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mCRPC patients receiving ^{225}Ac-PSMA-617 therapy in post androgen deprivation therapy setting: Response to treatment and survival analysis

Short title: ^{225}Ac-PSMA in the post-ADT setting

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ABSTRACT:

***Introduction**:* ^{225}Ac-PSMA-617, targeting the prostate-specific membrane antigen (PSMA) which is overexpressed on prostate cancer cells, has shown a remarkable therapeutic efficacy in heavily pre-treated metastatic castration-resistant prostate carcinoma patients. Here we report on treatment outcome and survival using this novel treatment modality in a series of 53 metastatic castration resistant prostate carcinoma patients directly following their androgen deprivation treatment.

Patients and methods: ^{225}Ac-PSMA-617 was administered to 53 mCRPC patients directly following their androgen deprivation therapy. ^{68}Ga-PSMA PET/CT was obtained at baseline, before every treatment cycle and on follow-up for selection of patients for treatment, to determine the activity to be administered and for response assessment. Serial prostate specific antigen (PSA) was obtained for PSA response assessment.

Results: The median age of the patient population under study was 63.4 yrs (range 45-83 years). A total number of 167 cycles were administered. The median number of cycles administered was 3 (range 1-7). Forty-eight patients (91%) had a PSA decline $\geq$ 50%, and 51 patients (96%) had any decline in PSA . ^{68}Ga-PSMA-PET images became negative in 30 patients. In the multivariate analysis a PSA decline $\geq$ 50 % proved predictive of both PFS and OS whereas platelet count also proved predictive for PFS. Median estimated OS for patients with a PSA decline < 50% was 9 months whereas the median OS of those patients with a PSA decline $\geq$ 50% was not yet reached at the date of latest follow-up (55 months). Estimated median PFS for patients with a PSA decline $\geq$ 50% was 22 months whereas that for patients with a PSA decline < 50% was 4 months. No severe of hematotoxicity was noted, whiles only 3 patients had grade III-IV nephrotoxicity. The commonest toxicity seen was grade I-II xerostomia observed in 81% of patients.

***Conclusion**:* In this series on 53 patients suffering from mCRPC, treatment with ^{225}Ac-PSMA-617 administered immediately following ADT, resulted in a $\geq$ 50% decrease in PSA level in 91% of the patients. Furthermore, a PSA decline of greater than or equal to 50% proved the single most important factor predicting PFS and OS following ^{225}Ac-PSMA-617 treatment. Of interest, median OS of those patients with a PSA decline $\geq$ 50% was not yet reached at the date of latest follow-up (55 months). These very favorable results obtained suggest a prospective randomized study

comparing ^{225}Ac-PSMA-617 to current standard of care treatment options, e.g. enzalutamide, abiraterone acetate and docetaxel, post ADT is of major clinical relevance.

Keywords: ^{225}Actinium-PSMA, ADT, Therapy response, PSA response, prostate carcinoma

INTRODUCTION

Prostate cancer is the second most frequent malignancy (after lung cancer) in men worldwide, accounting for approximately 4.0 % of all deaths caused by cancer in men (*1*,*2*). While the 5-year survival rate of localized prostate carcinoma is nearly 100%, the 5-year survival rate for patients with metastatic prostate carcinoma approximates is only 30% (*3*). Standard of care treatment for metastatic prostate carcinoma is androgen deprivation therapy (ADT) which normalizes serum levels of prostate-specific antigen and produces an objective tumor response in over 90 percent of patients. However, most of the patients suffering from metastatic prostate carcinoma eventually experience disease progression despite initial favorable response to ADT within an average of 18-36 months following treatment initiation (*4*,*5*). Once ADT-resistant or castration-resistant, metastatic prostate carcinoma patients (mCRPC) are treated by other treatment options such as abiraterone acetate, enzalutamide, chemotherapy, ^{223}Radium dichloride, or Sipuleucel-T, the choice of which depends substantially on patient preference, current symptoms burden of disease and local availability (*5*).

Treatment of prostate carcinoma patients in Low Middle Income Countries (LMIC) is challenging. Due to the lack of regular PSA-screening, the majority of prostate carcinoma patients in LMIC present with metastatic disease at initial diagnosis (*6*). In addition, due to fear of associated side-effects, some patients often refuse both ADT and chemotherapy. Furthermore, abiraterone and enzalutamide are not easily accessible to most patients.

^{225}Ac-PSMA-617, targeting the prostate-specific membrane antigen (PSMA) which is overexpressed on prostate cancer cells, has shown a remarkable therapeutic efficacy in heavily pre-treated mCRPC patients (*7*-*11*). When applied in dose-de-escalation fashion, the most prevalent treatment related toxicity associated with ^{225}Ac-PSMA-617 therapy is grade 1-2 xerostomia which makes it an acceptable treatment alternative for LMIC mCRPC patients that refuse chemotherapy because fear of associated side-effects or to whom novel treatment options such as enzalutamide or abiraterone are not readily available.

We previously reported on the favorable treatment outcome and toxicity results obtained using of ^{225}Ac-PSMA-617 therapy in a small group of seventeen patients suffering from metastatic prostate carcinoma (*12*). In this study, we report on treatment outcome and survival using this novel treatment modality in a series of 53 mCRPC patients directly following ADT.

PATIENTS AND METHODS:

This is a retrospective review of patients with histologically confirmed prostate cancer treated with ^{225}Ac-PSMA-617 radioligand therapy (RLT) for mCRPC. In the patients who presented with early-stage disease, primary therapy was by radical prostatectomy, external beam radiotherapy to the prostate gland or brachytherapy. In patients who presented with metastatic disease, initial therapy was by androgen deprivation therapy using surgical or medical castration. Progressive disease for ^{225}Ac-PSMA-617 RLT entry was based on PSA progression: minimum of two rising PSA values from a baseline measurement with an interval of $\geq$ 1 week between each other. Inclusion criteria included metastatic disease precluding treatment with localized therapy such as radiotherapy, patients refusal of chemotherapy and lack of access to second generation anti-androgen therapy such as abiraterone and enzalutamide (patients without medical insurance). Exclusion criteria included urinary tract obstruction and bone marrow suppression (common terminology criteria for adverse events grade 3 or more). The decision to treat patients with ^{225}Ac-PSMA-617 was made in a multidisciplinary setting in our hospital in patients who eventually experience disease progression despite initial favorable response to ADT within an average of 18 months following treatment initiation. At the time of treatment, all patients were aware that ^{225}Ac-PSMA-617 had not yet received regulatory approval for use in the routine care of patients with mCRPC. The patients understood that the treatment was applied on a compassionate ground in patients who refused available life-prolonging treatment options or had no access to these novel therapies. All patients, therefore, provided written informed consent to undergo treatment with ^{225}Ac-PSMA-617 with a full awareness of its possible complications including xerostomia, bone marrow suppression, renal impairment, and potential currently unknown side-effects. The institutional review board (The Research Ethics Committee of the Faculty of Health Sciences, University of Pretoria, Reference number: 173/2021) approved this retrospective study and the requirement to obtain informed consent was waived.

PATIENT PREPARATION

Patients first underwent ^{68}Ga-PSMA-11 PET/CT imaging and were deemed suitable candidates for therapy with ^{225}Ac-PSMA-617 if tracer uptake by the tumor lesions was considered higher than the physiologic tracer uptake in the normal liver parenchyma. Full blood count, liver function tests, electrolytes, urea and creatinine were performed prior to treatment commencement and repeated

two weeks prior to subsequent treatment cycles to determine patients fitness for more treatment cycles. ^{68}Ga-PSMA-11 PET/CT scan was repeated after each subsequent treatment cycle to determine the burden of residual tumor to guide dose de-escalation.

PREPARATION AND ADMININISTRATION of ^{225}Ac-PSMA-617

Radiolabeling of PSMA-617 to ^{225}Ac was done as described previously (*8,12*). The initial administered activity of ^{225}Ac-PSMA-617 was 8 MBq for all patients. For subsequent treatment cycles, administered activity was de-escalated to 7, 6 or 4 MBq based on response to earlier administered treatment assessed on repeat ^{68}Ga-PSMA-11 PET/CT as previously described (*12*). Treatments were repeated every 8 weeks provided continue response is demonstrated, no limiting toxicity developed and residual tumor demonstrating ^{68}Ga-PSMA-11 avidity is shown on PET/CT imaging.

SAFETY

All patients were observed for a minimum of four hours after ^{225}Ac-PSMA-617 administration to detect any immediate side effects. Within two weeks before the first cycle of treatment, all patients had determination of their hemoglobin level, leucocyte count, platelet count, glomerular filtration rate (GFR), and liver function tests for baseline assessment. Except when clinical situations warrants more frequent follow-up, these blood tests were repeated two weeks prior to subsequent cycles of treatment (i.e. every eight weeks). After completion of treatment cycles, these blood tests were repeated every 12 weeks until disease progression or death. Patients who developed toxicity were followed-up until resolution or death. In addition to blood tests, patients reported any observed side effects during treatment or on follow-up. During patients' visit for every cycle of treatment and for follow-up evaluations, each patient was asked about side effects known to occur with PSMA-based radioligand therapy. Toxicity was defined according to the common terminology criteria for adverse events version 5.0 (CTCAE v5.0).

TREATMENT RESPONSE EVALUATION

Treatment response was evaluated using serial measurements of serum PSA values and ^{68}Ga-PSMA-11 PET/CT imaging. ^{68}Ga-PSMA-11 PET/CT images were repeated every 8 weeks, prior to each treatment cycle, and subsequently every 12 weeks following treatment completion until

disease progression or death. PSA response was defined as a PSA decline of $\geq$ 50% of the baseline value, according the Prostate Cancer Working Group 3 (PCWG3) criteria. Follow-up ^{68}Ga-PSMA-11 PET/CT was used to define resolution of initially identified metastatic lesions fulfilling the inclusion criteria on the baseline PET/CT scan. We used PSMA PET/CT criteria to categorize patients as responders or non-responders. The categories of favorable responders included patients with stable disease, partial response, and complete response on PSMA PET/CT imaging; non-responders included patients with progressive disease on PSMA PET/CT (*13*). In this regard a definition of PSMA response as complete in case of disappearance of any lesion with tracer uptake; Partial as reduction of uptake and tumor PET volume by > 30%; Stable as change of uptake and tumor PET volume $\pm \leq$ 30% without evidence of new lesions; Progression as appearance of > 2 new lesions or increase of uptake or tumor PET volume >= 30% (*13*-*15*).

STATISTICAL ANALYSIS

Statistical analysis was performed using the commercially available software package SPSS, version 28.0 (IBM SPSS). The Kolmogorov-Smirnov test was used to check if data were normally distributed. Quantitative variables were compared using a paired student t test and ANOVA when normally distributed, or using a Mann-Whitney test and Kruskal-Wallis test when not normally distributed.

For univariate and regression analysis, we dichotomized values according to the median values in case of continuous variables. We also dichotomized the following clinical covariates: gleason score, number of treatment cycles, the presence of bone-, visceral- and lymph node metastases, PSA reponse ($\leq$ or > 50% reduction), undetectable PSA-levels and normalization of the ^{68}Ga-PSMA-11 scan. Progression-free survival (PFS) and overall survival (OS) were estimated by the Kaplan-Meier method and log rank testing to examine the predictive value of dichotomized variables and other clinical risk factors for disease control and OS. Multivariate analysis was performed using Cox-regression and included in sequential order of statistical significance variables that were found to be significant in the univariate analysis followed by the interactive terms.

Finally, the Chi-square test was used to determine differences in proportion when appropriate.

RESULTS

PATIENTS CHARACTERISTICS

Patient characteristics are shown in table1. Fifty-three mCRPC patients were included in the study. The median age of the patient population under study was 63.4 yrs (range 45-83 years). Twenty-three patients had an Eastern Cooperative Oncology Group (ECOG) score of 0, nineteen patients had an ECOG score of 1 and eleven patients had an ECOG score of 2. Six patients had isolated lymph node involvement (stage IVA disease), the remaining patients all had bone metastases (stage IVB disease) and 6 of these patients also had visceral metastases (1 patient with both brain and liver metastases, 4 patients with liver metastases and 1 patient with lung metastases). Median PSA level pre-treatment was 466 ng/ml (range 102-4405 ng/ml). Mean Hb level was 11.5 g/dl (range 6.1-16 g/dl), median platelet count was 293 000 /µl (range 48000-762000 / µl), mean white blood cell (WBC) count was 7090/µl (range 3100-14870/ µl) and median alkaline phosphatase level was 188 IU/l (range 82-1796 IU/l).

A total number of 167 cycles were administered. The median number of cycles administered was 3 (range 1-7). Seven patients received 1 cycle, 15 patients received 2 cycles, 11 patients received 3 cycles, 11 patients received 4 cycles, 2 patients received 5 cycles, 6 patients received 6 cycles and 1 patient received 7 cycles. Eight patients continued with hormonal treatment, the reason that some patients took hormonal treatment concurrently despite progressive disease under these agents was that their urologist or oncologists did not want to stop these medications because clinical benefit was still assumed.

SAFETY

Administration of ^{225}Ac-PSMA-617 was well tolerated. The commonest toxicity seen was grade I-II dry mouth observed in 81% of patients. No patient with grade III dry mouth was seen and no patient discontinued treatment due to this side effect. No patient with grade IV bone marrow toxicity was seen. Anemia was the most common manifestation of hematotoxicity seen in 15% of patients (7 patients with grade I-II and 1 patients with grade III anemia). Any grade of renal failure was seen in 19% of patients (grade I-II=7, grade III=2, and grade IV=1). The details of toxicity seen in the treated patients is shown in table 2.

RESPONSE TO ^{225}Ac-PSMA-617 THERAPY

Following ^{225}Ac-PSMA-617 treatment, 48 patients (91%) had a PSA decline of $\geq$ 50%, and 51 patients (96%) had any decline in PSA (see Figure 1). PSA became undetectable in 19 patients (36%). ^{68}Ga-PSMA-PET images became negative in 30 patients (57%); that is, avidity was similar to background bloodpool activity in all prostate cancer lesions after treatment with ^{225}Ac-PSMA-617.

OVERALL SURVIVAL

At the time of data analysis, 15 patients (28%) had died and all deaths seemed to be directly related to their underlying mCRPC. In the univariate analysis, only a PSA decline $\geq$ 50% proved significantly associated with a favorable OS ($p< 0.001$) (see table 3). When included in the multivariate analysis with age and Gleason score as covariates, it retained its level of statistical significance ($p < 0.001$). Median estimated OS for patients with a PSA decline < 50% was 9 months whereas the median OS of those patients with a PSA decline $\geq$ 50% was not yet reached at the date of latest follow-up (55 months) (see Figure 2). Overall survival of patients with stage III disease (LN involvement only, 6 patients) proved not significantly different to that of patients with stage IV disease (remaining 47 patients), p=0.186.

PROGRESSION-FREE SURVIVAL

During follow-up, 27 patients (51%) showed disease progression. In univariate analysis, the following parameters proved significantly related to PFS: a PSA decline $\geq$ 50% ($p< 0.0001$), PSA undetectable ($p= 0.014$), platelet count ($p=0.041$), ^{68}Ga-PSMA-11 PET/CT-based response ($p= 0.006$) and a negative ^{68}Ga-PSMA-PET examination ($p= 0.026$), (see table 3 and figures 2). When included in the multivariate analysis, only a PSA decline $\geq$ 50% ($p= 0.002$) and platelet count ($p=0.047$) retained their statistical significance. Estimated median PFS for patients with a PSA decline $\geq$ 50% was 22 months whereas that for patients with a PSA decline < 50% was 4 months. The number of patients that relapsed presenting with a negative PSMA PET scan following treatment (7 out of 23), proved not significantly different from those that relapsed that did not present with a negative PSMA PET scan following treatment (19/30, $p= 0.027$).

DISCUSSION

Various early preclinical and clinical studies have provided a rationale for combining ADT with radiation therapy (RT) for the management of localized prostate cancer (*16*). For instance, in nude mice bearing Shionogi adenocarcinoma allografts, Zietman et al. demonstrated that ADT reduced the dose of RT necessary to control 50% of the tumor and that the timing of ADT is important for achieving this effect; orchiedectomy performed 12 days before RT was significantly more effective than if performed during or after RT (*17*,*18*). In Dunning prostate cancer-bearing rats, temporary ADT for 14 days before RT resulted in a significant lengthening of tumor growth (*19*). Furthermore, ADT was shown to down-regulate expression of vascular expression of growth factor, causing apoptosis of endothelial cells and normalization of tumour vascularization, thereby increasing oxygenation (*20*). Also, in a series of 237 prostate carcinoma patients, Milosevic et al. identified a broad heterogeneity in prostate cancer oxygenation, a prerequisite for RT efficacy, with median p02 values ranging from 0 to 75 mmHg (*20*). Based on these studies, various randomized phase III trials have been conducted that showed a significant clinical benefit of adding ADT to RT when treating intermediate-risk primary prostate carcinoma (*21*). As opposed to the beneficial RT-enhancing effects of short-term ADT administered in combination with RT for treatment of primary intermediate prostate carcinoma, long term ADT administration in the metastatic setting resulting in androgen independence is often characterized by a remarkable resistance to treatment options that trigger apoptosis via the caspase cascade including radiation therapy. Various factors responsible for radiation-resistance in androgen-independent prostate carcinoma have been implicated including, amongst others, increased levels of interleukin-6, neuroendocrine differentiation, Ack-1 androgen receptor phosphorylation, the existence of intrinsic cancer stem cells, and epithelial-mesenchymal transition (*22*-*25*).

In the series presented, 91% of mCRPC patients had a $\geq$ 50% PSA reduction of their initial PSA value following ^{225}Ac-PSMA-617 treatment and both baseline PSA values as well as alkaline phosphatase levels proved not significantly different between responders and not responders. This value exceeds by far those derived from early clinical studies demonstrating a $\geq$ 50% PSA reduction in a total of approximately 10% of patients treated with ipilimumab, sunitinib, cabozantinib or Xofigo and approximately 30%, 40% and 50% of patients treated with abiraterone,

cabazitaxel or enzalutamide, respectively (*26*). Our findings suggest that radiation resistance to alpha-emitting agents following ADT is not a significant issue, as is the case when compared to, for instance, beta-emitting agents in some patients. In this regard, reported response rates of mCRPC patients to ^{177}Lu-PSMA-617 have varied from 10.6-69% (*27*). While these response rates were obtained in heterogeneous patient cohorts, receiving various other treatments following ADT, lower response rates to ^{177}Lu-PSMA-617 as opposed to ^{225}Ac-PSMA-617 may be anticipated given the low linear energy transfer value of 0.7 keV/micron of ^{177}Lu when compared to the 100keV/micron linear energy transfer value of ^{225}Ac (*28*). The high linear energy transfer value of ^{225}Ac results in a high level of radiobiological effectiveness when compared to beta-radiation, requiring fewer particle tracks to induce cell death via induction of predominant deoxyribonucleic acid-strand breaks amongst others, obviating the need for cellular oxygen in order to induce its therapeutic effect (*27,29*). Although Xofigo is also an alpha therapy targeting bone lesions only, it will most likely have lesser success than ^{225}Ac-PSMA-617 which targets both soft-tissue and bone lesions. This is also supported by recent information that both nodal and visceral metastases have been underestimated and understudied in advanced prostate cancer patients and the fact that visceral metastases invariably have a worse prognosis than patients with bone-only metastases (*30*).

In our series, hemoglobin-levels, a surrogate marker for molecular oxygen level, proved unrelated to treatment outcome. Furthermore, part of the high PSA-response observed in our series may be due to the "abscopal effect", attributed to irradiation induced immune mechanisms such as exposure of tumor antigen, increased maturation of antigen-presenting cells taking up antigen released by dying cells, production of interleukin-6 and tumor necrosis factor-alpha as well as changes in the tumor microenvironment for improved recruitment of effector T-cells (*31*). In this regard, Gorin et al. evaluating an alpha-emitting ^{231}Bismuth-labeled antibody for tumor cell irradiation of mice-xenograft found that the treatment induced a protective antitumor effect by induction of tumor specific T cells against a secondary tumor cell injection (*32*). Furthermore, Czernin and colleagues showed, in a mouse model of mCRPC, that a combination of ^{225}Ac-PSMA-617 and an inhibitor of PD-1 (program death-1) achieved better tumor control than monotherapy with either agent alone (*33*). In our series, two patients proved unresponsive to ^{225}Ac-PSMA-617 treatment in spite of high uptake of the ligand on the baseline scan. As shown by Kratochwil et al.,

in such patients mutations in DNA-damage repair and checkpoint genes are frequently found. Future studies assessing the role of DNA damage-repair-targeting agents in combination with ^{225}Ac-PSMA-617 therapy in overcoming radiation resistance in these patients are of interest (*34*).

A PSA decline of ≥ 50% to assess efficacy of treatment, as recommend by the PCWG3, proved the single most important factor predicting PFS and OS following ^{225}Ac-PSMA-617 treatment in our patient cohort. The importance of PSA decline was also demonstrated in our previous study (*35*). Median estimated PFS was 4 months for non-responders and 22 months for responders. While median OS in the non-responding group was 9 months, at the time of last follow-up (55 months), median overall survival was not yet reached (see figure 2). To this effect, a first patient exceeding 5-year complete remission after ^{225}Ac-PSMA-TAT in a chemotherapy-naïve patients was reported in Germany (*36*). Overall, our OS data in this small cohort suggest superior efficacy of ^{225}Ac-PSMA-617 when compared to chemotherapy, enzalutamide and abiraterone acetate or docetaxel administered in a comparable setting (post-ADT mCRPC patients having received no other treatment targeting their mCRPC) (*28-32*). Regarding the use of docetaxel in the mCRPC setting, two large phase three randomized controlled trials published in 2004, respectively the TAX327 and SWOG9916 trial, found a median overall survival of 18.9 months versus 16.5 months and 17.5 months versus 15.6 months for the control group receiving respectively mitoxantrone, considered standard of care at that moment (*37,38*). In the COU-AA-302 trial, comparing abiraterone acetate (1000 mg one daily) plus prednisone or placebo plus prednisone in a group of 1048 patients randomly assigned to receive either of both treatment options, median overall survival for patients in the abiraterone acetate group was 34.7 months (*39*). With regard to enzalutamide, in the double-blind, phase 3 PREVAIL trial in which 1717 patients were randomly assigned to receive either enzalutamide at a dose of 160 mg or placebo once daily, median estimated overall survival for the enzalutamide treated group was 32.4 months versus 30.2 months for the placebo group (median duration of follow-up for survival was approximately 22 months) (*40*). Recently TheraP trial demonstrated that ^{177}Lu-PSMA-617 compared with cabazitaxel in men with metastatic castration-resistant prostate cancer led to a higher PSA response and fewer grade 3 or 4 adverse events. ^{177}Lu-PSMA-617 is a new effective class of therapy and a potential alternative to cabazitaxel (*41*). Although not directly comparable between earlier and later stage application of ^{225}Ac-PSMA-617 or ^{177}Lu-PSMA-617, a couple of studies have shown a better

response of PRLT with ^{177}Lu-PSMA-617 in the chemotherapy-naïve patients (*42*). Furthermore, our group reported a unique cohort of chemotherapy-naïve men with mCRPC who had upfront treatment with ^{225}Ac-PSMA-617 (12), and demonstrated a remarkable 88% serum PSA declined by 50% or more after a median of three cycles of ^{225}Ac-PSMA-617, which is corroborated by this current series. This is in contrast to an average of 65.4% serum PSA declined by 50% in studies where there was a later stage application of ^{225}Ac-PSMA-617 or ^{177}Lu-PSMA-617 (*8-18,30*). While this remarkable response is exciting and holds much promise for applying ^{225}Ac-PSMA-617 in treating men with mCRPC, it may also represent a response achieved in less aggressive disease (*42*). mCRPC evolves, acquiring more aggressive behavior as different lines of treatments are applied to it. Additionally, of the patients presenting with liver metastasis, none presented with a negative PSMA PET scan following treatment nor responded favorably to the treatment as was also negatively correlated with OS in other studies (*30*). Thus, randomized controlled trials will be needed in the future to stratify patients to either ^{177}Lu-PSMA-617 or ^{225}Ac-PSMA-617 so that the better therapy is administered in the treatment sequence when it is likely to have the best impact.

Finally, in our study, a high platelet count also proved significantly negatively related to PFS. While the role of platelets is to stem blood loss after vascular injury, available data suggest that platelets may also interact with tumor cells and endothelial cells enabling metastases and thereby worsening prognosis of cancer patients (*43-45*). More specifically, platelets were shown to play a role in shielding tumor cells from immune elimination and in promoting arrest and extravasation of tumor cells and in protecting cancer cells from undergoing apoptosis. Furthermore, experimental data suggest that thrombocytosis is induced by tumor-derived growth factors. Finally, a high pretreatment baseline platelet count has been previously associated with a poor prognosis in patients suffering from ovarian, breast, lung, renal, colorectal and pancreatic carcinoma (*46*).

In terms to of the safety profile, xerostomia remains an adverse effect of concern and the majority of our patients experienced dry mouth commonly seen after the first cycle of treatment. To reduce the incidence and severity of treatment-induced xerostomia we still practiced the treatment de-escalation strategy. Administered activity is reduced to 6 or 4MBq in subsequent treatment cycles according to the volume of residual tumor load. This strategy is based on the principle of tumor

sink effect in which more radioligand is available for binding in normal organs with reducing tumor bulk induced by successful treatment (*47*). Like we reported previously, we believe that this strategy is partially successful as none of our patients has experienced grade III xerostomia or discontinued ^{225}Ac-PSMA-617 therapy due to dry mouth (*12*,*35*). Although anemia was also relatively a common toxicity (15%), no other grade 3/4 hematotoxicities were noted. Notably, only three patients experienced grade III-IV renal function impairment. All this three patients presented with suboptimal renal function prior to the ^{225}Ac-PSMA-617 therapy. This finding warrants medium to long term monitoring of renal function of patients treated with ^{225}Ac-PSMA-617.

Limitations: This study is a retrospective study and as a consequence bears all the disadvantages of such types of studies, including in this specific setting the lack of a control group. However, the very favorable results obtained suggest a prospective randomized study comparing ^{225}Ac-PSMA-617 to standard of care treatment options, e.g. enzalutamide, abiraterone acetate and docetaxel, post ADT is of major clinical relevance.

CONCLUSION: In this series of 53 patients suffering from mCRPC receiving ^{225}Ac-PSMA-617 therapy subsequent to their ADT resulted in a > 50% decrease in PSA level in 91% of the patients. A PSA decline of greater than or equal to 50% proved the single most important factor predicting PFS and OS following ^{225}Ac-PSMA-617 treatment. Median estimated PFS was 4 months for non-responders and 22 months for responders and median OS in the non-responding group was 9 months while at the time of last follow-up (55 months), median overall survival was not yet reached in the responding group. ^{225}Ac-PSMA-617 is a highly promising option for therapy of mCRPC directly following ADT and warrants further study in randomized trials.

DISCLOSURES

All authors disclose that they have no conflict of interest.

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KEY POINTS

QUESTION: What is the efficacy of ^{225}Ac-PSMA-617 in the post-ADT setting in men with mCRPC?

PERTINENT FINDINGS: ^{225}Ac-PSMA-617 administered in the post-ADT setting in men with mCRPC resulted in PSA response in 91% of patients and producing an undetectable level of serum PSA in 36% of patients. Decline in serum PSA of ≥50% was significant associated with a longer overall survival. PSA decline of ≥50%, low pre-treatment platelet level, and radiographic response on ^{68}Ga-PSMA-11 PET/CT were significant predictors of a longer progression-free survival.

IMPLICATIONS FOR PATIENT CARE: ^{225}Ac-PSMA-617 is a viable treatment option that may be considered in men who develop mCRPC after ADT, especially if approved treatment options are not available or contraindicated.

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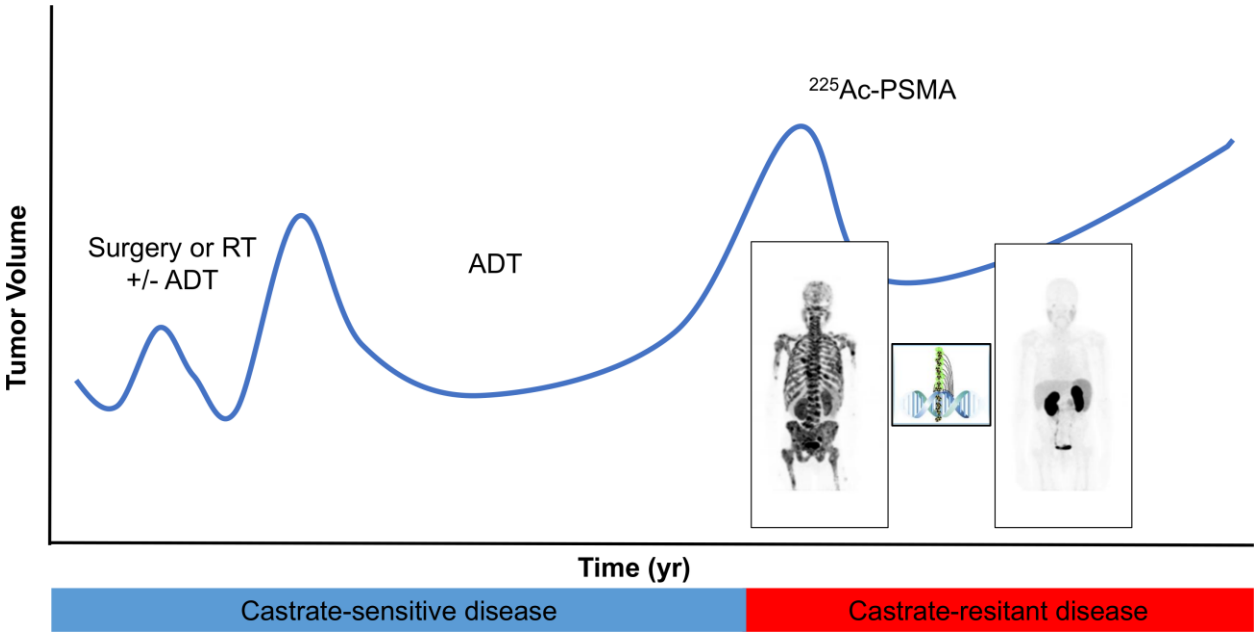
Graphical Abstract



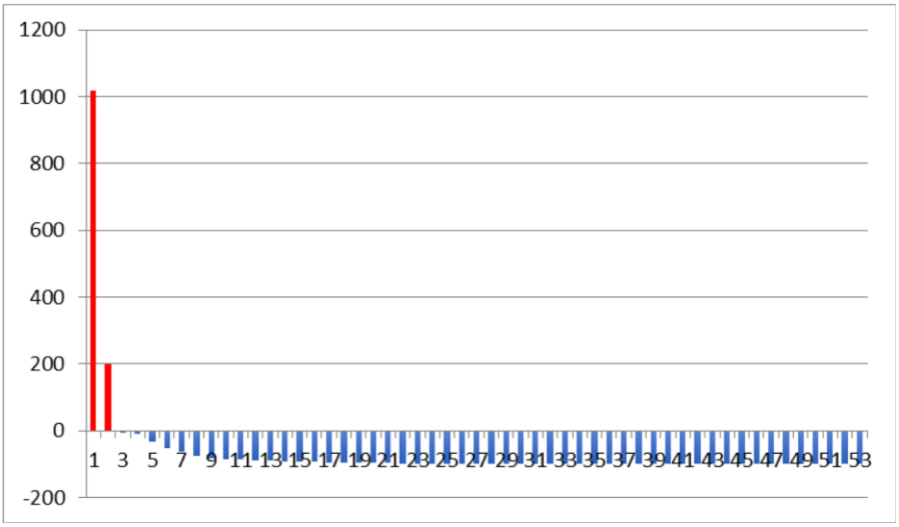


Figure 1. Waterfall plot demonstrating percentage change in PSA levels after treatment with 225Ac-PSMA-617 in the patient cohort (x-axis = number of patients, Y-axis = percentage change).

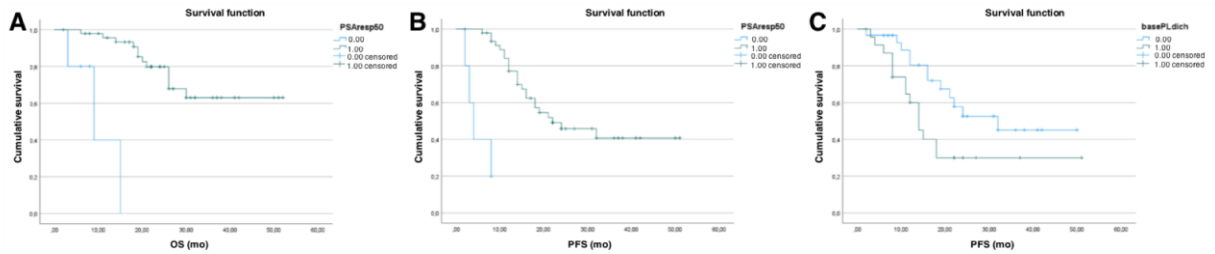


Figure 2. Kaplan–Meier curves of (A): PSA-based overall survival of the entire cohort; (B): progression-free survival of the entire cohort (PSA decline of $\geq$ 50% (green curve) and percentage of PSA decline < 50% (blue curve)); (C): progression-free survival stratified by platelet counts (green: partial remission (PR); red: progressive disease (PD) or stable disease (SD)). (platelet counts < 293000/ml (blue curve) and platelet counts > 293000 (green curve))

Table 1. Patient characteristics

Characteristics	Value
No. of patients included	53
Median age (yrs)	63.4
ECOG score of 0 or 1 (n)	42
ECOG score of 2 (n)	11
Median PSA level (ng/ml)	466
Median alkaline phosphatse level (IU/l)	188
Median Hemoglobin value (g/dl)	11.5
Bone metastases (n)	47
Lymph node metastases (n)	36
Visceral metastases (n)	6
Lung	1
Liver	5
Brain	1
Local therapy to prostate (n)	
Prostatectomy	31
Radiation therapy	11
No local therapy	11

Table 2. Toxicity Profiles of 73 Patients Treated with ^{225}Ac-PSMA-617

	Grade I-II	Grade III	Grade IV
Xerostomia	43 (81%)	0	0
Anemia	7 (13%)	1 (2%)	0
Leucopenia	4 (7%)	1 (2%)	0
Thrombocytopenia	5 (9%)	0	0
Renal failure	7 (13%)	2 (4%)	1 (2%)

Table 3. Univariate analysis of the relationship between studied variables and survival. Relevant p-values (< 0.05) are highlighted in bold.

Variable	**PFS**	**OS**
Age	0.180	0.748
ECOG score	0.077	0.772
Gleason Score	0.596	0.774
Previous local radiotherapy	0.304	0.916
Baseline PSA level	0.972	0.888
PSA $\geq$ 50% decline	**< 0.001**	**< 0.001**
PSA undetectable	**0.014**	0.132
Visceral metastases	0.937	0.772
LN involvement	0.289	0.942
Bone metastases	0.459	0.186
Nb of treatment cycles	0.650	0.097
ALP	0.727	0.886
Hemoglobin	0.090	0.132
Platelet count	**0.041**	0.602
WBC count	0.373	0.605
Radiological response	**0.006**	0.407
PSMA negative	**0.026**	0.418