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Brief communication

^{225}Ac-PSMA-617 for PSMA targeting alpha-radiation therapy of patients with metastatic castration-resistant prostate cancer

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ABSTRACT

Prostate-specific membrane antigen (PSMA) is a promising target in prostate cancer. Recently we started the first-in-man treatment with an alpha radionuclide labeled PSMA-ligand. While the case series is still ongoing, here we already report in advance about two patients in highly challenging clinical situations, who showed complete responses to ^{225}Ac-PSMA-617 therapy.

Methods

^{68}Ga-PSMA-11 positron-emission-tomography / computed-tomography (PET/CT) validated a PSMA-positive tumor phenotype. Activities of 100 kBq/kg body-weight of ^{225}Ac-PSMA-617 were administered bi-monthly. Prostate-specific antigen (PSA) response and hematological toxicity were measured at least every four weeks. Restaging was again performed with ^{68}Ga-PSMA-11 PET/CT.

Results

Both patients experienced a PSA decline below measurable and presented with complete imaging response. No relevant hematological toxicity was observed. Xerostomia was the only mentionable clinical side-effect.

Conclusion

Targeted alpha therapy with ^{225}Ac-PSMA-617, yet experimental, obviously offers a high potential to provide significant benefit to advanced stage prostate cancer patients.

Key Words: PSMA, Ac-225, alpha-therapy

INTRODUCTION

After introduction of ^{68}Ga-PSMA-11 as a new PET-tracer for prostate cancer (*1*), PSMA-617, a ligand with optimized tumor cell internalization and lowered kidney uptake containing the more universal DOTA chelator, has been developed for PSMA-targeted radioligand therapy (PSMA-RLT) (*2,3*). Different centers confirmatively report a favorable dosimetry (*4-6*) and convincing serum PSA responses as well as radiological responses for ^{177}Lu-PSMA-617 therapy of metastasized castration-resistant prostate cancer (mCRPC) (*4,7*). Nevertheless, there are around 30% of primary non-responders and despite a good tolerability in general, diffuse red-marrow infiltration was suggested as risk-factor for developing relevant hematological toxicity (*4*). It was already demonstrated that targeted alpha-radiation therapy (TAT) with ^{213}Bi-DOTATOC could break radio-resistance to beta-emitters while simultaneously reducing hematological toxicity in patients with diffuse red-marrow infiltration of neuroendocrine tumors (*8*).

Here we report initial experiences with PSMA-directed TAT using ^{225}Ac-PSMA-617 in one patient with diffuse red-marrow infiltration and one patient resistant to ^{177}Lu-PSMA-617.

MATERIALS AND METHODS

Patients

^{225}Ac-PSMA-617 was offered as salvage therapy in accordance with the updated Declaration of Helsinki, paragraph-37 “Unproven Interventions in Clinical Practice” and in accordance with German regulations which includes priority of approved treatments and confirmation of the indication by a nuclear medicine physician and an expert in urological oncology. One patient presented with diffuse red-marrow infiltration of mCRPC which was considered a contraindication for treatment with beta-emitters and one patient with peritoneal carcinomatosis and liver metastases was progressive under ^{177}Lu-PSMA-617. Both patients had extensive pretreatments (Table 1).

Radiopharmaceuticals

GMP-grade PSMA-11 and PSMA-617 were obtained from ABX (Radeberg, Germany). ^{225}Ac was produced by radiochemical extraction from ^{229}Th (*9,10*). ^{68}Ga was eluted from a ^{68}Ge/^{68}Ga-generator on-site. ^{177}Lu was obtained from ITG (Garching, Germany). The labeling conditions for ^{68}Ga-PSMA-11 and ^{177}Lu-PSMA-617 have been described previously (*4*).

For radiolabeling of ^{225}Ac-PSMA-617, an aliquot of ^{225}Ac stock solution was added into a microwave vial containing 0.1M Tris buffer (pH 9) and an appropriate amount of PSMA-617 stock solution. The reaction mixture was heated to 95°C for 5min using a microwave synthesizer (Biotage® Initiator).

Quality control was performed by instant thin layer chromatography with 0.05M citric acid (pH 5) as solvent. After development the chromatography-strip was stored for at least 1h until radiochemical equilibrium between ^{225}Ac ($T_{1/2}$=9.9d) and its daughter nuclide ^{221}Fr ($T_{1/2}$=4.8min) was obtained. Subsequently

radiochemical purity was determined by measuring the activity of the 218keV gamma emission of ^{221}Fr on the upper and lower part of the strip using high resolution gamma spectrometry (Ortec). Radiochemical purity of the radiolabeled peptide was 98.8±0.8% at a specific activity of 0.17±0.05MBq/nmol.

After synthesis an aliquot of ascorbic acid was added to the reaction mixture to minimize radiolytic degradation of ^{225}Ac-PSMA-617 together with an aliquot of diethylenetriaminepentaacetic acid to scavenge free radiometals. The final pH of the formulation was 7.4. Sterility was assured via sterile filtration.

Imaging

^{68}Ga-PSMA-11 PET/CT and ^{177}Lu-PSMA-617 emission scans were performed as described previously (*1,6*).

^{225}Ac-PSMA-617 post therapy scans were acquired using the 440keV gamma co-emission of ^{213}Bi (26% emission probability), the 218keV gamma co-emission of ^{221}Fr (12%) and the Bremsstrahlung of ^{209}Pb with a scan speed of 10 cm/min on a 1” crystal gamma camera (GE, Hawkeye) equipped with a high-energy collimator.

RESULTS

Clinical course of patient A

After exhausting conventional therapies (Table 1), imaging with PSMA-PET/CT was suspicious for diffuse red-marrow infiltration (Fig. 1A). This was considered a contraindication for ^{177}Lu-PSMA-617. Therefore, the patient was treated with 3 cycles of 9-10MBq (100kBq/kg body-weight) ^{225}Ac-PSMA-617 in bi-monthly intervals. Post-therapeutic emission scans validated sufficient tumor targeting (Supplemental Fig. 1). Two months later, in PSMA-PET/CT all previously PSMA-positive lesions had visually disappeared (Fig. 1B) and accordingly the PSA dropped from >3000ng/ml to 0.26ng/ml. The patient received additional 6 MBq ^{225}Ac-PSMA-617 as consolidation therapy resulting in a further PSA decline to <0.1ng/ml along with a complete imaging response (Fig. 1C).

After each cycle, blood cell count and alkaline phosphatase (AP) were checked every 2 weeks. Platelets never dropped below 100/nl (I°; CTCAE-V4), total white blood cells never dropped below 2.5/nl (I°) and hemoglobin never dropped below 9.5g/dl (II°) (Fig. 2A). Moderate but enduring xerostomia was the only clinically reported side-effect. Concordant decline of PSA and AP (Fig. 2B), further underlining the excellent treatment response.

Clinical course of patient B

Conventional treatments were also exhausted for this patient suffering from peritoneal carcinomatosis and liver infiltration (Fig. 3A), when ^{177}Lu-PSMA-617 (7.4GBq per cycle) was offered as salvage therapy. The initial PSA was 294ng/ml. Despite sufficient tumor targeting as demonstrated with post-therapeutic emission scans (Supplemental Fig. 2), after cycle-2 the PSA

increased to 419ng/ml and in PSMA-PET/CT most lesions demonstrated tumor progression (Fig. 3B). Therapy was changed to ^{225}Ac-PSMA-617 and the patient received 3 cycles of 6.4MBq (100kBq/kg body-weight) in a bi-monthly interval. Re-stagings based on PSMA-PET/CT finally presented a partial response after 2 cycles (Fig. 3C) and a complete remission after 3 cycles (Fig. 3D). Lab tests revealed no relevant hematological toxicity; PSA dropped below measurable (<0.1ng/ml) (Fig. 4). However, spray substitution of saliva had to be prescribed after the last cycle due to severe xerostomia.

DISCUSSION

Here we present a novel treatment concept for patients with mCRPC progressive under conventional therapy or beta-emitting ^{177}Lu-PSMA-617. Two patients in clinically critical situation experienced remarkable benefit from TAT with ^{225}Ac-PSMA-617. These findings are of such high interest for scientists and clinicians in the field that we already want to share these early observations as a brief report in advance.

PSMA-RLT with ^{177}Lu-PSMA-617, itself an investigational treatment, already demonstrated promising results (*6,7*). However, RLTs based on beta-particle emitters can have typical shortcomings, especially during treatment of late-stage patients.

One challenge is that the dose contribution of beta-particles arising from bone metastases to the red-marrow cannot be modeled sufficiently. If only a limited number of solid bone metastases are present it is possible to neglect this dose contribution because the 498keV beta-energy of ^{177}Lu corresponds to a tissue range of only 1.5 mm and the red-marrow dose is typically estimated by sampling of peripheral blood. However, the blood-dose based models are only valid if specific red-marrow uptake of the radiopharmaceutical can be excluded; in case of diffuse tumor infiltration the red-marrow self-dose can become the limiting factor. In this setting TAT can be beneficial because the 50-100µm range of an alpha-particle (2-3 cell diameters), translates into a much more cell specific radiotherapy (*11*). In analogy, targeting myeloblasts with a beta-labeled ^{131}I-CD33-antibody translates into bone marrow ablation (*12*), whereas an alpha-labeled ^{213}Bi-CD33-antibody can eliminate myeloblasts cell-selectively with tolerable hematological toxicity (*13*). Therefore the remarkable low hematological toxicity observed after treatment of patient-A is reasonable.

In the available reports about ^{177}Lu-labeled PSMA-ligands approx. 30% of the patients were refractory a priori (*6,7*). It has already been demonstrated for

patients with neuroendocrine tumors refractory to ^{177}Lu-labeled somatostatin analogues, that TAT can break radio-resistance to beta-radiation (*8*). In mCRPC, the alpha-emitting $^{223}RaCl_2$ but not its beta-emitting analogue $^{89}SrCl_2$ demonstrated to improve survival (*14*). Therefore it seems comprehensible, that patient-B, despite refractory to ^{177}Lu-RLT, could still be treated successfully with ^{225}Ac-TAT.

One the other hand, RLTs based on alpha-particle emitters are faced with other challenges. The nuclides suitable for medical application are often hampered by either an unfavorable half-life or they decay with multiple instable daughter nuclides. Due to the recoil of the alpha-decay and different chemical properties, the daughter nuclides can leave the chelator of the radioconjugate. If this happens on the cell surface the blood stream can translocate the activity into non-tumor tissue. ^{225}Ac ($T_{1/2}$ 9.9d) decays to the daughters ^{221}Fr ($T_{1/2}$ 4.8min), ^{217}At ($T_{1/2}$ 33ms) and ^{213}Bi ($T_{1/2}$ 45.6min); each of these nuclides disintegrates with emission of one alpha-particle. To ensure that most of the resulting 4 alpha-emissions are on target, carrier-mediated internalization into the tumor cells is aspired for ^{225}Ac-TAT.

The ligand PSMA-617 induces fast cellular internalization, with 54% and 75% of the total cell associated activity internalized after 1h and 3h of incubation on LNCaP (*2*). For the PSMA-targeted and then internalized antibody ^{225}Ac-J591 sufficient tumor retention of the ^{225}Ac daughter nuclides has already been demonstrated in-vitro (*15*). Thus, RLT with ^{225}Ac-PSMA-617 ideally matches the theoretical considerations for TAT of mCRPC.

Nevertheless, the limited availability of ^{225}Ac is still a key challenge for its clinical translation and this shortage has to be solved before large studies are feasible. However, several ways of accelerator-driven production of ^{225}Ac have already been described (*16,17*) and routine production of this radionuclide can be realized with manageable efforts once a relevant demand is predictable.

Already our early results indicate a high potential of ^{225}Ac-TAT for therapy of the epidemiologically important tumor entity prostate cancer, which presumably will further accelerate the routine availability of ^{225}Ac, e.g. for systematic clinical trials.

CONCLUSION

The two impressive responses reported here demonstrate the high potential of ^{225}Ac-PSMA-617 to provide significant benefit to mCRPC patients in critical condition, i.e. patients with diffuse red marrow infiltration and resistance against other therapies. Investigation of this therapeutic modality in larger patient cohorts is warranted.

Conflicts of interest

Patent application for PSMA-617 (regardless of the radiolabeling nuclide): Kopka K and Haberkorn U.

Ethical approval

As these cases concern retrospective reports on findings in regular clinical care but not a systematical clinical trial, ethical approval was not needed.

Informed consent

Patients were informed about the experimental nature of this therapy and gave written informed consent, both agreed with the publication of their individual patient history.

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Tables

Table 1: Overview of pretreatments

Patient-A	Patient-B
LHRH (urupeptyl, leuprorelin)	radical prostatectomy
Zoledronate	radiotherapy of lymphnode metastasis
Docetaxel (50 cycles)	LHRH (leuprorelin)
Carmustin/Epirubicin in hyperthermia	LHRH (leuprorelin) + bicalutamide 150mg/d
Arbiraterone	Docetaxel (11 cycles)
Enzalutamide	Cabazitaxel (10 cycles)
Ra-223 (6 cycles)	Arbiraterone
Arbiraterone re-exposition	Enzalutamide - NOT TOLERATED
Estramustine	

Figure legends

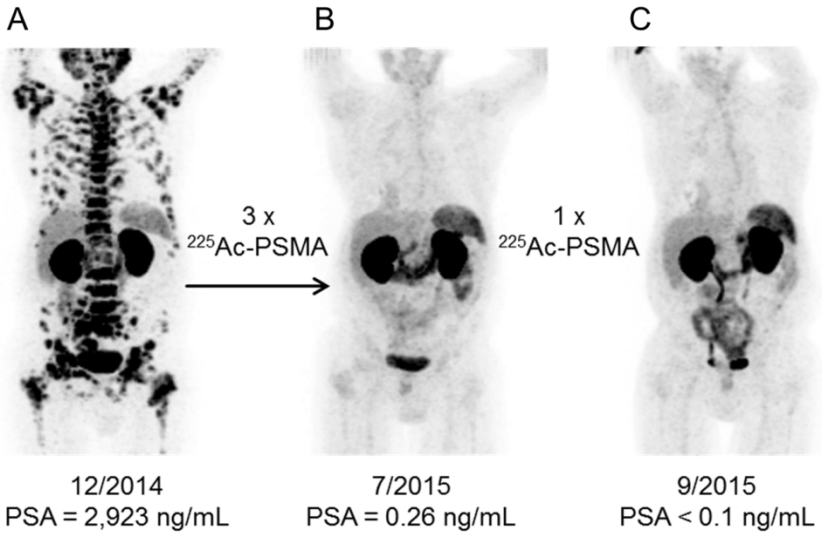

Figure 1: ^{68}Ga-PSMA-11 PET/CT-scans of patient A. Pre-therapeutic tumor spread (A), restaging 2 months after the third cycle of Ac-225-PSMA-617 (B) and 2 months after one additional consolidation therapy (C).

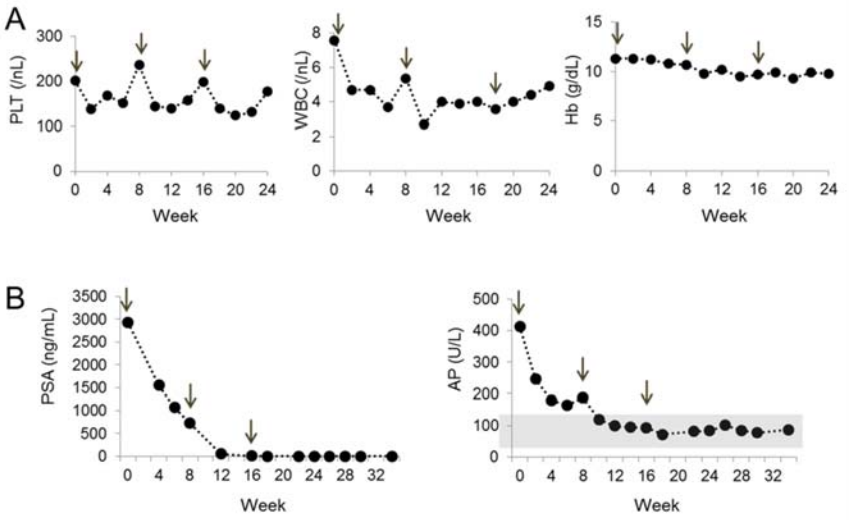

Figure 2: Lab test follow-up of patient A. Arrows indicate the administration of treatment-cycles. Blood cell count (A) demonstrates moderate hematological toxicity. Decline of tumor markers to none-measurable or normal range (B) correlate with imaging response.

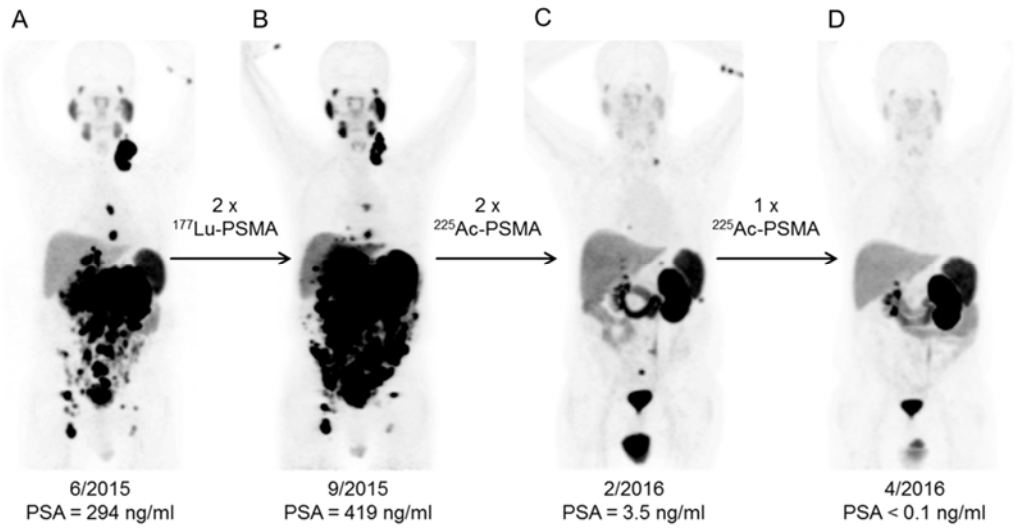

Figure 3: ^{68}Ga-PSMA-11 PET/CT-scans of patient B. In comparison to the initial tumor spread (A), restaging after 2 cycles of beta-emitting^{177}Lu-PSMA-617 presented progression (B). In contrast, restaging after 2nd (C) and 3rd (D) cycle of alpha-emitting ^{225}Ac-PSMA-617 presented impressive response.

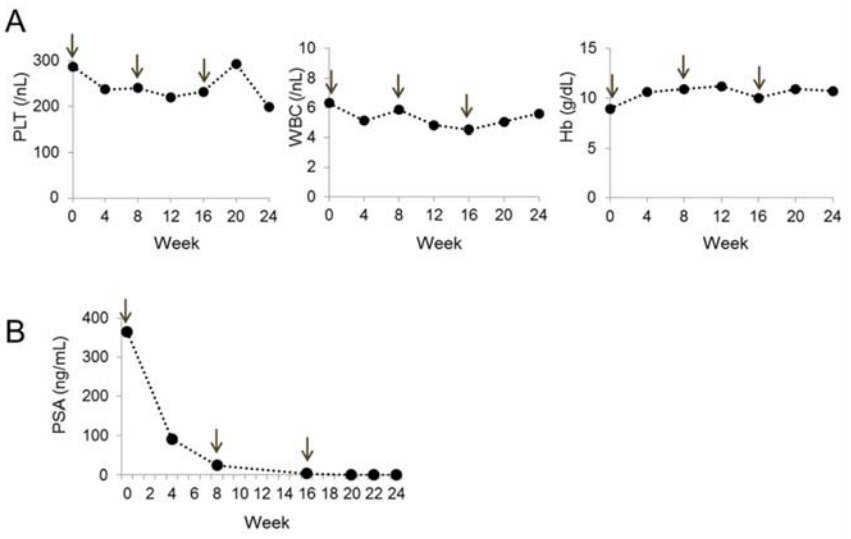

Figure 4: Lab test follow-up of patient B. Arrows indicate the administration of treatment-cycles. Blood cell count (A) always stayed in the normal range, the tumor marker PSA (B) finally declined to none-measurable.