First Clinical Results for PSMA-Targeted α-Therapy Using ^{225}Ac-PSMA-I&T in Advanced-mCRPC Patients

Mathias Johannes Zacherl[1], Franz Josef Gildehaus[1], Lena Mittlmeier[1], Guido Böning[1], Astrid Gosewisch[1], Vera Wenter[1], Marcus Unterrainer[1,2], Nina Schmidt-Hegemann[2], Claus Belka[2], Alexander Kretschmer[3], Jozefina Casuscelli[3], Christian G. Stief[3], Marcus Unterrainer[1,4], Peter Bartenstein[1], Andrei Todica[1], Harun Ilhan[1]

[1]Department of Nuclear Medicine, University Hospital, LMU Munich, Munich, Germany; [2]Department of Radiation Oncology, University Hospital, LMU Munich, Munich, Germany; [3]Department of Urology, University Hospital, LMU Munich, Munich, Germany; and [4]Department of Radiology, University Hospital, LMU Munich, Munich, Germany

Treatment of advanced metastatic castration-resistant prostate cancer after failure of approved therapy options remains challenging. Prostate-specific membrane antigen (PSMA)–targeting β- and α-emitters have been introduced, with promising response rates. Here, we present the first—to our knowledge—clinical data for PSMA-targeted α-therapy (TAT) using ^{225}Ac-PSMA imaging and therapy (I&T). **Methods:** Fourteen patients receiving ^{225}Ac-PSMA-I&T were included in this retrospective analysis. Eleven of the 14 had prior second-line antiandrogen treatment with abiraterone or enzalutamide, prior chemotherapy, and prior ^{177}Lu-PSMA treatment. Patients were treated at bimonthly intervals until progression or intolerable side effects. Prostate-specific antigen (PSA) was measured for response assessment. Hematologic and nonhematologic side effects were recorded according to the Common Terminology Criteria for Adverse Events, version 5.0. **Results:** Thirty-four cycles of ^{225}Ac-PSMA-I&T were applied (median dose, 7.8 MBq; range, 6.0–8.5), with 1 cycle in 3 patients, 2 cycles in 7 patients, 4 cycles in 3 patients, and 5 cycles in 1 patient. No acute toxicity was observed during hospitalization. Baseline PSA was 112 ng/mL (range, 20.5–818 ng/mL). The best PSA response after TAT (a PSA decline ≥ 50%) was observed in 7 patients, and a PSA decline of any amount was observed in 11 patients. Three patients had no PSA decline at any time. A subgroup analysis of 11 patients with prior ^{177}Lu-PSMA treatment showed any PSA decline in 8 patients and a decline of at least 50% in 5 patients. After TAT, grade 3 anemia was observed in 3 of the 14 patients, with 2 of them presenting with grade 2 anemia already at baseline. Grade 3 leukopenia was observed in 1 patient. Eight patients with preexisting xerostomia after ^{177}Lu-PSMA showed no worsening after TAT. Newly diagnosed grade 1 or 2 xerostomia after TAT was observed in 5 patients. One patient reported no xerostomia at all. **Conclusion:** Our first clinical data for TAT using ^{225}Ac-PSMA-I&T showed a promising antitumor effect in advanced metastatic castration-resistant prostate cancer. These results are highly comparable to data on ^{225}Ac-PSMA-617 TAT.

Key Words: metastatic castration-resistant prostate cancer; radioligand therapy; targeted α-therapy; ^{225}Ac and ^{177}Lu; PSMA

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Progression of prostate cancer after salvage therapy and androgen deprivation therapy marks the transition to metastatic castration-resistant prostate cancer (mCRPC), which describes the incurable and lethal form of advanced prostate cancer for which treatment remains highly challenging (*1*). Approved therapy options for mCRPC include second-generation antiandrogen therapy, taxane-based chemotherapy, and ^{223}Ra (*2*). Novel therapy options, including immunotherapy with checkpoint inhibitors, poly(adenosine diphosphate-ribose) polymerase inhibitors, and prostate-specific membrane antigen (PSMA)–targeting radionuclides, has been introduced in recent years (*2*).

PSMA overexpression in prostate cancer represents the ideal target for theranostic approaches using radiolabeled ligands for imaging and therapy (I&T) (*3*). Radioligand therapy (RLT) using ^{177}Lu-PSMA ligands is offered in many centers worldwide, and the results of the first phase III trial comparing ^{177}Lu-PSMA-617 RLT and best supportive care versus best supportive care alone are expected in 2021 (VISION, NCT03511664). Nonetheless, a considerable number of mCRPC patients do not show a sufficient response to RLT using the β-emitter ^{177}Lu. In the largest retrospective cohort, with 145 patients overall, 40% did not show any response at all (*4*). The efficacy of ^{177}Lu-PSMA RLT was confirmed in the phase 2 Lu-PSMA trial, with a prostate-specific antigen (PSA) decline of any amount observed in almost all patients (29/30, 97%) (*5*). However, the primary endpoint, defined as a best PSA decline of 50% or more, was not met in 43% of patients.

Targeted α-therapy (TAT) using ^{225}Ac-PSMA-617 has been introduced with substantial therapeutic efficacy and has the potential to overcome resistance to β-emitter therapy (*6*,*7*). However, clinical experience for TAT is still limited. Clinical data on 40 patients treated with 8 MBq (100 kBq/kg of body weight) every 2 mo have shown highly promising results, with a PSA decline of at least 50% in 63% of patients and any PSA response in 87% (*8*). Several approaches have been proposed to improve tolerability and determine the optimal treatment regimen for ^{225}Ac-PSMA-617 TAT with escalating or deescalating ^{225}Ac dose depending on individual PSA response (*9*). Such a protocol was also applied in 17 chemotherapy-naïve mCRPC patients, and an overall PSA decline of at least 50% was observed in 15 patients (88%) while maintaining low toxicity (*10*).

Up to now, all clinical data on PSMA TAT have been available only for ^{225}Ac-PSMA-617. However, the development and clinical implementation of new compounds are the hallmark of nuclear medicine theranostics (*3*). PSMA-I&T was introduced in 2014

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For correspondence or reprints contact Harun Ilhan (harun.ilhan@med.uni-muenchen.de).
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as a theranostic PSMA-targeting small molecule (*11*,*12*). The first clinical results for ^{177}Lu-PSMA-I&T were highly comparable to ^{177}Lu-PSMA-617 data (*13*). Considering the remarkable efficacy of TAT, the implementation and evaluation of ^{225}Ac-labeled PSMA-I&T expand the clinical armamentarium for the treatment of mCRPC. Here, we report our first clinical experience in patients receiving ^{225}Ac PSMA-I&T at a single center.

MATERIALS AND METHODS

Patients

This study was a retrospective analysis of mCRPC patients who were consecutively treated with ^{225}Ac PSMA-I&T between September 2018 and December 2019 at our institution and was approved by the local institutional review board. TAT was performed in accordance with the German Medical Products Act, §13.2b, and with the updated Declaration of Helsinki, § 37 (Unproven Interventions in Clinical Practice). ^{18}F-PSMA-1007 PET was performed on all patients to test for sufficient PSMA expression before TAT. The included patients either were not eligible for or rejected other approved therapy options. An interdisciplinary tumor board decided whether TAT was indicated. All patients gave written consent after being informed about the experimental nature of this unapproved therapy and about possible risks and side effects.

Radiopharmaceuticals and Treatment Regimen

PSMA-I&T was obtained from Scintomics/ATT GmbH. ^{225}Ac was obtained from ITM Medical Isotopes GmbH. ^{225}Ac-PSMA-I&T was radiolabeled by adding a mixture of 0.1 mL of PSMA-I&T (200 μg) and 0.9 mL of 0.1 M sodium ascorbate solution into a conical vial containing 10 MBq of ^{225}Ac in 100 μL of 0.1 M HCl (ITM Medical Isotopes GmbH). The vial was heated to 90°C for 30 min. After cooling, the reaction mixture was diluted with 8.9 mL of formulation buffer (0.25 M sodium ascorbate). Quality control was performed by instant thin-layer chromatography, with 0.05 M citric acid (pH 5) as the solvent. After development, the chromatography strip was stored for at least 1 h until radiochemical equilibrium was obtained between ^{225}Ac (half-life, 9.9 d) and its daughter nuclide, ^{221}Fr (half-life, 4.8 min). The radiochemical purity was determined by measuring the activity using a thin-layer chromatography scanner, miniGITA (Elysia-Raytest GmbH). Free ^{225}Ac migrates with the front, whereas labeled product stays on the bottom. The mean radiochemical purity of the radiolabeled peptide was 98.2% ± 0.8%. The final pH of the formulation was 7.2, and sterility was ensured via sterile filtration. A 100-kBq dose of ^{225}Ac-PSMA-I&T per kilogram of body weight was administered as a freehand injection over 30 s. The dose was adapted by Kratochwil et al. as a tradeoff between therapy efficacy and side effects (*14*). According to their data on ^{225}Ac-PSMA-617, a therapy activity of 100 kBq per kilogram of body weight represents the maximum tolerable dose, and activities of 150 and 200 kBq per kilogram of body weight are dose-limiting for the development of xerostomia and xeropthalmia, respectively. As a standard operating procedure, patients received cool packs 30 min before und up to 4 h after injection of ^{225}Ac-PSMA-I&T to cool the salivary glands to reduce perfusion. Furthermore, prednisone, 50 mg by mouth, was administered every day, and ondansetron, 4 mg by mouth, was administered on the day of therapy. Additionally, 2 L of 0.9% intravenous NaCl were infused on the day of therapy. Therapy was performed during an inpatient stay of at least 48 h in accordance with German radiation protection regulations.

Toxicity and Response Assessment

Vital signs, complete blood count, and blood chemistry were documented on the day of therapy and during hospitalization. Laboratory analysis included, among other parameters, a complete blood count and a metabolic panel, including sodium, potassium, calcium, liver enzymes (alanine aminotransferase and aspartate aminotransferase), albumin, bilirubin, alkaline phosphatase (ALP), lactate dehydrogenase, creatinine, estimated glomerular filtration rate, and PSA. During follow-up, blood parameters were checked every 4–8 wk. Follow-up further included clinical investigation, renal scintigraphy at 8-wk intervals, and PSMA PET/CT every 2–3 mo (shorter intervals during consolidation therapy and longer intervals after completion of TAT). Additional imaging and follow-up were performed if clinically indicated by the treating urologist or oncologist. All therapy-related adverse events were documented at baseline and during follow-up according to the Common Terminology Criteria for Adverse Events, version 5.0. Xerostomia was assessed using standardized questions regarding chewing and swallowing difficulties, food and beverage intake, and xerostomia-related symptoms.

Biochemical response was evaluated using PSA changes at defined time points and the best PSA response. Furthermore, the best ALP and lactate dehydrogenase response after TAT was documented.

Statistical Analysis

Patient and treatment data, as well as response characteristics, are presented as descriptive statistics in absolute and relative frequencies. The PSA and ALP change after TAT is presented using waterfall plots showing individual changes sorted by extent. Because of the small sample size, no statistical analysis was performed to test for differences between baseline and posttreatment values during follow-up.

RESULTS

Patients

Eighteen consecutive patients received TAT using ^{225}Ac-PSMA-I&T. Four patients were excluded from this analysis because of lack of access to medical records from outside our institution. Detailed patient characteristics, including baseline PSA values, pattern of metastatic disease, and prior therapies, are provided in Table 1. Eleven patients received prior ^{177}Lu-PSMA RLT (median, 2 cycles; 43 cycles in total). Early progression or therapy failure after a median of 2 cycles was observed in 4 patients. The remaining 7 patients showed an initial response and later progression after a median of 4 ^{177}Lu-PSMA RLT cycles, with a PSA decline of at least 50% in 6 patients and a PSA decline of 37% in 1 patient as the best PSA response.

In total, 34 cycles of ^{225}Ac-PSMA-I&T were applied (median dose, 7.8 MBq; range, 6.0–8.5). Three patients received 1 cycle (median dose, 7.0 MBq), 7 patients received 2 cycles (median cumulative dose, 16.0 MBq), 3 patients received 4 cycles (median cumulative dose, 27.6 MBq), and 1 patient received 5 cycles (cumulative dose, 39 MBq). Three patients (17%) refused further treatment because of xerostomia after 1 therapy cycle. The median follow-up time after ^{225}Ac-PSMA-I&T TAT was 23.6 wk (range, 8–77 wk).

Surrogate Markers for Response

Figure 1 shows waterfall plots of PSA, ALP, and lactate dehydrogenase response after PSMA TAT. Response assessment at 8 wk after 1 cycle of ^{225}Ac-PSMA-I&T showed any PSA decline in 8 of the 14 patients (57%) and a PSA decline of at least 50% in 3 patients (21%). Evaluation of the best PSA response after 1 (3 patients), 2 (7 patients), 4 (3 patients), or 5 (1 patient) cycles showed any PSA decline in 11 patients (79%) and a PSA decline of at least 50% in 7 patients (50%). Assessment of the best ALP response revealed any decline in 10 patients (71%) and a decline of at least 50% in 5 patients (36%). The best lactate dehydrogenase response was any decline in 11 patients (79%) and a decline of at least 50% in 1 patient (7%). In the subgroup of 11 patients

TABLE 1
Patient Characteristics

Characteristic	Value
Patients	14 (100%)
Age (y)	
Median	75 (64–80)
≥75	8 (57%)
ECOG performance score	
≤1	11 (79%)
2	3 (21%)
PSA at start of ^{225}Ac-PSMA-I&T (ng/mL)	112 (20.5–818)
Hemoglobin at start of ^{225}Ac-PSMA-I&T (g/dL)	10.3 (5.6–12.5)
Platelets at start of ^{225}Ac-PSMA-I&T (g/L)	246 (72–412)
ALP at start of ^{225}Ac-PSMA-I&T (U/L) (reference range, 40−130)	143 (67–695)
Site of metastases before ^{225}Ac-PSMA-I&T	
Bone (any)	13 (93%)
Bone (superscan pattern)	5 (36%)
Lymph node	10 (71%)
Visceral metastasis	3 (21%)
Liver	1 (7%)
Lung	3 (21%)
Other organs	1 (7%)
Therapy before start of ^{225}Ac-PSMA-I&T	
Prostatectomy	9 (64%)
Radiation therapy	12 (86%)
Prostate or locoregional lymph nodes	10 (71%)
Distant (nonregional lymph nodes, bone)	6 (43%)
Androgen deprivation therapy	14 (100%)
Abiraterone OR enzalutamide	11 (79%)
Abiraterone AND enzalutamide	4 (29%)
Docetaxel	11 (79%)
Docetaxel AND cabazitaxel	1 (7%)
^{177}Lu-PSMA RLT	11 (79%)
^{223}Ra-dichloride	2 (14%)

ECOG = Eastern Cooperative Oncology Group.
Qualitative data are number and percentage; continuous data are median and range.

(79%) with prior ^{177}Lu-PSMA RLT, any PSA decline was observed in 8 (73%) and a PSA decline of at least 50% was observed in 5 (45%).

Toxicity

After administration of ^{225}Ac-PSMA-I&T and during hospitalization, no therapy-related grade 1–4 tachycardia, hypertension, or fever was observed. A self-limiting slight increase in body temperature from normal values at baseline to subfebrile values was noted in 2 patients. Heart rate and blood pressure remained unchanged during hospitalization (Supplemental Table 1; supplemental materials are available at http://jnm.snmjournals.org).

Therapy-related adverse events during follow-up are provided in Table 2. Grade 3 anemia was observed overall in 3 patients (21%); grade 3 anemia was already present at baseline in 2 of these patients (14%), one having transfusion dependence and a history of docetaxel chemotherapy and the other having 2 cycles of ^{177}Lu-PSMA RLT. The remaining patient (7%) had mild anemia before TAT, with a history of docetaxel chemotherapy and 10 cycles of ^{177}Lu-PSMA RLT. One patient (7%) with a history of chemotherapy and 4 cycles of ^{177}Lu-PSMA RLT presented with grade 2 leukopenia before TAT, which worsened to grade 3. Therefore, TAT was suspended after 1 cycle of ^{225}Ac-PSMA-I&T and changed to best supportive care (patient 11; Fig. 2).

The main nonhematologic side effect after ^{225}Ac-PSMA-I&T was xerostomia. After TAT, grade 1 and 2 xerostomia was observed in 8 (57%) and 5 (36%) patients, respectively. However, 6 (43%) and 2 (14%) patients with prior ^{177}Lu-PSMA RLT already reported grade 1 and 2 xerostomia at baseline, respectively. No patient with preexisting xerostomia reported worsening after TAT. Newly diagnosed xerostomia after TAT was observed in 5 patients (36%), with 1 patient (7%) having grade 1 and 4 patients (29%) having grade 2. Two of these patients had prior ^{177}Lu-PSMA RLT without any xerostomia symptoms. Only 1 patient described no xerostomia after TAT (patient 14, with a history of 2 cycles of ^{177}Lu-PSMA RLT and 1 cycle of ^{225}Ac-PSMA-I&T).

Other nonhematologic adverse events included grade 1 or 2 anorexia in 9 patients (all with grade 1 anorexia at baseline) and newly diagnosed grade 1 or 2 nausea in 5 patients (36%). Grade 1 and 2 fatigue at baseline was observed in 10 (71%) and 1 (7%) patients at baseline, respectively; after TAT, grade 1 and 2 fatigue was observed in 6 (43%) patients each. Other adverse-event parameters are given in Table 2. No grade 4 hematologic, grade 3 or 4 renal, or nonhematologic adverse events were observed during follow-up. Likewise, the remaining laboratory parameters showed no relevant, therapy-related changes. Detailed numbers before and 8 wk after completion of the final ^{225}Ac-PSMA-I&T cycle are provided in Table 3.

DISCUSSION

PSMA-I&T was introduced as a PSMA-targeting small molecule enabling I&T of prostate cancer using the same compound (*11*). Since then, RLT using ^{177}Lu-labeled PSMA ligands have gained increasing clinical value, and the results of the first randomized phase 3 trial for ^{177}Lu-PSMA-617 are expected in 2021. TAT using α-emitters such as ^{225}Ac provides a higher biologic effectiveness than the β-emitter ^{177}Lu and can induce cell killing regardless of oxygenation, cell cycle position, or fluency (*14*,*15*). In the last few years, several groups have presented data showing remarkable clinical efficacy for PSMA TAT using ^{225}Ac-PSMA-617 in different settings, including chemotherapy-naïve, diffuse metastatic, and ^{177}Lu-PSMA RLT–refractory patients (*8*,*10*,*14*,*16*,*17*). Here, we present our first clinical results using ^{225}Ac-PSMA-I&T.

Our data confirm the antitumor effect of TAT in advanced-mCRPC patients. In our subgroup of 11 patients (79%) with prior ^{177}Lu-PSMA RLT, any PSA decline was observed in 8 patients (73%) and a PSA decline of at least 50% was observed in 5

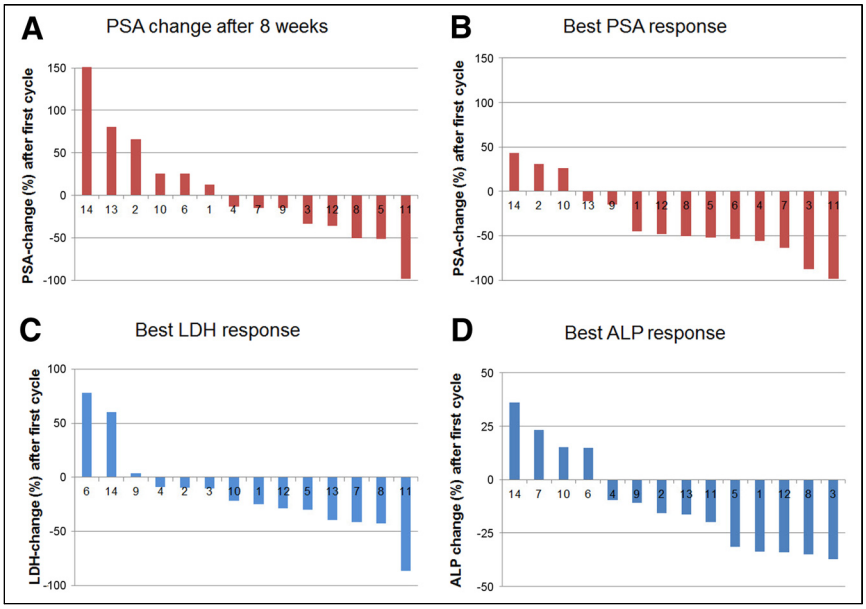

FIGURE 1. Waterfall plots of PSA, lactate dehydrogenase (LDH), and ALP response after TAT using ^{225}Ac-PSMA-I&T. A and B describe PSA changes after 8 wk and best PSA response after first TAT cycle. C and D describe best LDH and ALP response after median of 2 TAT cycles.

patients (45%). Preliminary data on ^{225}Ac-PSMA-617 TAT in 18 mCRPC patients after failure of ^{177}Lu-PSMA RLT were presented recently by the Technical University Munich (*17*). Any PSA decline was observed in 15 patients (83%), and PSA decline of at least 50% was observed in 5 patients (28%), indicating comparable results for ^{225}Ac-labeled PSMA-617 and PSMA-I&T after failure of ^{177}Lu-PSMA RLT (*17*). Recently, Khreish et al. presented data on the efficacy of PSMA TAT in 20 mCRPC patients after previous ^{177}Lu-PSMA RLT (*16*). Their approach introduced *tandem RLT,* a term describing a combination of a reduced ^{225}Ac-PSMA-617 dose (median, 5.3 MBq) with ^{177}Lu-PSMA-617 (median, 6.9 GBq), a concept that has also been presented by other groups (*18*). They observed any PSA decline and a PSA decline of at least 50% in 13 (65%) and 18 (90%) patients, respectively. Consolidation therapy after a PSA response was performed using ^{177}Lu-PSMA-617. A subgroup analysis of patients with an initial response to ^{177}Lu-PSMA treatment compared with patients with early failure showed a tendency toward a better response (best PSA response $\geq$ 50% in 83.3% vs. 50.0%) despite not reaching statistical significance. In summary, TAT represents a highly promising option for advanced-mCRPC patients, even after exhaustion of ^{177}Lu-PSMA RLT. Regardless of lower doses and consolidation therapy with ^{177}Lu-PSMA RLT, the results of Khreish et al. are comparable to our data using fixed doses of 100 kBq per kilogram of body weight. This result also indicates the clinical feasibility of deescalation after a response to PSMA TAT, as the main goal is to reduce TAT-induced toxicity while maintaining the high therapeutic efficacy of α-emitter therapy (*9*,*16*,*18*).

Despite encouraging antitumor activity, high doses of PSMA TAT result in the requirement for dose reduction or therapy discontinuation in a considerable number of patients (*14*). Xerostomia represents the main side effect of TAT. Khreish et al. reported grade 1 and 2 xerostomia in 8 (40%) and 5 (25%) of 20 patients, respectively. Unfortunately, preexisting xerostomia after initial

TABLE 2
Therapy-Related Hematologic and Renal Adverse Events After ^{225}Ac-PSMA-I&T According to Common Terminology Criteria for Adverse Events, Version 5.0

Event	Before TAT				After TAT			
	Gr. 1	Gr. 2	Gr. 3	Gr. 4	Gr. 1	Gr. 2	Gr. 3	Gr. 4
Hematologic								
Anemia	8 (57%)	4 (29%)	2 (14%)		3 (21%)	8 (57%)	3 (21%)	—
Thrombopenia	3 (21%)	1 (7%)	—	—	3 (21%)	3 (21%)	—	—
Leukopenia	2 (14%)	1 (7%)	—	—	4 (28%)	—	1 (7%)	—
Renal	1 (7%)	—	—	—	1 (7%)	1 (7%)	—	—
Gastrointestinal								
Xerostomia	6 (43%)	2 (14%)	—	ND	8 (57%)	5 (36%)	—	ND
Dysgeusia	—	—	—	—	5 (36%)	1 (7%)	—	—
Anorexia	9 (64%)	—	—	—	7 (50%)	2 (14%)	—	—
Nausea	—	—	—	—	4 (29%)	1 (7%)	—	—
General								
Fatigue	10 (71%)	1 (7%)	—	—	6 (43%)	6 (43%)	—	—
Weight loss	NA	NA	NA	NA	4 (29%)	—	—	—

Gr. = grade; ND = not defined; NA = not applicable.
Data are number and percentage.

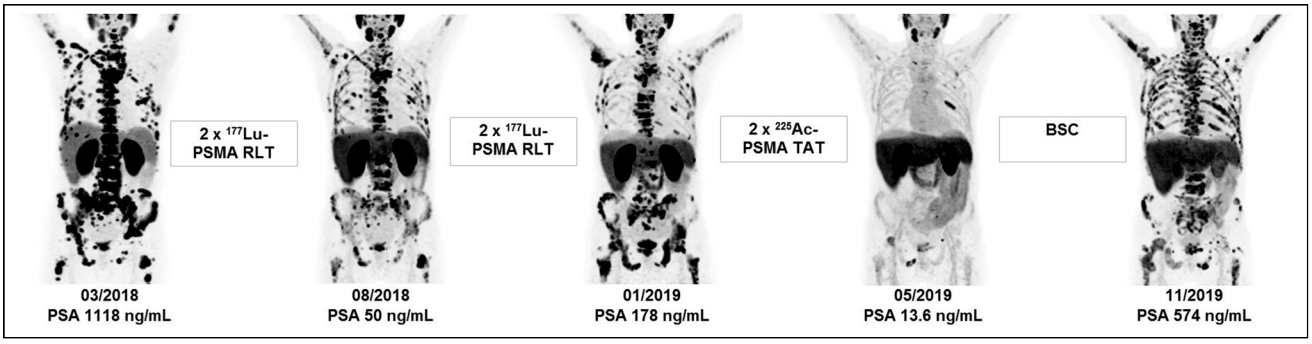

FIGURE 2. A 79-y-old mCRPC patient (patient 11) with lymphatic and bone metastases. Patient received 2 cycles of ^{177}Lu-PSMA RLT (cumulative activity, 10.5 GBq) after failure of docetaxel and showed initial response. However, disease progression was observed in January 2019 after 2 additional ^{177}Lu-PSMA RLT cycles (cumulative activity, 12 GBq), and patient was admitted for ^{225}Ac-PSMA-I&T TAT. PSA follow-up and PSMA PET showed impressive response after 2 cycles (cumulative activity, 13.4 MBq). Unfortunately, patient developed grade 3 leukocytopenia, and TAT could not be continued. Disease progression was observed in November 2019 after best supportive care (BSC).

^{177}Lu-PSMA RLT is not mentioned in their report. Surprisingly, in our cohort no patient with preexisting xerostomia after ^{177}Lu-PSMA RLT (grade 1 in 6/14 patients and grade 2 in 2/14 patients) reported worsening after ^{225}Ac-PSMA-I&T. However, grade 1 and 2 xerostomia was reported in 2 and 3 patients, respectively, without prior xerostomia. Only 1 patient reported no xerostomia at all; however, this patient was treated with only 2 previous cycles of ^{177}Lu-PSMA-617 and 1 cycle of ^{225}Ac-PSMA-I&T. Three patients discontinued treatment because of side effects, with xerostomia as the main complaint. Data on the value of sialendoscopy, saline irrigation, and steroid injection after TAT describe a significant improvement in symptoms (*19*). No such methods were applied in the current analysis because of the difficulty of clinical implementation and lack of patient acceptance of such invasive procedures. However, straightforward salivary gland protection and mitigation of xerostomia represent a major challenge for PSMA TAT (*20*).

Further toxicities in our analysis include grade 3 anemia in 3 (21%) of our 14 patients, with 2 of these patients already presenting with grade 3 anemia at baseline. The remaining patient (patient 2) had grade 1 anemia at baseline, with a history of docetaxel chemotherapy and 10 cycles of ^{177}Lu-PSMA RLT, which might explain the cumulative hematotoxicity after ^{225}Ac-PSMA-I&T. Furthermore, grade 3 leukopenia was observed in 1 patient (patient 11; Fig. 2). This patient had diffuse bone metastases with a history of docetaxel chemotherapy and 4 cycles of ^{177}Lu-PSMA RLT. Despite the fact that deterioration of preexisting hematologic toxicities after TAT is not uncommon (*16*), the higher linear-energy transfer and significantly shorter penetration range of ^{225}Ac than of ^{177}Lu favor

TABLE 3
Laboratory Parameters at Baseline and After ^{225}Ac-PSMA TAT

Parameter	Before ^{225}Ac-PSMA-I&T TAT	After ^{225}Ac-PSMA-I&T TAT
Hemoglobin (g/dL)	10.11 ± 1.94	9.15 ± 1.52
Platelets (g/L)	225.29 ± 99.11	190.00 ± 104.28
Leukocytes (g/L)	5.59 ± 1.92	4.89 ± 1.78
Sodium (mmol/L)	138.00 ± 2.66	137.69 ± 4.31
Potassium (mmol/L)	4.39 ± 0.65	4.15 ± 0.32
Calcium (mmol/L)	2.20 ± 0.08	2.27 ± 0.09
Creatinine (mg/dL)	0.96 ± 0.18	0.95 ± 0.37
eGFR (mL/min)	82.57 ± 17.42	79.57 ± 18.72
BUN (mg/dL)	41.36 ± 14.68	35.69 ± 10.85
ALT (U/L)	16.77 ± 6.92	20.14 ± 11.35
AST (U/L)	41.36 ± 31.56	49.69 ± 33.96
Albumin (g/dL)	4.05 ± 0.45	3.80 ± 0.66
Bilirubin (mg/dL)	0.35 ± 0.20	0.49 ± 0.35
ALP (U/L)	237.21 ± 188.85	409.64 ± 312.49
LDH (U/L)	505.14 ± 416.90	618.62 ± 551.64

eGFR = estimated glomerular filtration rate; BUN = blood urea nitrogen; ALT = alanine aminotransferase; AST = aspartate aminotransferase; LDH = lactate dehydrogenase.
Data are mean ± SD.

^{225}Ac-PSMA TAT over ^{177}Lu-PSMA RLT in terms of hematologic toxicity (*7*,*21*). However, although newly developed hematotoxicity was rare in our cohort (2 patients with grade 1 thrombopenia and 3 with grade 1 leukopenia), 4 patients with grade 1 anemia at baseline developed grade 2 anemia after ^{225}Ac-PSMA-I&T, and a further patient developed grade 3 anemia (patient 2). This development of anemia is also reflected by significantly lower hemoglobin levels after treatment (Table 3), as might be associated with our therapy protocol of fixed doses of 100 kBq per kilogram of body weight without therapy deescalation and the fact that most patients were pretreated with chemotherapy and ^{177}Lu-PSMA RLT.

Our study had several limitations. The retrospective design and inclusion of consecutively treated patients resulted in a mixed patient cohort. The sample size was small, and median follow-up was relatively short, at only 26.3 wk. Nonetheless, because TAT represents one of the most rapidly developing topics for radiopharmacy and nuclear medicine, we feel encouraged sharing our promising clinical results already at this early stage. The clinical implementation of ^{225}Ac-PSMA-I&T TAT provides an interesting new option, particularly in patients with advanced disease and no further therapeutic options.

CONCLUSION

^{225}Ac-PSMA-I&T TAT showed promising antitumor effects comparable to ^{225}Ac-PSMA-617. Grade 3 or 4 hematologic side effects were rare. Grade 1–2 xerostomia remained the main side effect. Nonetheless, the fact that overall toxicity was only moderate indicates that PSMA TAT is an additional therapy option in end-stage mCRPC patients.

DISCLOSURE

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

KEY POINTS

QUESTION: What are the first clinical findings, including therapy-related adverse events and response after TAT, using ^{225}Ac-PSMA-I&T in patients with mCRPC?

PERTINENT FINDINGS: ^{225}Ac-PSMA-I&T TAT was well tolerated in 18 patients, without acute side effects. The best PSA response in 14 patients after ^{225}Ac-PSMA-I&T was any PSA decline (11 patients, 79%) and a PSA decline of at least 50% (7 patients, 50%). The best ALP response was any decline (10 patients, 71%) and a decline of at least 50% (5 patients, 36%). Therapy-related toxicity included grade 2 anemia in 4 patients (29%), grade 3 anemia in 1 patient (7%), grade 3 leukopenia in 1 patient (7%), grade 1 xerostomia in 2 patients (14%), and grade 2 xerostomia in 3 patients (21%). No further grade 3 or 4 hematologic or nonhematologic toxicities were observed.

IMPLICATIONS FOR PATIENT CARE: TAT using ^{225}Ac-PSMA-I&T is a novel therapy option for mCRPC, with encouraging results in end-stage patients.

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