Hematologic toxicity profile and efficacy of [^{225}Ac]Ac-PSMA-617 α-radioligand therapy of patients with extensive skeletal metastases of castration-resistant prostate cancer

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Abstract

Purpose: Actinium-225-labeled prostate-specific membrane antigen ([^{225}Ac]Ac-PSMA-617) is safe and effective in the treatment of metastatic castration-resistant prostate cancer (mCRPC). No study has specifically assessed its safety in patients with extensive skeletal metastases of mCRPC. We aimed to investigate the hematologic toxicity and efficacy of [^{225}Ac]Ac-PSMA-617 therapy in patients with extensive skeletal metastases of mCRPC.

Methods: We retrospectively reviewed the medical record of patients treated with [^{225}Ac]Ac-PSMA-617 for mCRPC. We included patients with a superscan pattern of skeletal metastases and those with 20 or more multifocal sites of skeletal metastases on baseline [^{68} Ga]Ga-PSMA-11 PET/CT. We reviewed the levels of hemoglobin, white blood cell (WBC), and platelet prior to each cycle of treatment and determined the presence of impaired bone marrow function at baseline and the grade of toxicity in the hematologic parameters induced by treatment. We evaluated the predictors of hematologic toxicity using binary logistic regression analysis. We also determined the presence of renal dysfunction before or during treatment. We assessed response to treatment using prostate-specific antigen response and the progression-free survival (PFS) and overall survival (OS).

Results: A total of 106 patients were included. Skeletal metastasis was in the superscan pattern in 34 patients (32.1%) and multifocal in 72 patients (67.9%). The median treatment cycle was 4 (range = 1–9). Ninety-eight patients (92.5%) had abnormal baseline hematologic parameters. One patient had grade 4 thrombocytopenia. Grade 3 anemia, leukopenia, and thrombocytopenia were seen in 1 (0.9%), 3 (2.8%), and 2 (1.9%) patients, respectively. Age,

the number of treatment cycles, and the presence of renal dysfunction were significant predictors of hematologic toxicity. Eighty-five patients (80.2%) achieved PSA response. The median PFS and OS of the study population were 14:00 (95%CI: 8.15–19.86) months and 15.0 (95%CI: 12.8–17.2) months, respectively.

Conclusions: [^{225}Ac]Ac-PSMA-617 induces a good anti-tumor effect in about 80% of patients with extensive skeletal metastases of mCRPC with a rare incidence of severe hematologic toxicity. Age, number of treatment cycles, and the presence of renal dysfunction were significant risk factors for hematologic toxicity of [^{225}Ac]Ac-PSMA-617 therapy.

Keywords: Targeted alpha therapy; [^{225}Ac]Ac-PSMA; Superscan; Skeletal metastases; Prostate cancer; Hematologic toxicity

Introduction

The skeletal system is one of the systems that bear the highest burden of prostate cancer metastases. The incidence of skeletal metastases increases with the increasing stage of the disease [1]. The skeletal system may be the only site of distant prostate cancer metastases in up to 62% of patients and often with a multifocal pattern of involvement [2, 3]. The presence of skeletal metastases is predictive of an unfavorable outcome of prostate cancer treatment, including shorter time to treatment failure, poorer overall survival, and poor quality of life resulting from the occurrence of skeletal-related events [2, 4]. In addition to drug therapies such as chemotherapy with docetaxel and cabazitaxel and next-generation anti-androgen therapy with abiraterone and enzalutamide with activity against soft tissue and skeletal metastases of metastatic castration-resistant prostate cancer (mCRPC) [5,6,7,8], radium dichloride has also been shown to prolong survival in patients with bone-only or bone-predominant metastases of prostate cancer [9]. Despite the availability of these life-prolonging therapy agents, mCRPC remains a highly fatal stage of prostate cancer, creating a need for newer alternative treatment agents.

The availability of ligands for prostate-specific membrane antigen (PSMA) overexpressed on prostate cancer cells and their successful labeling to therapeutic radionuclides have made PSMA radioligand therapy become an attractive treatment modality in mCRPC. The efficacy and safety of Lutetium-177 PSMA [^{177}Lu]Lu-PSMA in the treatment of mCRPC have been shown in studies reporting data from real-world practice and clinical trials [10,11,12,13,14,15]. Hematologic toxicity is one of the commonest treatment-induced side effects from [^{177}Lu]Lu-PSMA-617 therapy of mCRPC [16]. Several factors contribute to the hematologic toxicity of [^{177}Lu]Lu-PSMA-617 radioligand therapy, including the preponderance of skeletal metastases of prostate cancer and the longer path length of the beta particles emitted by Lutetium-177. Actinium-225 is an alpha-emitting therapy radionuclide that has been successfully labeled to PSMA ligands [16]. Following early promising results from the Heidelberg group in Germany [18,19,20], our group and others have reported the safety and efficacy of [^{225}Ac]Ac-PSMA-617 in mCRPC patients in different clinical settings [21,22,23,24,25,26]. Due to the shorter path length of alpha particles in tissues, [^{225}Ac]Ac-PSMA-617 has been advocated, where available, for the treatment of patients with extensive skeletal metastases of mCRPC with the goal of protecting the bone marrow from treatment-induced toxicities [27, 28]. To date, no study has specifically reported the hematologic toxicity profile and efficacy of [^{225}Ac]Ac-PSMA-617 in patients with extensive skeletal

metastases of mCRPC. Therefore, this study aimed to investigate the hematologic toxicity and efficacy of targeted alpha therapy with [^{225}Ac]Ac-PSMA-617 in patients with extensive skeletal metastases of mCRPC.

Methods

This is a retrospective study of patients with mCRPC treated with [^{225}Ac]Ac-PSMA-617 at the Department of Nuclear Medicine, Steve Biko Academic Hospital, Pretoria, South Africa between April 2017 and September 2021. All patients had a baseline [^{68} Ga]Ga-PSMA-11 PET/CT scan prior to therapy. For inclusion in this study, we identified patients with extensive skeletal metastases alone or in addition to soft tissue metastases in the lymph nodes and visceral organs on the baseline [^{68} Ga]Ga-PSMA-11 PET/CT scan. We defined extensive skeletal metastases as either a diffuse pattern of axial skeletal involvement with or without appendicular skeletal involvement in the typical pattern of a superscan [29] or a multifocal pattern of skeletal metastases. For a patient with a multifocal pattern of skeletal involvement to qualify for inclusion in this study, 20 or more foci of skeletal metastases must be present. In the patients treated, [^{225}Ac]Ac-PSMA-617 was applied on compassionate ground to patients who have exhausted treatment options available to them in the context of our practice. Therefore, no strict exclusion criteria were applied in selecting patients for treatment. To qualify for treatment, however, all lesions due to prostate cancer metastases must demonstrate tracer avidity above background activity in normal liver tissue on the baseline [^{68} Ga]Ga-PSMA-11 PET/CT scan. Patients who had only received one cycle of [^{225}Ac]Ac-PSMA-617 and had no full blood count results evaluating the impact of treatment on their hematologic profile were excluded from this study. The decision to treat patients was based on the outcome of a multidisciplinary discussion. All patients gave written informed consent to undergo treatment with [^{225}Ac]Ac-PSMA-617. The Human Research Ethics Committee of the Faculty of Health Sciences, University of Pretoria approved this study (Ethics Reference Number: 173/2021).

Treatment administration

[^{225}Ac]Ac-PSMA-617 was prepared in-house as previously reported [17, 19]. All patients received 8 MBq of [^{225}Ac]Ac-PSMA-617 at the beginning of treatment. This treatment activity was an extrapolation from the 100 kBq/kg recommended in the dosimetry analysis of Kratochwil and colleagues assuming an 80-kg man [19]. Details regarding the administration of [^{225}Ac]Ac-PSMA-617 are as previously published [30]. Due to the high burden of disease in the patients treated with [^{225}Ac]Ac-PSMA-617, we administer 8 MBq for the first and second treatment cycles. For the third and subsequent treatment cycles, we used the residual tumor burden on the repeat [^{68} Ga]Ga-PSMA-11 PET/CT obtained prior to each treatment cycle to determine the activity of [^{225}Ac]Ac-PSMA-617 to administer for treatment. When a patient has responded to prior treatment cycles and has moderate residual tumor burden (less than 10 tumor foci without metastatic lesions in soft tissue visceral or conglomerate of lymph node metastasis), we gave 6 MBq of [^{225}Ac]Ac-PSMA-617 for treatment. For patients with minimal residual metastatic lesions (less than 5 foci of metastatic disease, no visceral metastases, and no conglomerate of metastatic nodal disease), we gave 4 MBq of [^{225}Ac]Ac-PSMA-617 for treatment. Treatment was administered every 8 weeks. We continued treatment administration provided a patient had residual disease on [^{68} Ga]Ga-PSMA-11 PET/CT scan, no evidence of disease progression per PSA or PET/CT imaging findings, and no serious adverse effects of treatment. Following completion of treatment, patients were followed up with serial PSA measurements every 3 months and [^{68} Ga]Ga-PSMA-11 PET/CT

scan every 6 months to assess for disease recurrence. The patients were also followed up by their oncologist. We defined the follow-up period as the time from treatment completion until the date of last communication with patient/clinic visit or date lost to follow-up or date of death.

Assessment of hematologic toxicity of [^{225}Ac]Ac-PSMA-617

All patients had a baseline full blood count within 2 weeks of the first treatment cycle. We perform a repeat full blood count within 2 weeks of each subsequent treatment cycle. Patients who developed grade 3 more toxicity in their hematologic profile were followed up with a more frequent repeat of full blood count as deemed necessary. We compared the baseline levels of hemoglobin, white blood cell (WBC) count, and platelets count with the levels obtained after each subsequent treatment cycle to determine the grade of hematologic toxicity induced by treatment. For each patient, the grade of toxicity was determined by the lowest level of hematologic indices recorded during treatment. We performed the grading of hematologic toxicity of [^{225}Ac]Ac-PSMA-617 according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 [31]. We defined significant treatment-induced hematologic toxicity as a one-grade decline in the level of at least two of the three peripheral blood indices (hemoglobin level, WBC count, or platelet count) or a two-grade decline in any one of the three indices of peripheral blood cell levels. We described patients with hemoglobin level, WBC count, or platelet count below the lower limit of normal (less than 13.4 g/dL, 3.92×10^9 /L, and 171×10^9 /L, respectively) on the baseline full blood count assessment to have baseline bone marrow dysfunction. We determined the proportion of patients who developed renal dysfunction at baseline or during treatment. We defined renal dysfunction as an estimated glomerular filtration rate (eGFR) of less than 60 mL/min/1.73 m^2 body surface area.

Assessment of efficacy of [^{225}Ac]Ac-PSMA-617

All patients had a baseline assessment of their prostate-specific antigen (PSA) serum levels. We repeated the assessment of serum PSA level within 2 weeks of each subsequent treatment cycle. We dichotomized patients into those who achieved PSA response and those who did not. We defined PSA response as those patients who achieved a PSA decline of 50% or more as per the recommendation of the Prostate Cancer Clinical Trials Working Group (PCWG1) [32]. We also determined treatment efficacy in terms of progression-free survival (PFS) and overall survival (OS). We defined PFS as the time from the day of the first treatment cycle to PSA progression as per the PCWG3 criteria [33], death, or last contact with the patient. We defined overall survival as the time from the day of first treatment cycle administration to death or the day of the last contact with the patient.

Statistical analysis

We performed descriptive statistics of the baseline clinical and demographic characteristics of the patients included in the study. We performed univariate and multivariate logistic regression to determine factors that significantly predict the occurrence of hematologic toxicity in patients with extensive skeletal metastases of mCRPC who were treated with [^{225}Ac]Ac-PSMA-617. We used Kaplan–Meier curve analysis to estimate the median PFS and OS of the entire study population as well as sub-groups of the study population. We used log-rank analysis to compare the median PFS and OS in patients with superscan pattern of skeletal metastases versus the multifocal pattern of skeletal metastases and patients with

bone-only metastases versus bone plus soft tissue metastases of mCRPC. We also used log-rank analysis to compare median PFS and OS in patients who achieved PSA response versus those who did not. We set statistical significance at a p-value of < 0.05. We used IBM SPSS Statistics (IBM Corp., Armonk, NY) for statistical analysis.

Results

A total of 106 men with a mean age of 68.98 ± 8.43 years who were treated with [^{225}Ac]Ac-PSMA-617 for mCRPC with extensive skeletal metastases were included. The median Gleason score at prostate cancer diagnosis was 8 (range = 6–19). Forty-nine patients (46.2%) had primary therapy for their prostate cancer with radical prostatectomy ($n = 23$) or radiation therapy ($n = 26$). In 57 patients (53.8%), prostate cancer was metastatic at diagnosis, and no primary treatment of the local disease was given. All patients experienced disease progression on androgen deprivation therapy with either surgical castration or anti-androgen therapy (ADT)—mCRPC. Docetaxel was the most common agent offered to the patients for the treatment of mCRPC (45.3%). In 34 patients (32.1%), skeletal metastasis was in the superscan pattern, while 72 patients (67.9%) had the multifocal pattern of extensive skeletal metastases. In addition to skeletal metastases, 64 patients (60.4%) and 16 patients (15.1%) had associated lymph node and visceral metastases, respectively. The median treatment cycle administered to the patients was 4 (range = 1–9). Table 1 shows the details of the patients' baseline clinical and demographic characteristics. Abnormalities in hematologic indices were prevalent in the study population, with 98 patients (92.5%) having at least one hemoglobin, WBC count, or platelet count below the lower normal limit prior to therapy commencement (Table 1).

Table 1. Baseline clinical and pathological characteristics of the patients

Variable	Frequency	Percent
Age		
Mean ± SD	68.98 ± 8.43	
Range	44–86	
Gleason score		
Median (Range)	8 (6–10)	
Primary treatment		
No primary treatment	57	53.8
Radical prostatectomy	23	21.7
Radiation therapy	26	24.5
Prior treatment for mCRPC		
Docetaxel	48	45.3
Cabazitaxel	6	5.7
Abiraterone	7	6.6
Enzalutamide	8	7.5
Radium dichloride	2	1.9
[^{177}Lu]Lu-PSMA-617	7	6.6
Type of skeletal metastasis		
Superscan	34	32.1
Multifocal skeletal metastases	72	67.9
Lymph node metastases		
Yes	64	60.4
No	42	39.6
Visceral metastasis		
Yes	16	15.1
No	90	84.9
Number of treatment cycles		
1	2	1.9
2	25	23.6
3	25	23.6
4	16	15.1
5	12	11.3
6	20	18.9
7	3	2.8
8	2	1.9
9	1	0.9
Median (range)	4 (1–9)	
Baseline bone marrow dysfunction		
None	8	7.5
Anemia alone	68	64.2
Anemia and leukopenia	6	5.7
Anemia, leukopenia, and thrombocytopenia	3	2.8
Anemia and thrombocytopenia	17	16.0
Leukopenia alone	1	0.9
Thrombocytopenia alone	3	2.8
Hemoglobin (baseline), g/dL		
Median (IQR)	10.65 (9.20–12.13)	
White blood cell count (baseline) × 10^9/L		
Median (IQR)	6.10 (4.61–8.20)	
Platelet count (baseline) × 10^9/L		
Median (IQR)	229.50 (173.50–340.00)	

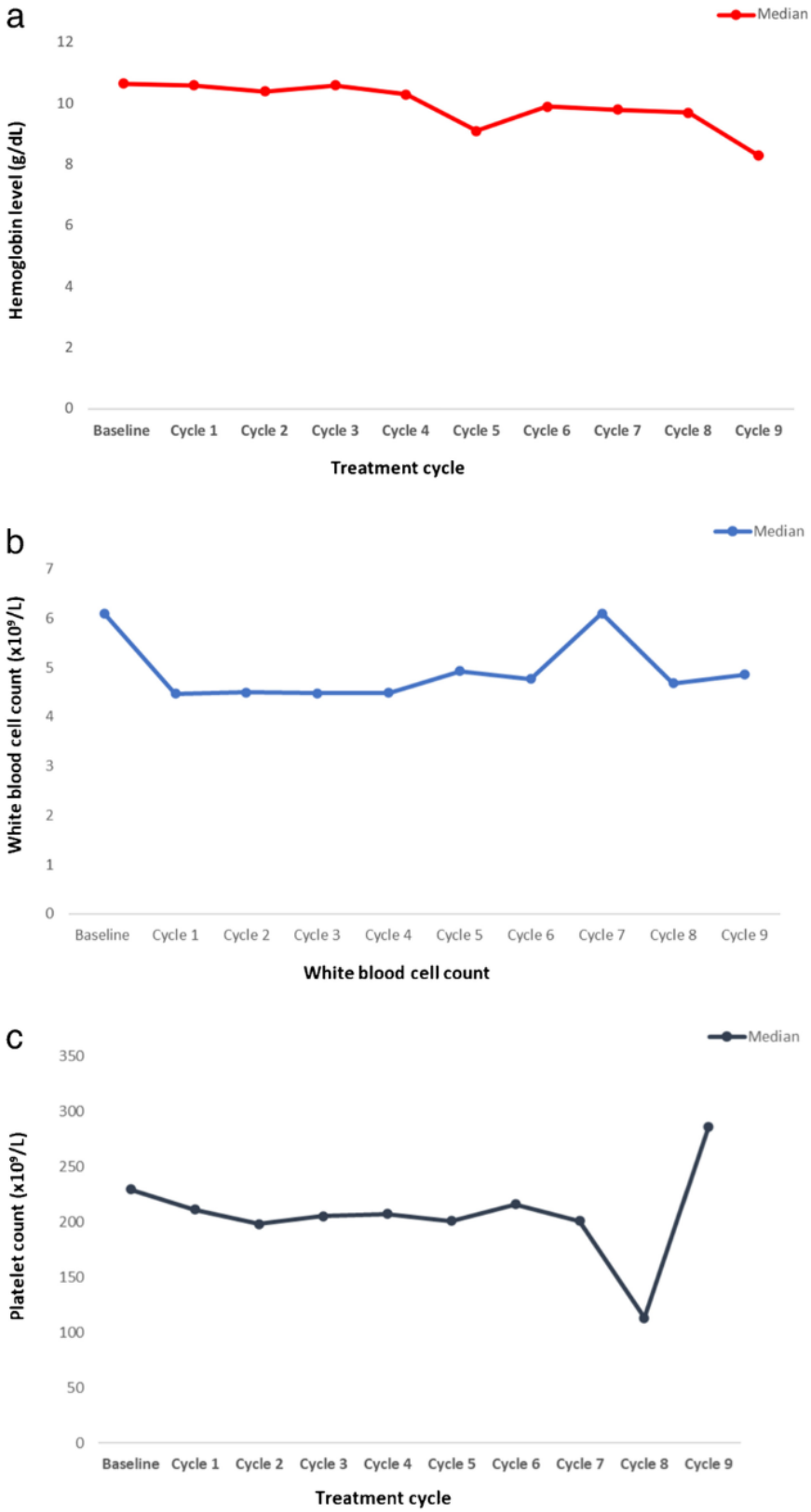

Fig. 1. Trajectories of the median levels of (**a**) hemoglobin, (**b**) white blood cell count, and (**c**) platelets count from baseline through the duration of [^{225}Ac]Ac-PSMA-617 treatment of patients with extensive skeletal metastases of castration-resistant prostate cancer

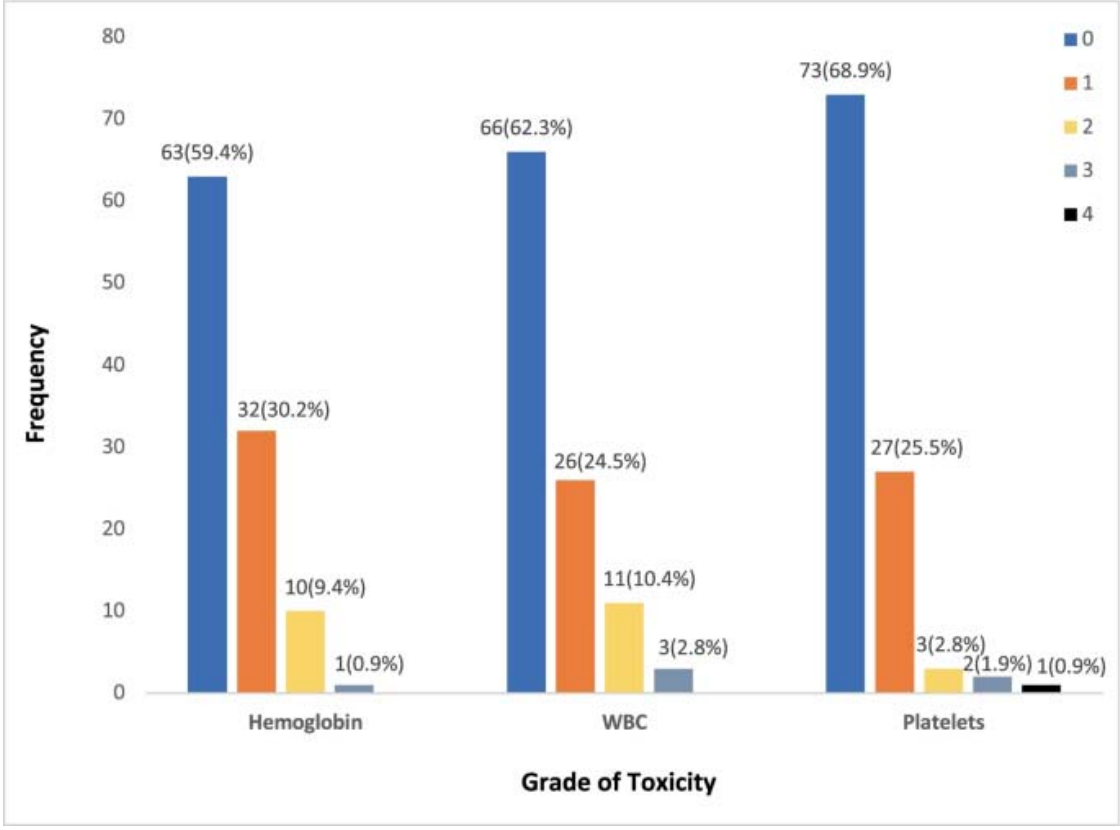

Fig. 2. Chart showing the frequency of [^{225}Ac]Ac-PSMA-617-induced toxicity to hemoglobin, white blood cell, and platelets levels during treatment of patients with extensive skeletal metastases of castration-resistant prostate cancer

Hematologic toxicity due to [^{225}Ac]Ac-PSMA-617 therapy

During treatment, the median levels of hemoglobin, WBC count, and platelet count stayed fairly stable (Fig. 1a–c). Only one patient had a grade 4 thrombocytopenia. No grade 4 or higher level of anemia or leukopenia was seen. Grade 3 anemia, leukopenia, and thrombocytopenia were seen in 1 (0.9%), 3 (2.8%), and 2 (1.9%) patients respectively. In 63 (59.4%), 66 (62.3%), and 73 (68.9%) patients, blood levels of hemoglobin, WBC, and platelets remained stable (grade 0 toxicity) throughout treatment, respectively (Fig. 2).

We performed a univariate analysis to assess the impact of the following on the occurrence of hematologic toxicity: age, baseline abnormality in hematologic indices, presence of renal dysfunction at baseline or during the treatment, history of prior treatment with bone marrow-suppressing agents (docetaxel, cabazitaxel, radium dichloride, and [^{177}Lu]Lu-PSMA-617), PSA response, the number of treatment cycles administered, the pattern of skeletal metastases, and the presence of soft tissue metastases in addition to skeletal metastases. In the analysis, we found age, the presence of renal failure, and the number of treatment cycles administered to be significant predictors of the occurrence of hematologic toxicity among patients with extensive skeletal metastases who were treated with [^{225}Ac]Ac-PSMA-617 (Table 2). These three factors remained significant predictors of treatment-induced hematologic toxicity in a multivariate analysis.

Table 2. Predictors of significant hematologic toxicity to [^{225}Ac]Ac-PSMA-617 therapy of castration-resistant prostate cancer with extensive skeletal metastases

Variable	Univariate analysis					Multivariate analysis				
	B	*p* value	OR	95% CI		B	*p* value	OR	95% CI	
				Lower	Higher				Lower	Higher
Age	−0.051	**0.040**	0.950	0.905	0.998	−0.057	**0.040**	0.944	0.894	0.997
Baseline abnormality in hematologic indices										
Yes	1.658	0.128	5.250	0.622	44.317					
No			1							
Renal failure										
Yes	1.217	**0.004**	3.378	1.480	7.710	1.047	**0.024**	2.849	1.149	7.064
No			1					1		
Prior therapy with BM suppression drug										
Yes	0.049	0.902	1.050	0.483	2.281					
No			1							
PSA response										
Yes	0.656	0.216	1.927	0.682	5.448					
No			1							
Number of treatment cycle	0.498	**<0.001**	1.646	1.267	2.137	0.471	**0.001**	1.601	1.210	2.119
Type of skeletal metastasis										
Multifocal skeletal metastases	−0.037	0.930	0.963	0.420	2.209					
Superscan			1							
Metastasis										
Bone alone	−0.310	0.456	0.734	0.325	1.655					
Bone and soft tissue			1							

B, coefficient of binary logistic regression; *BM*, bone marrow

Efficacy of [^{225}Ac]Ac-PSMA-617 therapy

The median baseline PSA was 250.2 ng/mL (range = 2.8–4494.0). A total of 85 patients (80.2%) achieved PSA response (PSA decline of 50% or more), while 21 patients (19.8) failed to achieve a PSA decline of at least 50% during treatment with [^{225}Ac]Ac-PSMA-617 therapy (Fig. 3). The median follow-up period was 8 months (range = 2–39). During follow-up, 54 patients (50.9%) experienced disease progression, while 81 patients (76.4%) died from their disease. The median PFS and OS for the entire study population were 14:00 (95%CI: 8.15–19.86) and 15.0 (95%CI: 12.8–17.2) months, respectively (Supplementary figure). The median PFS for patients with a superscan pattern of skeletal metastases was 12.0 (95%CI: 8.0–16.0) months versus 15.0 (95%CI: 4.5–25.5) months in patients with a multifocal pattern of skeletal metastases, $p = 0.432$. Similarly, median OS was not significantly different between patients with superscan pattern versus multifocal metastatic pattern; 13.0 (95%CI: 9.8–16.2) months versus 16.0 (95%CI: 13.2–18.7) months, respectively, $p = 0.151$ (Fig. 4). The median PFS and OS were similarly not significantly different between patients with bone-only metastases compared with various combinations of bone and soft tissue metastases (Fig. 5 and supplementary tables 1&2). Compared with patients who did not achieve a PSA response, those who attained PSA response had significantly longer median PFS [20.0 (95%CI: 14.0–26.1) months versus 4.0 (95%CI: 3.0–5.0) months, $p < 0.001$] and OS [16.0 (95%CI: 14.0–18.0) months versus 8.0 (95%CI: 5.9–10.1) months, $p < 0.001$] (Fig. 6).

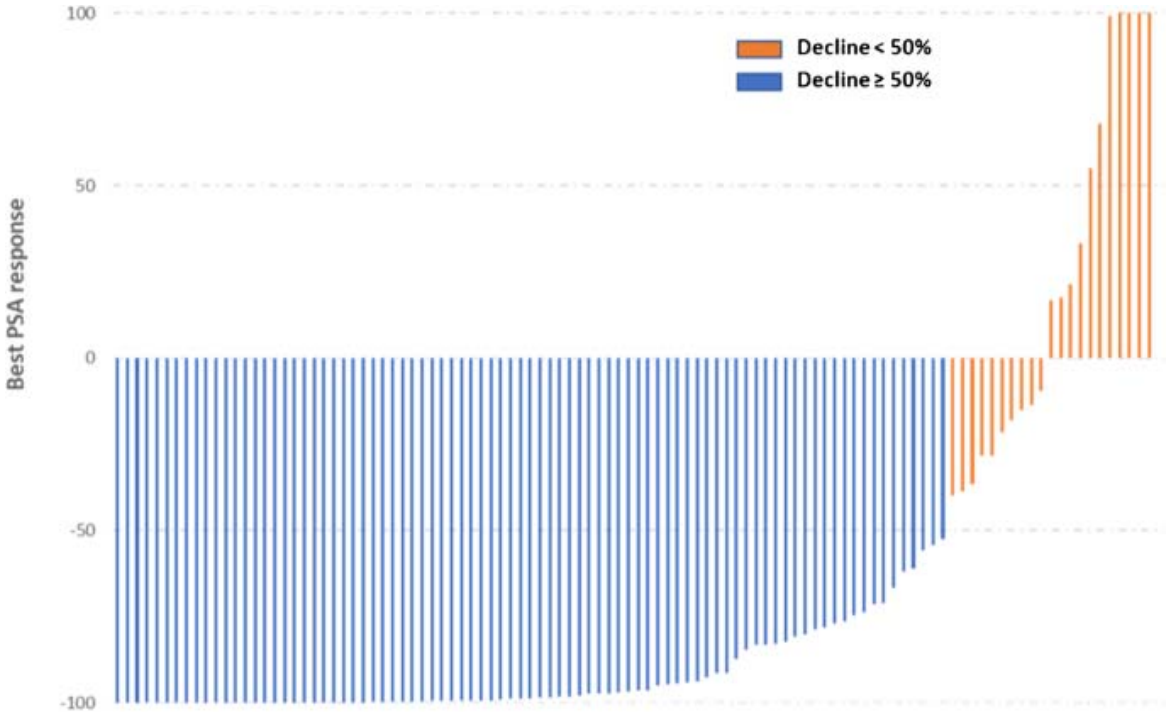

Fig. 3. Waterfall plot showing the best PSA response achieved by the study cohort during the entire treatment duration

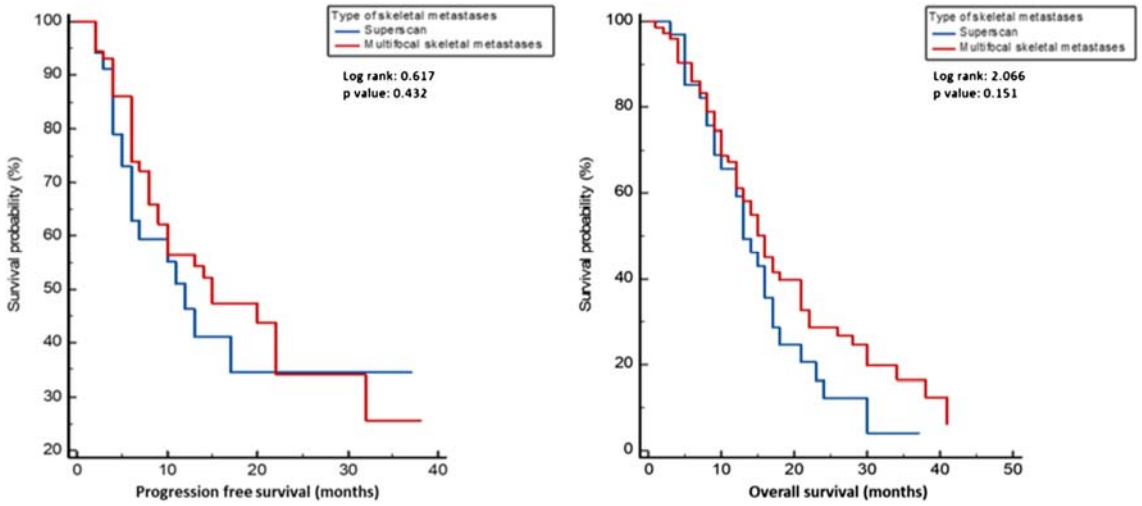

Fig. 4. Kaplan–Meier curves comparing progression-free survival and overall survival in patients with superscan pattern versus the multifocal pattern of skeletal metastases of castration-resistant prostate cancer

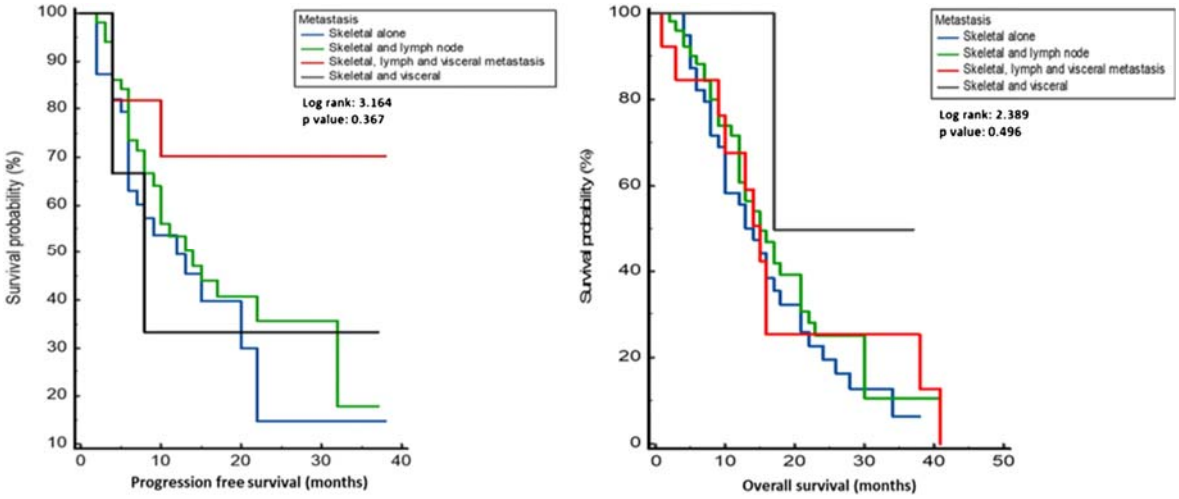

Fig. 5. Kaplan–Meier curves showing comparable progression-free survival and overall survival among patients with bone-only, bone with lymph node, bone with lymph node and visceral, and bone with visceral metastases of castration-resistant prostate cancer

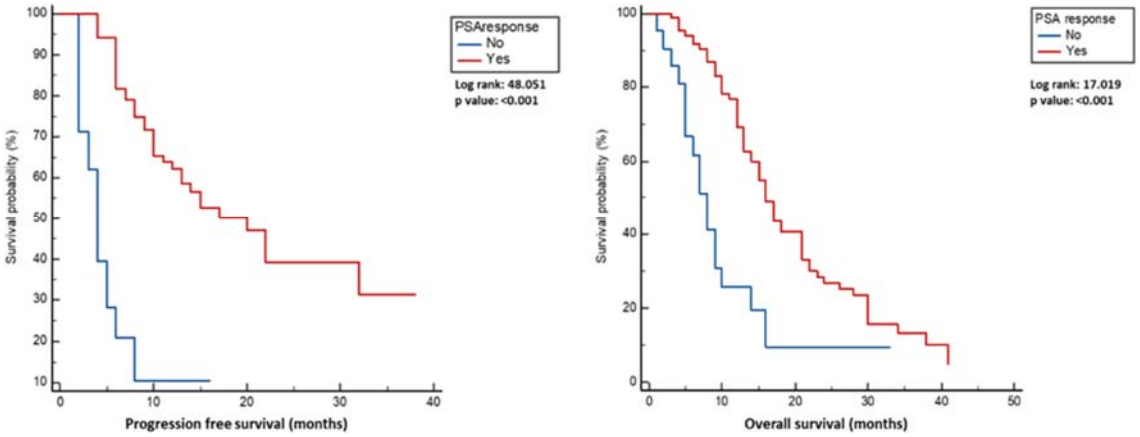

Fig. 6. Kaplan–Meier curves show significantly better progression-free survival and overall survival in patients who achieved PSA decline of 50% or come versus those who did not

Discussion

In this study, we present the first evidence of the effect of [^{225}Ac]Ac-PSMA-617 therapy on the hematologic profile and its efficacy in patients with extensive skeletal metastases of castration-resistant prostate cancer. Despite the high prevalence of impaired baseline bone marrow reserve as evident by 92.5% of our study population having at least one of their hematologic parameters below the lower limit of normal, we found a very low level of treatment-induced deterioration in the hematologic profile of the treated patients. Only one patient had a grade 4 toxicity (thrombocytopenia). We saw this toxicity in a 57-year-old male who received prior docetaxel for mCRPC. He received seven cycles of [^{225}Ac]Ac-PSMA-617 therapy with a favorable response (baseline PSA was 200.0 ng/mL and best PSA response was 15.0 ng/mL). He, unfortunately, developed grade 3 anemia, grade 3 leukopenia, and grade 4 thrombocytopenia after the seventh cycle of [^{225}Ac]Ac-PSMA-617 therapy. Apart from this patient, two other patients each developed grade 3 leukopenia and thrombocytopenia. The majority of patients had a stable hematologic profile throughout treatment. Our results suggest that [^{225}Ac]Ac-PSMA-617 therapy, even when applied in very

dire circumstances of impaired baseline bone marrow reserve and high tumor burden within the red marrow, is safe to the bone marrow with a stable hematologic profile in the majority of patients.

The high prevalence of impaired baseline bone marrow reserve seen in our study cohort was not unexpected, considering the high tumor load involving the axial skeleton where the largest bulk of the active red marrow is housed. Impaired bone marrow function has been reported by others in patients with skeletal metastases of prostate cancer regardless of prior history of chemotherapy [34]. Interestingly, in our binary logistic regression analysis, the presence of impaired bone marrow function at baseline was not a significant predictor of the occurrence of significant bone marrow toxicity. We speculate that this may be due to the high prevalence of baseline impaired bone marrow function in the study population, with only eight of 106 patients having normal baseline bone marrow function. The factors that were significant predictors of the occurrence of significant hematologic toxicity of [$^{2\,25}$Ac]Ac-PSMA-617 therapy were age, the number of treatment cycles administered for therapy, and the presence of renal failure. The age of the patients had a surprising relationship with the occurrence of significant hematologic toxicity. We expected the occurrence of hematologic toxicity to show a direct relationship with the patient age due to the presence of factors such as declining bone marrow reserve with age, the likelihood of the older patients to have had more lines of therapy, and the renal functional impairment due to the disease, comorbidities, and prior treatments. Our data, however, showed an inverse relationship between the age of the patient and the occurrence of significant hematologic toxicity due to [^{225}Ac]Ac-PSMA-617 therapy. This discordance may be due to other factors present in the younger patients in our cohort that were not identified. Expectedly, the number of treatment cycles administered for therapy had a direct relationship with the occurrence of significant hematologic toxicity suggesting that patients who received more treatment cycles are at higher risk of this treatment-induce side effect. The total activity of [^{225}Ac]Ac-PSMA-617 administered for treatment is a closely related variable to the number of treatment cycles; hence, we did not include it as a separate variable in our model. Due to its close relationship with the number of treatment cycles, we believe that the total activity administered for treatment would also show a direct relationship with the occurrence of hematologic toxicity.

Our group has routinely applied the concept of dose-de-escalation in which the activity of [^{225}Ac]Ac-PSMA-617 administered for therapy is titrated against tumor load as seen on [^{68} Ga]Ga-PSMA-11 PET/CT, which is done prior to each cycle of treatment [21, 22, 35, 36]. This strategy has been effective in reducing the incidence and severity of xerostomia, the most troublesome side effects of [^{225}Ac]Ac-PSMA-617 therapy, in our practice. In the current study, however, the number of treatment cycles has a direct relationship with the occurrence of significant bone marrow toxicity, which suggests that while dose-de-escalation may be effective in mitigating the impact of treatment on salivary gland function, administering more cycles of treatment exposes the patients to a higher risk of significant hematologic toxicity. Some recent studies have shown the dynamics of radioligand uptake in normal organs as a function of tumor burden [37,38,39]. These studies, mostly validating the concept of the "tumor sink effect," support our dose-de-escalation practice. While titrating administered activity against tumor load may be a promising avenue at reducing the dose to off-target organs and helpful in reducing the incidence and severity of treatment-induced side effects, it is not adequate alone in mitigating hematologic toxicity as other factors may come into play. In this study, renal dysfunction was also a significant predictor of the occurrence of significant bone marrow toxicity. Therefore, it suggests that a consideration of the combination of tumor burden and renal functional status, especially considering renal

dysfunction that occurs during treatment, may be more robust in mitigating against treatment-induced toxicity. This combined approach to treatment activity determination has been routinely practiced in some of the landmark trials of [^{177}Lu]Lu-PSMA-617 therapy of mCRPC [14, 40].

Two studies have recently reported the hematologic toxicity of [^{177}Lu]Lu-PSMA-617 in patients with diffuse skeletal metastases of mCRPC [41, 42]. In the first study that used the involvement of at least 50% of the axial skeleton as the inclusion criteria, 22% of patients had grade 3 anemia, 8% of patients had grade 3 neutropenia, while 18% and 8% of patients had grade 3 and 4 thrombocytopenia, respectively [41]. In the other study that defined inclusion as patients with diffuse involvement of the axial skeleton, 38%, 13%, and 13% of patients had grade 3 anemia, leukopenia, and thrombocytopenia during or at the end of treatment, respectively [42]. In addition, 4% of patients had grade 4 thrombocytopenia [42]. It is always difficult to compare treatment outcomes between studies due to the inherent differences between study populations. In this case, such significant differences among study populations with potential impact on treatment outcome may include the stage of the disease, the intensity of prior treatment, the tumor burden, and the tumor genetics. Despite this, it may be safe to assume that [^{177}Lu]Lu-PSMA-617 impacts more significant toxicity on bone marrow function than [^{225}Ac]Ac-PSMA-617. Beyond the data shown in this study, evidence from preclinical studies has shown that radiation dose delivered by emitted alpha particles are confined to a smaller sphere compared with the medium-ranged beta particles emitted by ^{177}Lu [43]. Our results, therefore, suggest that [^{225}Ac]Ac-PSMA-617 should be the preferred agent, when available, in the treatment of patients with extensive skeletal metastases of castration-resistant prostate cancer.

In this present cohort, 80.2% of patients (85 out of 106 patients) achieved a PSA response. The median PFS and OS were significantly longer in those who achieved a PSA response compared with those who did not. These findings are consistent with results from our previous study showing a concordance between PSA response and improvement in survival of patients with mCRPC treated with [^{225}Ac]Ac-PSMA-617 [22]. The presence of soft tissue metastases in addition to skeletal metastases appeared not to have a significant impact on PFS or OS in our present cohort. The presence of visceral metastases is known to occur at a very advanced stage of mCRPC, and its presence has been shown to negatively impact survival among patients treated with [^{225}Ac]Ac-PSMA-617 mCRPC [24]. The lack of a significant impact of the presence of soft tissue metastases, including visceral metastases, in addition to skeletal metastases, in our study, may be due to the relatively fewer incidence of visceral metastases in our study cohort seen only in 16 patients (15.1%). We showed similar survival (PFS and OS) between patients with a superscan pattern of skeletal metastases versus patients with a multifocal pattern of skeletal metastases. This indicates that a higher burden of skeletal metastases in patients with a superscan pattern did not negatively impact survival in our study population.

Our study has many merits, including a reasonably large study population treated with a comparatively higher number of cycles of [^{225}Ac]Ac-PSMA-617. This makes it possible to demonstrate the real impact of applying PSMA-targeted alpha therapy on the hematologic profile of patients. For the first time, we show that, indeed, [^{225}Ac]Ac-PSMA-617 therapy may be safe in patients with extensive skeletal metastases of castration-resistant prostate cancer even in the presence of impaired baseline bone marrow reserve. On the contrary, our study has also got some important limitations, most especially resulting from its retrospective design and the biases inherent in such study design. The findings from this study may need

validation by a prospectively designed study. We evaluated the impact of [^{225}Ac]Ac-PSMA-617 on the hematologic profile while treatment was ongoing. Therefore, the impact of this treatment on bone marrow function in the long term remains unknown. mCRPC is the terminal phase of prostate cancer with a modest survival duration despite the arrays of available life-prolonging agents. This makes the long-term effect of treatments administered at this terminal stage of the disease less critical.

Conclusion

Impaired bone marrow function is prevalent in patients with extensive skeletal metastases of castration-resistant prostate cancer. Despite this baseline impaired marrow function, severe hematologic toxicity is rare, and [^{225}Ac]Ac-PSMA-617 induces a good anti-tumor effect in about 80% of treated patients. In this cohort of patients, a younger age, increased number of treatment cycles, and renal dysfunction were significant risk factors for hematologic toxicity of [^{225}Ac]Ac-PSMA-617 therapy.

Data availability

All data collected during the conduct of this study are included in this report.

Ethics declarations

Ethical approval

This study was performed per the ethical standard of our institutions and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Consent to participate

All patients gave written informed consent to participate in the study.

Consent for publication

All patients provided informed consent to allow for the publication of their anonymized data collected during this study.

Conflict of interest

The authors declare no competing interests.

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