	Minimum	Maximum	Mean	Median
ALP (U/L) (norm, 34–117)	38	1,607	247.3	176.5
LDH (U/L) (norm, <248)	147	1,875	411.4	257
CRP (mg/L) (norm, <3)	0.2	128	24.9	16.2
PSA (ng/mL)	4.73	2,360	495.1	325.5

ALP = alkaline phosphatase; LDH = lactate dehydrogenase.

TABLE 4
SUVs of 40 Patients Before ^{177}Lu-PSMA Therapy

Parameter	Minimum	Maximum	Mean	Median
SUVmaxBN	4.50	100.68	26.07	20.76
SUVmaxBN/liver	0.60	13.51	4.17	3.66
SUVmaxBN/spleen	0.69	19.55	4.27	2.98
SUVmaxLn	4.0	98.60	26.24	14.10
SUVmaxLn/liver	0.41	15.91	3.76	2.53
SUVmaxLn/spleen	0.38	33.65	4.95	2.10

TABLE 5
Linear Regression Analysis of Different Pretherapeutic Parameters and Their Impact on PSA Change

Parameter	P	Parameter	P
Amount of activity (MBq)	NS	Creatinine	NS
Activity (MBq)/weight (Kg)	NS	Total bilirubin	NS
Abiretarone	NS	Hb	NS
Enzalutamide	NS	RBC	NS
Chemotherapy	NS	WBCs	NS
^{223}Ra	NS	PSA level	NS
Bisphosphonate or denosumab	NS	SUV$_{max}$ (bone)	NS
Number of bone metastases	NS	SUV$_{max}$ (lymph node)	NS
Extent of lymph node metastases	NS	SUV$_{max}$ bone/liver	NS
Existence of liver metastases	NS	SUV$_{max}$ bone/spleen	NS
ECOG performance status	NS	SUV$_{max}$ lymph node/liver	NS
Albumin	NS	SUV$_{max}$ lymph node/spleen	NS
AST and ALT	NS	Plt	0.0005
ALP	NS	CRP	0.0203
GGT	NS	Age	0.0139
LDH	NS	Gleason score	0.0096
GFR	NS	Regular need for pain medication	0.0050

NS = not significant; Hb = hemoglobin; RBC = red blood cells; WBCs = white blood cells; AST = aspartate aminotransferase; ALT = alanine transaminase; Plt = platelets; ALP = alkaline phosphatase; LDH = lactate dehydrogenase; GFR = glomerular filtration rate.

to percentage PSA changes (Table 5). Figure 1 shows the significant correlation between age and better PSA response ($r^2 = 0.149$; $P = 0.013$), and Figure 2 shows the significant correlation between the platelet count and worse PSA response ($r^2 = 0.274$; $P = 0.0005$).

**Impact of Pretherapeutic Parameters on Any PSA Decline**

The univariate analysis showed that higher levels of γ-glutamyl transferase (GGT) (>100U/L; $P = 0.001$), platelet counts (>300 G/L; $P = 0.001$), high CRP (>20 mg/L; $P = 0.006$), a Gleason score of 10, younger age (cutoff, 65 y; $P = 0.001$), high lactate dehydrogenase, lower pretherapeutic hemoglobin, and regular need for pain medication had a negative impact on any PSA decline. The other factors, including SUVs, did not have any significant

impact on PSA (Table 6). In the multivariate analysis, only a high platelet count and regular need for pain medication kept their significance (Table 5).

Impact of Pretherapeutic Parameters on PSA Decline of More Than 50%

The univariate analysis showed that only a Gleason score of 10 and regular need for pain medication had a negative impact on PSA decline of more than 50%. No patient with a Gleason score of 10 showed a PSA decline, and only 2 from 15 patients (13.3%), who had a regular need for analgesics, showed a PSA decline of more than 50%. Again, the regular need for pain medication kept its significance in the multivariate analysis (Table 7).
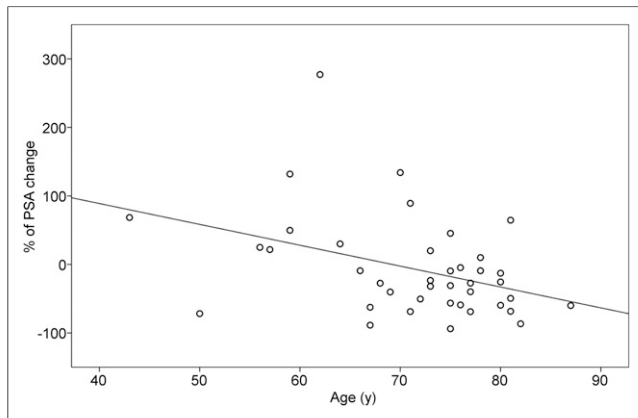
FIGURE 1. Correlation between age and percentage PSA changes ($R^2 = 0.149$).
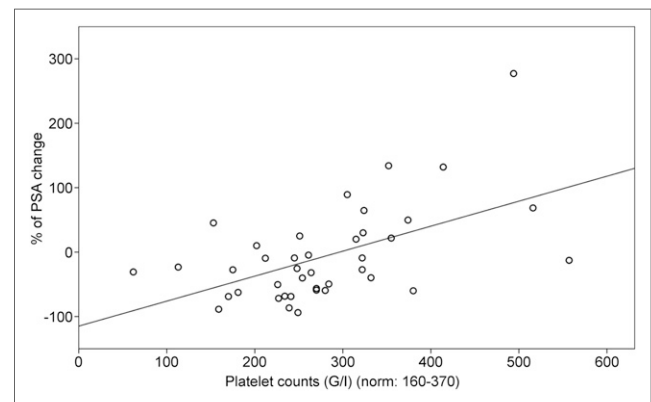
FIGURE 2. Correlation between platelet counts and percentage PSA changes ($R^2 = 0.274$).

TABLE 6
Univariate and Multivariate Analyses of Different Pretherapeutic Parameters Regarding Any PSA Decline

Parameter	Odds ratio	95% CI	P	P multivariate analysis
Activity (MBq)/weight (kg)	0.989	0.944–1.035	0.62	
Abiretarone	0.846	0.368–1.944	0.69	
Enzalutamide	0.932	0.398–2.181	0.87	
Chemotherapy	0.828	0.426–1.609	0.57	
^{223}Ra	0.436	0.097–1.958	0.27	
Bisphosphonate or denosumab	0.848	0.231–3.109	0.80	
No. of bone metastases	1.165	0.444–3.061	0.75	
Extent of lymph node metastases	1.281	0.731–2.243	0.38	
Existence of liver metastases	1.114	0.202–6.158	0.90	
ECOG performance status	1.685	0.761–3.733	0.19	
Albumin	0.987	0.847–1.149	0.86	
AST	1.018	0.988–1.048	0.23	
ALT	1.043	0.976–1.115	0.21	
GGT	1.024	1.006–1.041	0.008	NS
ALP	1.003	0.999–1.006	0.15	
LDH	1.002	1.000–1.005	0.04	NS
Creatinine	4.714	0.464–47.907	0.19	
Total bilirubin	0.014	<0.001–7.401	0.18	
Hb	0.574	0.341–0.967	0.04	NS
RBC	0.429	0.127–1.444	0.17	
WBCs	1.220	0.890–1.674	0.21	
PSA level	0.999	0.997–1.000	0.15	
SUV$_{max}$ (bone)	0.974	0.931–1.020	0.26	
SUV$_{max}$ (lymph node)	0.980	0.944–1.018	0.30	
SUV$_{max}$ bone/liver	0.746	0.529–1.053	0.09	
SUV$_{max}$ bone/spleen	0.635	0.394–1.022	0.06	
SUV$_{max}$ lymph node/liver	0.752	0.501–1.130	0.16	
SUV$_{max}$ lymph node/spleen	0.828	0.612–1.120	0.22	
Plt	1.010	1.001–1.018	0.02	0.01
CRP	1.047	1.011–1.085	0.009	NS
Age	0.885	0.805–0.972	0.01	NS
Gleason score	4.121	1.304–13.016	0.01	NS
Regular need for pain medication	0.091	0.017–0.501	0.005	0.0018

CI = confidence interval; NS = not significant; AST = aspartate aminotransferase; ALT = alanine transaminase; ALP = alkaline phosphatase; LDH = lactate dehydrogenase; Hb = hemoglobin; RBC = red blood cells; WBCs = white blood cells; Plt = platelets.

DISCUSSION

In addition to docetaxel, which until 2010 was the only drug with a positive effect on overall survival, in recent years, 5 new drugs (abiraterone, enzalutamide, sipuleucel-T, cabazitaxel, and ^{223}Ra) have shown efficacy in prolonging survival in castration-resistant PC patients (9–14). However, despite all of these new and effective therapies, patients with hormone-refractory metastatic PC still reach an endpoint at which no approved therapy is effective or indicated.

According to retrospective studies, RLT with ^{177}Lu-PSMA-617 has been shown to be effective, inducing PSA decline in almost 70% of patients who were in a salvage situation, with a favorable toxicity profile and mild side effects (3–8).

In our recently published study (8), we demonstrated the treatment response and side effects of ^{177}Lu-PSMA-617 therapy in 24 patients, who were treated with up to 2 cycles. In this small group of patients, we found that the only pretherapeutic factor that had a negative impact on PSA decline was the regular use of opioids. No other pretherapeutic factors, inclusive of prior therapies, had any impact on the treatment response according to PSA decline.

We also showed the reliability of PSA for treatment follow-up. There was a significant correlation between the treatment response according to PSMA PET/CT imaging and PSA changes, which shows the value of PSA changes for the follow-up of patients on PSMA therapy. In the current study, we evaluated more parameters

TABLE 7
Univariate and Multivariate Analysis of Different Pretherapeutic Parameters Regarding PSA Decline of More Than 50%

Parameter	Odds ratio	95% CI	P	P multivariate analysis
Activity (MBq)/weight (kg)	1.028	0.979–1.079	0.26	
Abiretarone	0.986	0.427–2.280	0.97	
Enzalutamide	0.738	0.315–1.728	0.48	
Chemotherapy	1.526	0.775–3.005	0.22	
^{223}Ra	1.324	0.322–5.439	0.69	
Bisphosphonate or denosumab	1.179	0.322–4.320	0.80	
No. of bone metastases	1.351	0.538–3.392	0.52	
Extent of lymph node metastases	1.189	0.721–1.961	0.49	
Existence of liver metastases	0.661	0.088–4.956	0.68	
ECOG performance status	2.150	0.918–5.036	0.07	
Albumin	1.042	0.894–1.215	0.59	
AST	1.009	0.983–1.035	0.49	
ALT	1.017	0.948–1.092	0.63	
GGT	1.013	0.995–1.033	0.16	
ALP	1.002	0.998–1.006	0.36	
LDH	1.005	0.999–1.010	0.12	
Creatinine	3.031	0.218–42.194	0.40	
Total bilirubin	0.024	<0.001–1.908	0.09	
Hb	0.868	0.560–1.345	0.52	
RBC	1.014	0.326–3.158	0.98	
WBCs	1.377	0.956–1.984	0.08	
PSA level	1.000	0.999–1.001	0.77	
SUV$_{max}$ (bone)	1.023	0.979–1.070	0.30	
SUV$_{max}$ (lymph node)	0.988	0.960–1.016	0.39	
SUV$_{max}$ bone/liver	1.199	0.900–1.597	0.21	
SUV$_{max}$ bone/spleen	1.120	0.898–1.398	0.31	
SUV$_{max}$ lymph node/liver	0.971	0.785–1.200	0.78	
SUV$_{max}$ lymph node/spleen	0.990	0.896–1.094	0.84	
Plt	1.007	0.999–1.015	0.10	
CRP	1.051	0.995–1.110	0.07	
Age	0.953	0.876–1.036	0.25	
Gleason score	1.598	0.853–2.991	0.01	NS
Regular need for pain medication	0.156	0.036–0.669	0.01	0.01

CI = confidence interval; AST = aspartate aminotransferase; ALT = alanine transaminase; ALP = alkaline phosphatase; LDH = lactate dehydrogenase; Hb = hemoglobin; RBC = red blood cells; Plt = platelets; WBCs = white blood cells; NS = not significant.

in a greater number of patients after the first cycle. The data regarding the treatment response and toxicity as well as treatment tolerability of the included patients in this study have been published together with the data from 3 other centers as a multicenter study (*7*). In the current study, we first tried to determine whether there was a correlation between the percentage of PSA change and any of the pretherapeutic factors (Table 5). One of the first issues for the treatment planning is the influence of prior therapies on the treatment response. Although all of our patients had received different treatments before ^{177}Lu-PSMA-617, in this patient collective, these therapies did not have any influence on the treatment response; however, the influence of prior therapies

in combination with RLT on toxicity should be evaluated. It is still unclear whether the treatment response could be better using ^{177}Lu-PSMA-617 as first- or second-line therapy.

In theranostics, 2 issues should be clarified using diagnostic scans before planning radionuclide therapy: first, whether there is any tracer uptake in the tumor, and second, the amount of the uptake.

Concerning the first point, in the case of thyroid cancer or neuroendocrine tumors without any tracer uptake, ^{131}I diagnostic scanning or somatostatin receptor imaging, respectively, is generally excluded from ^{131}I or ^{177}Lu-DOTATATE therapy. This also applies to ^{177}Lu-PSMA-617 therapy. Moreover, only metastases that show PSMA expression can be treated with PSMA therapy.

The second point implies that the amount of tracer uptake is also of considerable importance, because higher radioiodine uptake predicts a better treatment response. In the case of neuroendocrine tumors, there is a positive correlation between the degree of somatostatin receptor expression and the treatment response as well as prognosis (15,16); however, in the current study, the SUV_{max} of ^{68}Ga-PSMA-11 did not significantly influence the treatment response. One explanation for this difference between somatostatin receptor imaging and PSMA imaging may be the physiopathologic mechanism of tracer uptake. There is an inverse association between somatostatin receptor type 2A (SSTR2A) with the Ki-67 index, and SSTR2A is highly expressed in G1 and G2 neuroendocrine tumors but is significantly less abundant in neuroendocrine carcinomas (G3) (17); thus, higher expression of SSTR2A is correlated with lower grade of the neuroendocrine tumor. In contrast, the amount of PSMA expression is directly correlated with metastases, androgen independence, and progression of PC (18). More aggressive tumors may express higher PSMA levels, but despite better uptake of ^{177}Lu-PSMA-617, because of the rapid growth of metastases, the response rate does not correlate with uptake. Another explanation could be the different washout times of ^{177}Lu-PSMA-617 in the respective metastases. These should both be confirmed in studies with more patients.

Compared with prior therapies and the SUV of PSMA-11, there were some parameters shown to have a negative impact on the treatment response. A higher platelet count, high CRP level, younger age, higher Gleason score, and a regular need for pain medication had a negative impact on the PSA response according to percentage PSA changes. In our study, 8 patients were younger than 65 y, of whom 4 had PC with a Gleason score of 10 and the others a Gleason score of 8 or greater, which could explain the worse response in these patients.

Bensalah et al. (19) reported the prognostic value of thrombocytosis in 774 patients with renal cell carcinoma. They reported that platelet count was strongly correlated with T stage, Fuhrman grade, tumor size, nodal invasion, and the presence of distant metastasis. Thrombocytosis had an impact on prognosis in localized and metastatic disease. In their study on patients with a platelet count of less than 450,000/mm^3, the 5-y survival rate was 70%, compared with 38% when the platelet count was 450,000/mm^3 or greater. The negative impact of thrombocytosis on prognosis has been also reported in other cancer types, such as bladder cancer (20), gynecologic malignancies (21–23), and gastrointestinal cancers (24), as well as in early and advanced breast cancer (25,26). According to different published studies, cytokines, in particular IL-6, play an important role in the development of thrombopoiesis and thrombocytosis (22–24). Circulating tumor cells may use platelets as a protective shield against attack by the immune system and as facilitators for attachment to endothelial cells at metastatic sites (27,28). Antiplatelet agents and anticoagulants have potent inhibitory effects on tumor cell platelet interactions and can prevent metastases in experimental settings in various malignancies (27,29–32).

In our study, there was also a significant correlation between the number of platelets and the negative percentage change in PSA (Fig. 2). In the univariate analysis of different pretherapeutic factors regarding any PSA decline, a platelet count of more than 300 G/L also had a negative impact on the therapeutic response in addition to high GGT (>100U/L), high CRP (>20 mg/L), and a Gleason score of 10, younger age (cutoff: 65 y), lower pretherapeutic hemoglobin, and regular need for pain medication; however, in the multivariate analysis, only the platelet count and regular need for pain medication retained their significance.

Regarding a PSA decline of more than 50%, only a Gleason score of 10 and regular need for pain medication had a negative impact on the therapeutic response in the univariate analysis; in the multivariate analysis, only the regular need for pain medication was significant. Patients with advanced disease and high tumor load often suffer from pain, which affects their quality of life. A regular need for pain medication is an indirect sign of advanced disease, which explains its negative impact on the treatment response.

CONCLUSION

According to the results of this study, a favorable response rate (PSA decline > 50%) may be observed significantly more in patients without a regular need for analgesics. The results of the current study should be confirmed by prospective trials especially in respect to the effect of these parameters on survival.

DISCLOSURE

No potential conflict of interest relevant to this article was reported.

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