Cancer Treatment and Research Communications 18 (2019) 100114

Contents lists available at ScienceDirect

Cancer Treatment and Research Communications

journal homepage: www.elsevier.com/locate/ctarc

Impact of timing of administration of bone supportive therapy on pain palliation from radium-223

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ARTICLE INFO

Keywords:
mCRPC
Radium223
Pain flare
Pain response
Bisphosphonate
Denosumab
Prostate cancer
Rank ligand

ABSTRACT

Background: Skeletal-related events cause significant morbidity in patients with metastatic castration-resistant prostate cancer. In the ALSYMPCA study, radium-223 (Ra223) was found to provide pain palliation in addition to prolonged survival and reduced skeletal-related events (SREs). Given previous evidence that bisphosphonates impacted pain relief from the radiopharmaceutical samarium-153, we evaluated whether the timing of bone supportive therapy (BST) such as zoledronic acid or denosumab affected pain palliation from Ra223.

Methods: We identified patients who received Ra223 at University of Southern California or Mayo Clinic Arizona. Patients were evaluable for pain response if they had baseline pain score > 0 and at least 1 pain score documented after Ra223 with pain medication use data. Patients were evaluable for pain flare if they had known baseline pain score and at least 2 pain scores documented after Ra223. Pain response was defined as > 2 point decrease in pain on a 10-point scale; flare was defined as > 2 point increase followed by return to baseline or lower.

Results: Of 65 patients, 22 (34%) received BST. Median number of doses Ra223 was 5 (range 2–6). Fourteen patients were evaluable for pain response and 34 for pain flare. Eighteen patients received concurrent abiraterone (abi) or enzalutamide (enza), and 16 did not. Pain response occurred in 6/6 (100%) patients who received BST within 1 month prior to first Ra223 dose and 4/8 (50%) patients who did not receive BST. Pain flare occurred in 6/21 patients (29%) without BST and 2/13 (15%) with BST ($p = 0.44$). 6/10 (60%) patients with pain response had a decline in alkaline phosphatase (ALP) level, but there was no consistent pattern of ALP changes in patients with flare. 8/8 patients with pain response had no PSA decline. 6/8 (75%) and 2/18 (11%) patients on abi/enza had pain response and flare respectively, and 4/6 (67%) and 6/16 (38%) patients without concurrent abi/enza had response/flare.

Conclusions: BST within 1 month prior to first Ra223 dose was associated with increased likelihood of pain palliation and might prevent pain flare. Concurrent use of abi/enza was not associated with increased likelihood of pain response but was associated with decreased likelihood of pain flare.

Introduction

Bone is the most common site of distant metastases in prostate cancer. The resultant skeletal-related events (SREs) result in substantial morbidity and adversely impact quality of life in patients with metastatic castration-resistant prostate cancer (mCRPC). Bisphosphonates, specifically zoledronic acid (ZA), have been commonly utilized to decrease SREs in patients with mCRPC [1] by interfering with bone remodeling. More recently denosumab, a fully humanized monoclonal antibody that binds to RANK ligand, was also approved by FDA for prevention of SREs in patients with mCRPC [2]. This agent also targets the microenvironment rather than being toxic to cancer cells themselves, interfering with signaling between cancer cells and osteoblasts/osteoclasts. Both treatments have been shown to delay and reduce SREs

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https://doi.org/10.1016/j.ctarc.2018.100114
Received 9 October 2018; Received in revised form 7 November 2018; Accepted 9 November 2018
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including spinal cord compression and fractures, albeit without evidence of an immediate pain response [3].

In addition to bone supportive agents targeting bone turnover by acting on the microenvironment, radioactive calcium mimetic compounds such as samarium-153 and strontium-89 have been utilized to palliate pain related to bone metastases [4,5]. These agents are intended to target the cancer cells themselves, by releasing energy in areas of active bone turnover. While these agents were effective from a palliative standpoint, myelosuppression limited repeated dosing and no improvement in overall survival has been demonstrated. Radium-223 (Ra223) was designed as an alpha-emitting radiopharmaceutical to allow repeated dosing, and was approved in 2013 for castrate-resistant prostate cancer (CRPC) with symptomatic bone metastases based on the phase 3, randomized, double-blind, placebo-controlled ALSYMPCA study [6]. In addition to reducing SREs and palliating pain, Ra223 was found to prolong overall survival in men with mCRPC and symptomatic bone metastases [7,8]. The improvement in median survival is comparable to chemotherapy using docetaxel. [9,10]

Concurrent use of bisphosphonates with Ra223 has been reported to prolong median time to skeletal-related events in comparison with Ra223 alone (19.6 months vs 11.8 months) based on the ALSYMPCA protocol [11]. The most common SRE in ALSYMPCA was the need for external beam radiation therapy for bone pain, thus raising the possibility that concurrent use of bone-supportive therapy (BST) with Ra223 might reduce SREs in large part by improving pain response. This hypothesis is supported by an older experience published by Rasulova et al who reported that ZA administration within 24–48 hours prior to samarium-153 was associated with an earlier onset of pain relief (3 days vs 10 days if ZA was given ≥ 7 days prior to samarium-153, $p < 0.001$; 3 days vs 21 days if ZA was given 7 days after samarium-153, $p < 0.001$) [12].

Little information exists about the use of denosumab during Ra-223 therapy, since only 30 patients (40%) in the expanded access population [13] and none of the ALSYMPCA patients were reported to have received denosumab. Further information about the impact of either BST during Ra223 is needed to help clinicians optimize their use of these various bone-targeted therapeutics. We sought to evaluate whether concurrent BST impacted pain outcomes during Ra223 therapy in a cohort of patients receiving both agents, in a contemporary setting in which some patients also received concurrent abiraterone or enzalutamide.

Methods

This study was a retrospective analysis of a cohort of patients with mCRPC and bone metastases who were treated with Ra223 at University of Southern California/Norris Comprehensive Cancer Center (USC) and Mayo Clinic Arizona between November 2013 and February 2016. Study data were collected from the patients' electronic medical records. The study was performed with the approval from the USC and Mayo Institutional Review Board.

The study data collected include Ra223 administration dates, pain scores, pain medications, ZA or denosumab administration dates, alkaline phosphatase (ALP) levels, prostate specific antigen (PSA) levels, and concurrent prostate cancer therapy.

Patients were evaluable for pain response if they had baseline pain score greater than 0 and at least 1 pain score documented after Ra223 with pain medication use data. Pain was documented using the 10-point visual analog scale. Patients were evaluable for pain flare if they had known baseline pain score and at least 2 pain scores documented after Ra223. Pain response was defined as a 2-point or more decrease in pain without increased pain medication use; flare was defined as a 2-point or more increase following the first or second dose of Ra223 followed by return to baseline or lower.

Baseline PSA was defined as PSA measured within 1 month prior to or on the date of first Ra223 dose. PSA at 12 +/− 4 weeks after the first dose of Ra223 was compared to baseline PSA, and the percent change in PSA was calculated. A PSA change > 25% was used as the cutoff to categorize patients as having PSA increase or decrease; changes of < 25% were categorized as stable. Baseline ALP was defined as ALP measured within 1 month prior to or on the date of first Ra223 dose. ALP levels of 130 or less were considered normal. Any increase or decrease, regardless of percentage from baseline or absolute change was labeled as increase or decrease, given the lack of established parameters for changes in this blood test.

Graphical depictions of pain score, Ra223 doses, and BST doses

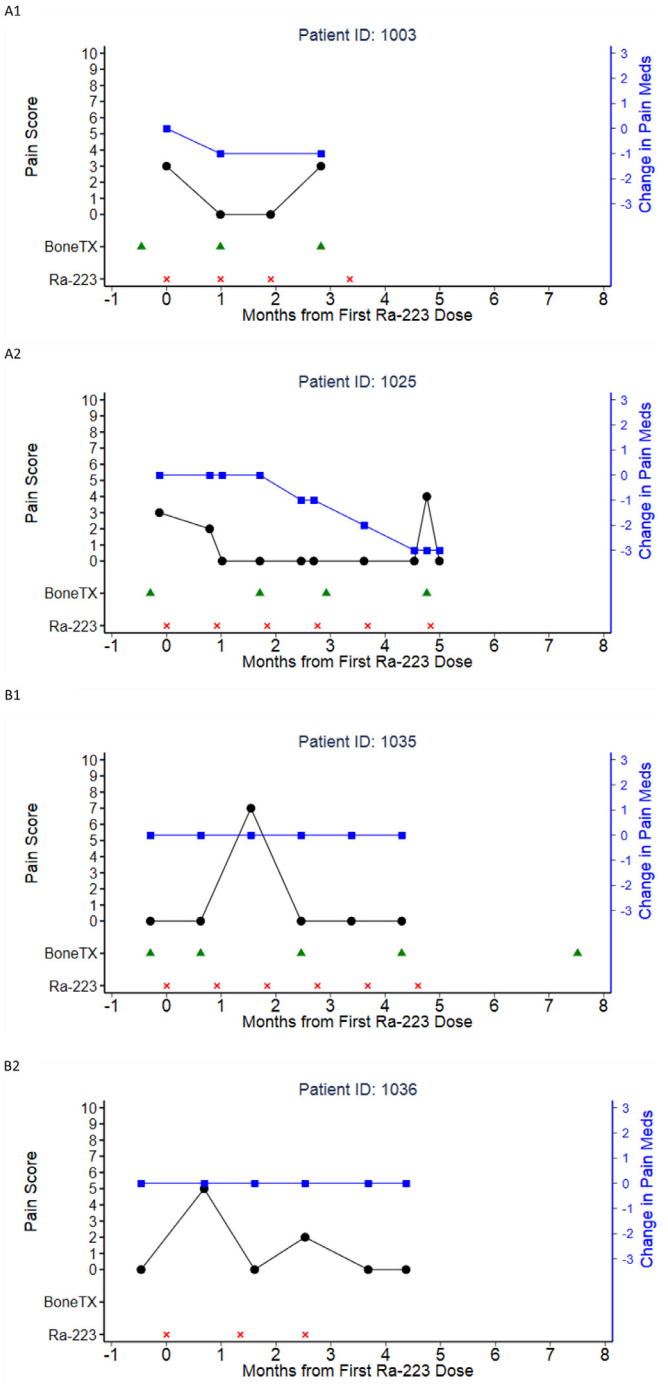
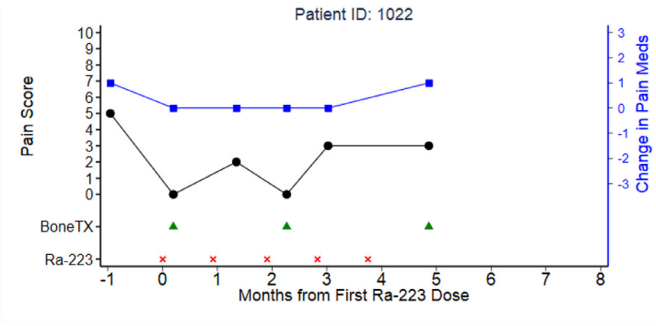


Fig. 1. Graphical representations of unique patients with patterns of pain response (A), pain flare (B), and pain progression (C). Analgesic dose levels are represented in blue, pain scores are in black. Green triangles show dosing timing of BST, and red x marks administration timing of Ra223.

C1



C2

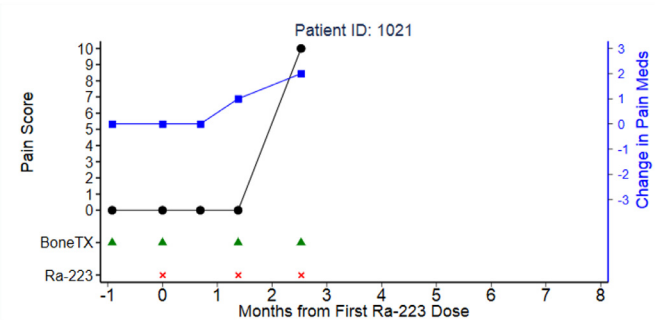


Fig. 1. (*continued*)

were created in order to identify pain flare or response (Fig. 1); this was cross-referenced with opioid analgesic use in the medication list in EMR at each time point as well as using the physician's narrative to identify whether more or less or the same amount of analgesic medication was being consumed.

Statistical analyses

P values for the comparisons of patients with or without BST or with or without concurrent abi/enza in the likelihood of having pain response, pain progression or pain flair were based on Fisher's exact tests. All reported p-values are two-sided. All analyses were performed using the STATA software version 11.0.

Results

Sixty-five patients were identified, fifty of whom were treated at USC and fifteen at Mayo Clinic Arizona. Baseline characteristics are summarized in Table 1. Overall, 38 subjects received "concurrent" BST when including doses within 6 months prior or at any time during Radium223 treatment (29 denosumab, 9 zoledronic acid). For the purposes of this study, we analyzed those who received BST within one month of radium; twenty-two patients (34%) received BST within one month; sixteen received denosumab and six received ZA. The median number of Ra-223 doses was five (range 2 to 6). Overall, 14/22 patients receiving BST (63.6%) also received abi or enza during Ra223 therapy, while 20/43 patients (46.5%) not receiving BST did receive abi or enza during Ra223 treatment.

Fourteen patients were evaluable for pain response and thirty-four patients were evaluable for pain flare. Given the small sample size, the results in this study remained largely descriptive. A summary of pain response and pain flare events relative to BST and the use of abiraterone or enzalutamide in this subset is presented in Table 2. Pain response occurred in all of the six evaluable patients (100%) who received BST within 1 month prior to first Ra223 dose. In contrast, only 4 out of 8 evaluable patients (50%) who did not receive BST within 1 month prior to first Ra-223 experienced pain response. Pain flare occurred in 6 out of 21 patients (29%) without BST and 2 out of 13 (15%) with BST (which consisted of one patient on zoledronic acid and one on denosumab).

Table 1
Characteristics of study population.

	N (%)
Total number of patients	65
Bone supportive therapy within 1 month prior to Ra-223	
Denosumab	16 (25%)
Zoledronic acid	6 (9%)
None	43 (66%)
Median number of Ra-223 dose	5 (2–6)
Concurrent antiandrogen therapy	
Abiraterone	8 (12%)
Enzalutamide	10 (15%)
None	47 (72%)
ALP level before Ra-223	
≤130	23 (35%)
>130	34 (52%)
Unknown	8 (12%)
PSA level before Ra-223	
<10	8 (12%)
10–50	15 (23%)
>50	30 (46%)
Unknown	12 (18%)

Six out of ten patients with pain response had a decline in alkaline phosphatase (ALP) level but there was no consistent pattern of ALP changes in patients with pain flare. Of the seven patients with pain flare, four had ALP decline. Of the twenty-three patients with no pain flare, twelve (74%) had ALP decline.

Eight of 10 patients with pain response had PSA data, all of whom had no PSA decline. There was no consistent pattern of PSA changes in patients with pain flare. Seven of eight patients with pain flare had PSA data, three of whom had PSA decline, two had PSA increase and two had stable PSA. Twenty of 26 patients with no pain flare had PSA data, two had PSA decline, fourteen had PSA increase, and four had stable PSA.

Of the patients who received concurrent abiraterone or enzalutamide, six out of eight patients (75%) had pain response and 2 out of 18 (11%) had pain flare. Both patients with pain flare were receiving concurrent enzalutamide, and one was receiving BST. In contrast, four out of six (67%) and six out of sixteen (38%) patients without concurrent abiraterone or enzalutamide had pain response and pain flare respectively.

Discussion

Although the ALSYMPCA trial documented pain palliation in addition to survival prolongation with the use of Ra223 in mCRPC, bone pain was recorded as an adverse event in ALSYMPCA, and case reports have identified pain flare as a possible adverse event [14]. Understanding how to optimally use Ra223 in men with mCRPC necessitates understanding the interactions between this bone-targeted agent and the non-cytotoxic bone supportive therapies (ZA and denosumab). This retrospective review suggests that receiving ZA or denosumab within 1 month prior to Ra223 may be associated with increased likelihood of pain palliation and may prevent pain flare. This fits with an earlier experience, in which earlier onset of pain relief was reported in patients receiving zoledronic acid before samarium-153 [12].

The major limitation of our study is the small number of patients, which resulted in our data analysis being descriptive and precluded multivariate analysis. Despite this, the rates of pain response (50%) and pain flare (29%) are comparable to that reported in the US Expanded Access Programme (US EAP). Of the 109 patients who participated in the US EAP, 42% had improved pain, 28% had worsening of pain without any subsequent improvement (i.e. progression), and 10% had

Table 2
Pain response and pain flare in the subset of patients who were evaluable for at least pain flare, detailing concurrent medication (BST = bone supportive therapy; ZA = zoledronic acid; Denos = denosumab; Abi = abiraterone; Enza = enzalutamide) and changes in levels of blood markers (ALP = alkaline phosphatase; PSA = prostate specific antigen).

Patient ID	Evaluable for pain response	Pain Response/ Progression or Flare or none	BST	Concurrent Abi or Enza	ALP	PSA
1001		None		Abi	Decreased	Increased
1003	x	Response	Denos	Enza	Increased	Increased
1004		Flare		None	Decreased	Decreased
1005		None		Abi	Decreased	Increased
1007		None		Enza	Decreased	Increased
1009	x	Progression		Abi	Increased	Stable
1011		None		Abi	Normal baseline	Increased
1012	x	Progression		None	NA	NA
1013		None		Abi	Normal baseline	Decreased
1014	x	Response		None	Decreased	NA
1016		None	Denos	Abi	NA	NA
1018		Flare		None	Normal baseline	Increased
1020		Flare	ZA	None	Increased	Decreased
1021		None	Denos	Enza	Decreased	Increased
1022	x	Response + Flare		None	Normal baseline	Stable
1023	x	Response		None	Decreased	Increased
1024		None		Enza	NA	NA
1025	x	Response	ZA	Abi	Increased	Increased
1028	x	None*		Enza	Increased	Increased
1030	x	Progression + Flare		None	Normal baseline	NA
1031	x	Response + Flare		Enza	Decreased	Stable
1033		None	Denos	Enza	Normal baseline	Decreased
1034		None		None	Normal baseline	Stable
1035		Flare	Denos	Enza	Decreased	Decreased
1036		Flare		None	Decreased	Increased
1039	x	Response	Denos	Abi	Decreased	NA
1040		None		None	Normal baseline	NA
1042	x	Response	Denos	Enza	Decreased	Increased
1043	x	Response	Denos	None	Normal baseline	Increased
1046		None	Denos	None	Decreased	Stable
1050	x	Response	ZA	Enza	Decreased	Stable
2002		None	Denos	None	Normal baseline	Increased
2010		None		None	Decreased	Increased
2013		None		None	Decreased	Increased

NA = not available.
* Stable pain, meaning pain level was not 0 at baseline, and neither increased nor decreased

improvement and worsening pain at different times, likely representing flare [15]. The smaller data set allowed us to evaluate pain changes in the context of analgesic medication use in greater detail.

Lack of PSA decline from Ra223 treatment is fairly common. Only 16% of patients had greater than 30% decline in PSA level at week 12 in the ALSYMPCA trial [5]. PSA rise alone is not typically considered an indication to stop treatment with Ra223. Wong et al recently reported that 80% of the patients treated at Mayo Clinic had a PSA rise greater than 25% during Ra223 treatment, and this was found to be associated with worse survival [16]. Interestingly, lack of PSA decline does not appear to affect pain response. All the patients in our study with pain response had no PSA decline; five out of eight of these patients had an increase in PSA level of greater than 50%. Thus oncologists must rely on clinical features such as pain, more than laboratory parameters in order to determine whether patients are benefitting from Ra-223. ALP has also emerged as a marker that can be used to elucidate benefit; ALP decline was associated with survival [8]. Acknowledging the potential for flare, and the survival benefit with Ra-223 having been seen in the context of most patients receiving the 6 dose course, it is prudent to treat past first pain increase to avoid early discontinuation due to flare rather than actual progression.

Abiraterone and enzalutamide prolong survival in mCRPC who are chemotherapy-naïve or previously treated with docetaxel [17–20]. These novel endocrine treatments also improve pain response and delay SREs [18, 21–23]. In addition, concurrent use of Ra-223 with abiraterone or enzalutamide prolonged survival in the single phase 3b International EAP with similar safety profile to Ra-223 alone [24]. Our study suggested that combining Ra-223 with abiraterone or enzalutamide may decrease pain flare. However, in light of the recently presented data regarding increased fracture and deaths from Ra-223 and abiraterone combination therapy in the Phase III ERA223 trial [25], combination therapy with abiraterone and perhaps enzalutamide should not be routinely used outside of clinical trials, until additional level 1 evidence becomes available. The increased fracture and mortality risks were observed in both patients who received BST and those who did not, however fewer fractures occurred in patients receiving BST. A summary of fractures and BST use in reported trials of Ra-223 is presented in Table 3. The importance of BST during Ra-223 therapy has become clear from these experiences, and BST should be administered routinely during Ra-223 therapy unless there are contraindications since no safety signals have emerged for these combinations. Further attention to outcomes based on use of BST during Ra223 and other therapies for mCRPC, as well as investigation of pathologic changes in bone related to mCRPC therapies, will be critical in optimizing care.

Conclusion

Bone supportive therapy prior to first Ra223 may be associated with increased likelihood of pain palliation and decreased risk of pain flare. Confirmation of these findings is needed given the small sample size. However, taken together with increasing evidence that BST reduces fractures during Ra223, concurrent BST should be considered a standard of care. PSA/ALP changes do not predict pain response. Concurrent use of abi/enza was not associated with increased likelihood of pain response but was associated with decreased likelihood of pain flare.

Table 3
Use of bone supportive therapy in published experiences with radium223.

Trial, Author [ref]	Usage of bone support (%)	Fractures
ERA223, Smith [25]	39% in rad223 group 42% in placebo group	37% rad223 without BST 15% placebo without BST 15% rad223 with BST 7% placebo with BST
iEAP, Miller [26] n = 708	17% bisphosphonates 18% denosumab	4% fracture with prior abi 3% fracture without prior abi
REASSURE, Sternberg [27] n = 1439	49% prior BST 38% concurrent BST	1% fracture without BST 2% fracture with BST
ALSYMPCA, Parker, Sartor [6,15]	40% concurrent BST (bisphosphonate only)	5% fracture* Rad223, 7% placebo HR 0.8 [95% CI 0.5–1.3] for fracture

*symptomatic pathologic bone fracture.

Conflict of interest

TD – Astra Zeneca (consulting), Bayer (consulting), Exelixis (promotional speaker), Intas (consulting), Janssen (consulting), Prometheus (promotional speaker). DI - Astrazeneca, Bayer, Janssen, Genzyme-Sanofi, Dendreon, Clovis, Pfizer (consulting).

Acknowledgment

This work was partially supported by Award Numbers U54CA143906 P30CA014089 from the National Cancer Institute. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Cancer Institute or the National Institutes of Health who had no influence on the design, analysis, or conclusions of the study.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ctarc.2018.100114.

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