Pain response in a population-based study of radium-223 (Ra223) for metastatic castration-resistant prostate cancer

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Abstract

Introduction: Clinical trials have shown that radium-223 (Ra223) can prolong survival and improve quality of life in patients with metastatic castration-resistant prostate cancer (mCRPC). The objectives of this study were to evaluate pain responses with Ra223 at a population-based level and to determine if there is an association between pain response and alkaline phosphatase (ALP) response.
Methods: All patients from the Vancouver and Kelowna Cancer Centers (CC) in British Columbia who were treated with Ra223 between June 2015 and December 2016 were identified. Patients completed the Brief Pain Inventory (BPI) just prior to each Ra223 injection. Pain response was defined as a two or more point improvement in worst pain relative to baseline, without an increase in pain medication level. ALP was determined at each visit, with a response threshold defined as a 30% decrease from baseline, consistent with the definition of response used in the ALSYMPCA trial.
Results: A total of 65 patients in Vancouver and Kelowna CC received Ra223 during the study period and 56 patients had at least one BPI record, of which 44 (79%) patients were assessable for change in worst pain. Of the assessable patients, 23 (52%, 95% confidence interval [CI] 38–67) had a pain response, although the use of concurrent external beam radiotherapy was a confounder in four cases. Of the 44 patients assessable for change in worst pain, 59% had ALP responses greater than 30%. An ALP response was seen in 56% of pain-responders vs. 43% of non-pain-responders. There was no association between pain response and ALP response (Phi =-0.05; p=0.77).
Conclusions: Ra223 administration was associated with a meaningful pain response rate in this cohort. There was no correlation between pain response and ALP response.

Introduction

Bone metastases from prostate cancer frequently cause bone pain. Radiaum-233 (Ra223) is an alpha-emitting calcium mimetic that is incorporated into areas of active bone turnover and delivers alpha-particle radiation to the areas of active bone involvement in patients with prostate cancer. In the ALSYMPCA trial, Ra223 improved overall survival (OS), prolonged time to first symptomatic skeletal event (SSE) by 5.8 months (hazard ratio [HR] 0.66; 95% confidence interval [CI] 0.52–0.83), delayed time to opiate use, and improved quality of life compared to placebo in patients with symptomatic bone metastases from castration-resistant prostate cancer (CRPC).[1] A phase 2 trial by Nilsson et al additionally demonstrated that 56% of patients with metastatic CRPC (mCRPC) demonstrated a pain response after a single injection of standard-dosage Ra223, where "pain response" was defined as a decrease on a pain index comprised of a visual analog scale and analgesic usage.[2] US Early Assess Program (EAP) analysis also reported a 59% pain improvement of at least two points over baseline on Brief Pain Inventory (BPI) in eligible patients.[3] Active bone turnover is associated with increased bone alkaline phosphatase (ALP) levels in the blood. OS benefit has been correlated with a decrease in ALP levels during Ra223 therapy; however, it is unclear whether a declining ALP level with Ra223 is also associated with improved pain.

The aim of this study was to evaluate baseline pain and pain response in prostate cancer patients treated with Ra223 in the general population of patients being treated for CRPC, and to ascertain whether pain response correlates with ALP response during Ra223 therapy.

Methods

BC Cancer is the single provider of Ra223 in British Columbia (BC), Canada. All treated cases are centrally registered. Each of the six regional cancer centers (CC) in BC has a defined population-based catchment area. Data from all patients treated with Ra223 has been collected from the BC Cancer Provincial Radiation Therapy Program's electronic medical records. Starting in June 2015, patients treated with Ra223 who resided in the Kelowna and Vancouver CC catchment areas were asked to complete the BPI through an electronic patient-reported outcomes (PRO) platform.

The PRO platform was used for data abstraction and charts were reviewed for data augmentation. All CRPC patients from the Vancouver and Kelowna centre catchments who were prescribed six cycles of Ra223 therapy between June 2015 (when the PRO platform was activated for Ra223 patients) and December 2016 (to allow for minimum of six months' followup) were included in the study. At each visit, patients completed PRO questionnaires, which included the BPI. Patients were asked about pain medication use at each visit, which was classified as 1) no opioids; 2) weak opioids; or 3) strong opioids. A change between pain medication groups was categorized as increased, decreased, or stable, accordingly. Neither actual doses of opioids and morphine equivalent units, nor daily opioid diaries were captured. Patients were also asked to rate their pain at its worst on a 10-point scale at each visit. Pain response was determined by calculating the degree of change in worst pain relative to baseline. Eight (20%) patients did not have a baseline pain score prior to first dose of Ra223; these cases were assessed for response using their pain score prior to their second dose of Ra223. In an effort to assess the impact of these patients on the response rate, we performed maximizing and minimizing sensitivity analyses. Patients who demonstrated a decrease in pain of at least two units from baseline and whose pain medication category decreased or remained stable were considered pain-responders, using BPI pain response criteria described by Chow et al.[4] An ALP level was also taken at each visit and analyzed for response. An ALP response was defined as a decrease of 30% or more from baseline values consistent with definition used in ALSYMPCA trial. Correlation between pain response and ALP responses was assessed using a Phi statistic.

To further characterize the participants involved, a number of additional baseline factors were recorded, including age, Eastern Cooperative Oncology Group (ECOG) performance status, number of bone metastases, analgesic use, palliative radiotherapy to bone during the course of Ra223, and lines of therapy (including palliative radiotherapy to bone) prior to Ra223. Laboratory values, such as levels of hemoglobin, albumin, lactate dehydrogenase (LDH), prostate-specific antigen (PSA), and ALP before Ra223 injections were also assessed.

Results

In total, 65 patients from the Vancouver and Kelowna catchment areas were treated with Ra223 and 56 (86%) of the patients from these centers had at least one BPI record. We were able to assess change in worst pain in 44 (79%) of the patients (Fig. 1). Baseline factors for all 65 patients that received Ra223 (Ra223 group), the subgroup of 56 patients who had a PRO record (PRO group), and the 44 PRO patients that were evaluable for pain response (pain group) are presented in Table 1. The summary of time 1 pain scores for the pain group displayed in Table 1 includes cases where the pain score prior to the second dose of Ra223 was used in the absence of a true baseline value.

There were 39 of the 56 PRO group patients who had a true baseline pain measure; 92% of these had at least some pain, 70% had a pain score of at least 3, and 31% scored 7 or above (Fig. 2). Of the 44 patients that were assessable for change in worst pain, 36 had a true baseline pain measure. For the eight patients that did not have a pain score prior to first dose, the baseline was the pain score prior to second dose. A sensitivity analysis was performed to show that the impact of having eight patients without a documented pain score prior to first dose was small. Of those eight patients, two exhibited a pain response and six did not. The reported percentage of responders was 52% (95% CI 38–67%). Had all six cases been scored as pain responders, this would have changed the percentage of responders to 66% (95% CI 52–80%). Had all six cases been scored as non-responders, this would have changed the percentage to 48% (95% CI 33–62%). Of note, all of the three confidence intervals overlapped in this analysis.

In total, 24 pain group patients (55%) showed an improvement of at least two units on worst pain score, and 23 (52% of all pain group patients; 95% CI 38–67%) had a pain response. Four (17%) of the 23 pain responders also received palliative external beam radiation therapy (EBRT) during the course of Ra223 that could have impacted their pain response. Of those with pain score of 3 or higher at baseline, 65% showed pain improvement of at least two units during the course of Ra223 treatment. Fig. 3 shows the maximum decrease in worst pain score for the pain group. Fig. 4 plots the sequence of pain response/non-response from baseline for each patient, with an indicator for the timing of EBRT. Pain responses were often short-lived and did not have a clear time pattern, although for 13 of 21 cases (62%) with complete time records, the pain response was seen after the first dose.

Fig. 5 plots the maximum decrease in ALP for each patient in the pain group. ALP response measured in the 44 pain group patients indicates that 59% of patients had an ALP response greater than 30%. Comparison of pain response to ALP response showed that 56% of pain-responders had an

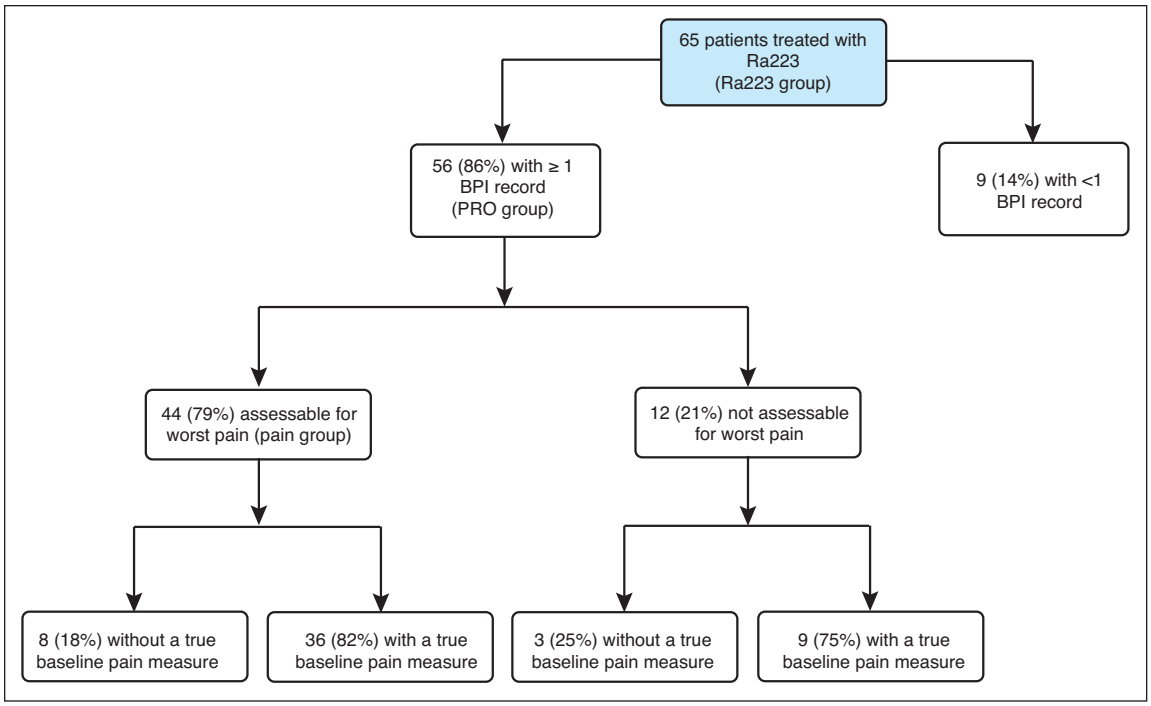

Fig. 1. Consort diagram. BPI: Brief Pain Inventory; PRO: patient-reported outcomes; Ra223: Radium-223.

Table 1. Baseline characteristics

	Ra223 group	PRO group	Pain group
	(n=65)	(n=56)	(n=44)
Age, median (range)	76 (57–94)	76 (57–94)	74 (59–94)
ECOG			
<2, n (%)	48 (74)	45 (80)	35 (80)
≥2, n (%)	17 (26)	11 (20)	9 (20)
Bone mets			
<6, n (%)	13 (20)	8 (15)	8 (18)
≥6, n (%)	52 (80)	45 (85)	36 (82)
HB, median (range)	125 (94–146)	123 (94–146)	124 (98–146)
ALP, median (range)	148 (27–1294)	148 (27–1294)	144 (27–1294)
Albumin, median (range)	40 (20.6–99)	40 (20.6–99)	40 (27–99)
LDH, median (range)	295 (130–2115)	345 (130–2115)	337.5 (130–2115)
PSA, median (range)	84.88 (0.24–2800)	98.7 (0.24–2800)	99.215 (0.24–2800)
Previous systemic treatments, median (range)	2 (0–5)	2 (0–5)	2 (0–5)
Docetaxel, n (%)	25 (38)	19 (36)	15 (34)
Abiraterone, n (%)	43 (66)	37 (70)	32 (73)
Enzalutamide, n (%)	47 (72)	36 (68)	29 (66)
Cabazitaxel, n (%)	4 (6)	2 (4)	2 (5)
Previous clinical trial, n (%)	25 (39)	19 (37)	16 (36)
Baseline pain*, median (range)			4 (0–10)
Baseline pain medication*			
None, n (%)			13 (29.5)
Non-opioids, n (%)			10 (23)
Weak opioids, n (%)			8 (18)
Strong opioids, n (%)			13 (29.5)

*Includes cases where the pain score prior to the second dose of Ra223 was used in the absence of a true baseline value. ALP: alkaline phosphatase; ECOG: Eastern Cooperative Oncology Group; HB: hemoglobin; LDH: lactate dehydrogenase; PRO: patient-reported outcomes; PSA: prostate-specific antigen; Ra223: radium-223.

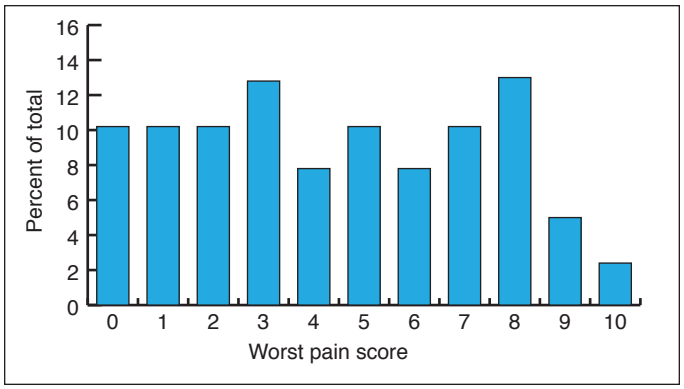

Fig. 2. Worst pain score for patients with a true baseline (on or up to 35 days before the first injection) in the patient-reported outcomes group (n=39).

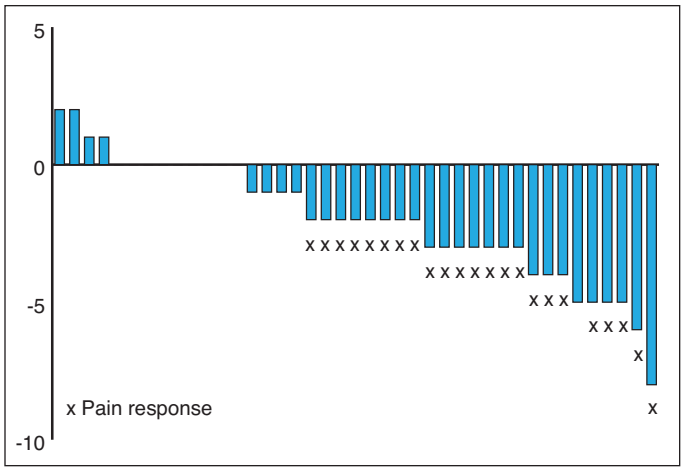

Fig. 3. Waterfall plot of maximum decrease in worst pain for the pain group (n=44).

ALP response and 43% of non-pain-responders had an ALP response. ALP and pain responses were assessed using a Phi statistic, and ALP response was not significantly correlated to pain response (Phi =-0.05; p=0.77).

As a secondary analysis, pain response was evaluated at any time during Ra223 therapy. In this case, pain response was determined by calculating the degree of change in worst pain relative to any worst pain score that occurred prior. In this secondary analysis, patients who demonstrated a decrease in pain of at least two units from any prior score and whose pain medication category decreased or remained stable for the relevant period were considered pain responders.

Results using this approach were similar to those comparing pain to baseline; 27 of the pain group patients (61%) showed an improvement of at least two units over the worst pain score at some point during the course of Ra223 therapy, with stable or improved pain medication category. Four (17%) of the 27 pain responders also received palliative EBRT during the course of Ra223 that could have impacted their pain response. Comparing pain response at any time to ALP response indicates that 59% of pain-responders had an ALP response and 41% of non-pain-responders had an ALP response. ALP response at any time was not significantly correlated to pain response (Phi =0.004; p=1.00).

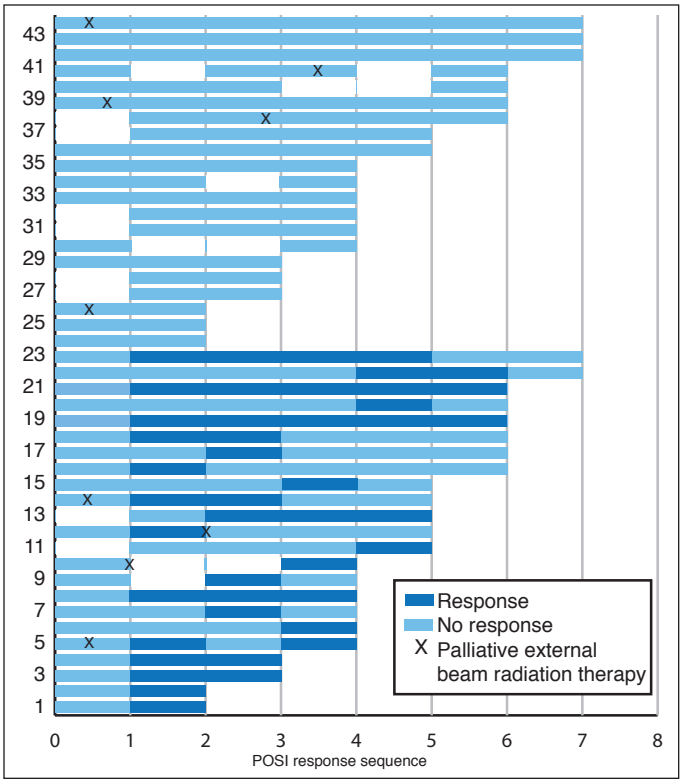

Fig. 4. Sequence of pain response/non-response from baseline by patient in the pain group (n=44).

Discussion

A baseline pain level of 3 or higher was present in 70% of patients, and 52% of evaluable patients had a pain response. This finding is consistent with the findings in other studies of a longer median time to initial opioid use for Ra223 compared to placebo (HR 0.621; 95% CI 0.46–0.85), as well as a longer time to EBRT for bone pain (HR 0.67; 95% CI 0.53–0.85), and prolonged time to first symptomatic skeletal event (HR 0.66; 95% CI 0.52–0.83) (defined as first use of EBRT for bone pain, new symptomatic pathological fracture, spinal cord compression, or cancer-related orthopedic surgery intervention).[1,5] Clinical trials patients tend to have more favorable outcomes than those treated in non-trial settings, often due to the rigorous eligibility criteria that have to be met. Population-based data increases the generalizability of results by reflecting a broader range of patient experiences, institutional practices, and physician expertise.[6,7] Our analysis provides such population-based data and is consistent with the pain improvement rate seen with Ra223 in the US EAP program data.[3]

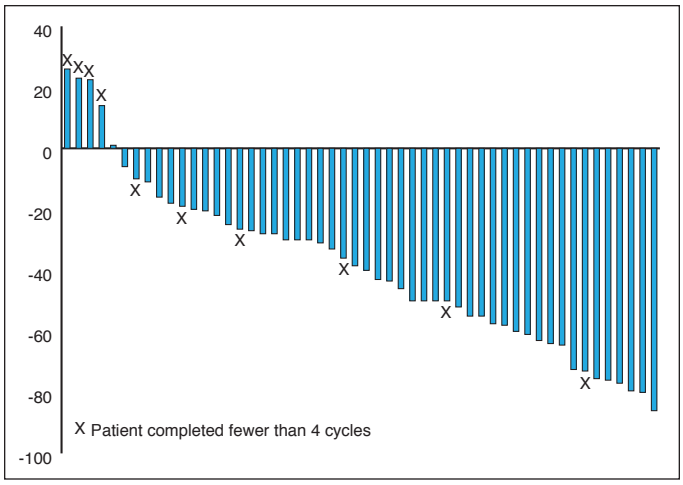

Fig. 5. Waterfall plot of the maximum alkaline phosphatase decline for each patient in the pain group (n=44).

As ALP levels can reflect bone activity, we postulated that the pain response during Ra223 treatment may correlate with ALP response. Our study failed to show such a relationship, which is the second major finding of this paper. This suggests that ALP levels alone do not reflect the pain experienced by patients with CRPC experience during Ra223. It is also possible that our study was too small to see a correlation, and further work in this area should continue. Ra223 has an effect on tumor cells within the bone, surrounding osteoblasts,[8] and the cancer microenvironment.[9-11] Any or all of these mechanisms could contribute to pain relief, yet not all would lead to a decline in ALP, which is primarily a marker of osteoblastic activity in this context.[12] Our data suggest that neither the ALP response, nor the absence of response, gives the treating physician an indication of a lack of eventual pain response in an individual patient.

This study is limited by small patient numbers, its retrospective nature, and that not all patients are willing and able to complete a BPI form at every visit in a population-based setting. The characterization of pain responses, while informative, must also be scrutinized. An analgesic response may have been augmented due to the use of EBRT during the trial period, although only four of the 23 patients characterized as eligible responders in our analysis had EBRT during the course of Ra223 that could have affected the pain response. It is also possible that pain responses could have been over- or underestimated, as under-reporting of pain by cancer patients is a common issue.[13] It must also be acknowledged that increases or decreases in opiate medications could have taken place once these agents were started, which was not fully assessed, and could confound the true nature of changes in pain, as the BPI tool used at monthly intervals does not capture pain medication use in a way that allows for conversion to morphine equivalent units. The role of PRO measures in our institutions is evolving and will be increasingly used to identify and address symptom burden in the future. We did not collect the use of bone-protecting agents (such as bisphosphonates or RANK-L inhibitors), which could have meaningful impacts on the bone-pain.[14-16] However, such agents are rarely used in BC for patients with prostate cancer.

Future studies would be helpful to explore baseline clinical factors that predict analgesic benefit from Ra223. Studies are now also exploring Ra223 administered with more contemporary mCRPC agents.[17,18] Future studies of the relationship between ALP response and pain response during Ra223 should include more patients and ideally daily pain medication logs to allow for more accurate pain assessment.

Conclusions

This population-based analysis suggests that meaningful pain responses are observed during a course of Ra223 in a population-based setting, although the changes are difficult to attribute entirely to the use of Ra223. While ALP levels declined in many cases during a course of Ra223, as expected, there was no observed correlation identified between pain response and ALP response.

Competing interests: Dr. Parimi has received honoraria from Astellas, AstraZeneca, Amgen, Ipsen, Janssen, and Pfizer; and has participated in clinical trials supported by Astellas and Janssen. Dr. McKenzie has been an advisory board member for Janssen; has received honoraria from Amgen and Bayer; and has participated in clinical trials supported by Janssen. Dr. Bachand has received an honorarium from Bayer. Dr. Alexander has received an honorarium from Bayer. Dr. Olson has received a grant (unrelated to this work) from Varian Medical Systems. Dr. Pai has been an advisory board member for and received honoraria from Amgen and Bayer; and has been a coinvestigator for the following trials: ASSERT, ASCEND RT, RADICALS, ATLAS, and SABRS. Dr. Chi has received honoraria from Astellas, Bayer, Janssen, and Sanofi; and has participated in clinical trials supported by Astellas, Astra Zeneca, Bayer, Eli Lilly, Essa, Janssen, Merck, Novartis, Pfizer, Roche, and Sanofi. Dr. Tyldesley has received speaker fees and advisory board participation honoraria from Bayer. The remaining authors report no competing personal or financial interests related to this work.

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