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Radium-223 in the Treatment of Metastatic Castrate-Resistant Prostate Cancer

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Abstract

Background

Radium 223 (Ra-223) has been successfully utilised for the treatment of men with metastatic castrate resistant prostate cancer (mCRPC). To date, no real world outcomes from its use in the Irish population have been described.

Methods

All men referred to our institution for Ra-223 from September 2016 to March 2019 were included. Patient demographics, treatments received, toxicities and outcomes were recorded. Overall survival (OS) and progression free survival (PFS) were analysed using the Kaplan-Meier method.

Results

Complete data was available for 54 men. Median age was 75 years (range 61-86 years). The median number of prior systemic treatments for mCRPC was 2 (range 0-4). Median ECOG performance status was 1 at the start of treatment and 2 at completion. The median number of Ra-223 cycles received was 4 with 37%(n=20) completing all 6 planned cycles. The most common treatment-related toxicity was fatigue seen in 52% of patients (n=28). Improved pain scores were documented in 76% of men requiring opioid analgesia at the start of treatment. The median OS was 7 months. A good ECOG performance status, fewer than 6 bone metastases, normal alkaline phosphatase level at start of treatment and chemotherapy naivety were associated with improved OS.

Conclusions

Ra-223 is a moderately well tolerated palliative treatment amongst Irish men with mCRPC.

Background

Metastatic prostate cancer accounts for over 500 deaths in Ireland each year with the emergence of castrate resistance a poor prognostic indicator. Over 90% of men with mCRPC have demonstrable bone metastases.[1] The development of skeletal related events (SRE) defined as: a pathologic fracture, spinal cord compression, necessity for radiation to bone (for pain or impending fracture) or surgery to bone, leads to disability, poor quality of life and death in these patients.[2,3] Although bisphosphonates and newer RANK-L inhibitors have been shown to reduce pain and the incidence of SRE, they do not impact on overall survival.[4,5] Radium 223 dichloride (Ra-223) is a bone seeking calcium mimetic that binds to areas of increased bone turnover and emits high energy alpha particle radiation inducing double stranded DNA breaks.[6,7] It has been shown to improve overall survival, time to first skeletal event and quality of life.[2]

Given the highly selective nature of patients enrolled on clinical trials, real world data is essential. Previous real world studies have demonstrated mixed efficacy of Ra-223 in the real world setting. Kuppen et al. demonstrated comparable results to the Phase III ALSYMPCA trial amongst the Dutch population, whilst Jiang et al demonstrated inferior results amongst the UK population.[8,9] To date, no real world studies regarding Irish men treated with Ra-223 have been conducted. Herein, we describe our findings from the first real world study of Ra- 223 in the Irish population

Methods

This was a single centre retrospective cohort study. Ethical approval was obtained through the Irish Clinical Research Ethics Committee. All men referred for Ra-223 to Cork University Hospital between September 2016 and March 2019 were included. Patient demographics, disease characteristics and survival data were collected using both electronic and paper medical records. Data regarding treatment received and tolerability of treatment was collected using an electronic chemotherapy/radiotherapy prescribing system. SPSS version 2.0 was used to analyse the data. Chi-squared statistical analysis was used for comparing results between groups. A p value cut-off of 0.05 was taken as statistically significant. Kaplan Meier analysis was used to calculate overall survival. Cox regression analysis was used to identify prognostic factors for overall survival.

Results

Patient Demographics and Disease Patterns

Between September 2016 and March 2019, 81 patients were referred to Cork University Hospital. Due to a lack of availability of full medical records, 27 patients were excluded from study, and thus 54 patients were analysed. The median age at referral for Ra-223 was 75 years (range 61-86 years). The majority of patients referred (78%, n= 42) had an ECOG performance status of 0-1 with the remaining 22% (n=12) having an ECOG performance status of 2. Concurrent co-morbidities were common with the median Charlson co-morbidity score at referral of 4 (range 2-12). Amongst our patient cohort, the median time to development of castrate resistant disease was 24 months (range 8-130 months). The burden of skeletal disease is outlined in *Table 1.*

Table 1: Demographic factors of Cork University Hospital cohort compared to that of the ALSYMPCA trial cohort.

	Cork University Hospital	ALYSMPCA
Aged Median (Range)	76 years (61-86 years)	71 years (49-90 years)
% of patients >75 years old	52%	28%
ECOG PS 0-1	78%	87%
Median Alkaline Phosphatase U/litre (range)	125 (16-2527)	211 (32-6431)
Median Hemoglobin g/dl	12 (9-15.5)	12.2 (7.7.-15.1)
No of prior treatments mCRPC (range)	2 (0-5)	1(0-2)
No of Bone Metastases		
<6 metastases	18.5%	16%
6-20 metastases	52%	43%
>20 metastases	26%	32%
Super scan	3.5%	9%
Prior Palliative Radiotherapy*	12%	16%

**within 12 weeks of trial randomisation*

In our cohort of patients, 53% (n=29) had a prior skeletal event. This was most commonly the requirement of palliative radiotherapy to a painful bone metastasis. Further skeletal events included spinal cord compression in 14% of patients (n=4) and a pathological fracture in one patient. Additionally, 55% (n=30) patients required opioid analgesia at their time of referral.

The median number of total prior treatments was 3 (range 1-6) and the median number in the mCRPC setting was 2 (range 0-5). The most commonly prescribed agents in the mCRPC setting were Abiraterone (46%), Enzalutamide (27%) and Docetaxel(26%).

The median time of cessation of systemic treatment prior to Ra-223 was 6 weeks. Eight patients remained on systemic anticancer therapy whilst receiving concurrent Ra-223 as no safety alerts regarding combinations had been released at that time. All ten patients were on bone sparing agents, most commonly Zoledronic acid (56%).

The demographic factors of the cohort of patients referred to Cork University Hospital compared to the cohort in the ALSYMPCA trial are presented in *Table 1.*

Tolerability and Toxicity

The median number of Ra-223 treatments received was four (range 1-6), with 37% (n=20) patients completing all six cycles of Ra-223.

The most common reason for early cessation of treatment was deterioration in the ECOG performance status. The median ECOG performance status at the instigation of treatment was 1 and at the completion or cessation of treatment 2.

Just 25% (n=14) of patients proceeded to further treatment during the follow up period of 13 months. The most common toxicities experienced are highlighted in *Table 2*. The most common toxicities across all grades were anemia and fatigue. No patients experienced Grade 4 toxicity. There were two deaths during Ra-223, one case of mesenteric ischemia and one cardiac arrest.

Table 2: Most common toxicities experienced.

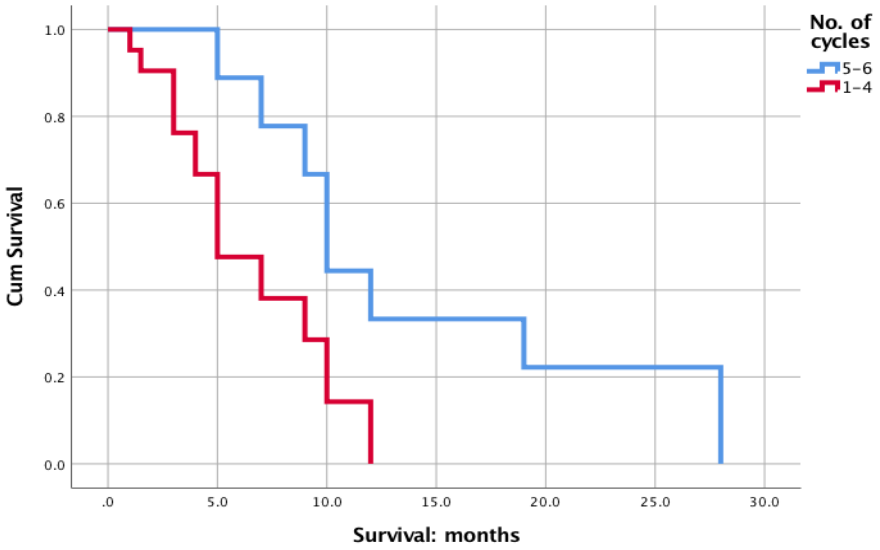
Adverse Events	All grade N (%)	Grade 1 N (%)	Grade 2 N (%)	Grade3 N (%)	Grade 4 N(%)
Hematologic					
Anaemia	11 (20%)	-	6(11%)	5(9%)	-
Neutropenia	2 (3.7%)	-	2(3.7%)	-	-
Thrombocytopenia	1 (1.8%)	-	-	1(1.8%)	-
Non Hematologic					
Fatigue	28 (52%)	11(20%)	13(24%)	4(7.4%)	-
Infection	6 (11%)	-	4(7.4%)	2(3.7%)	-
Nausea	5 (9%)	3(5.5%)	1(1.8%)	1(1.8%)	-
Weight loss	2 (3.7%)	2(3.7%)	-	-	-
Diarrhoea	3 (5.5%)	1(1.8%)	-	-	-

Efficacy and Overall Survival

Twenty four patients had an elevated alkaline phosphatase at the beginning of treatment. Sixty six percent (n=16) of these patients had >30% decline in alkaline phosphatase at the end of treatment and 50% (n=12) had complete normalisation. 30 patients were using opioid analgesia at the start of treatment, their median pain score prior to cycle 1 of Radium 223 was 5(range 2-7). Of these 30 men,74% (n=22) reported an improvement in their pain score, median pain score following completion of treatment was 3 (range 1-5), representing a median reduction in pain scores pre and post treatment of 2.

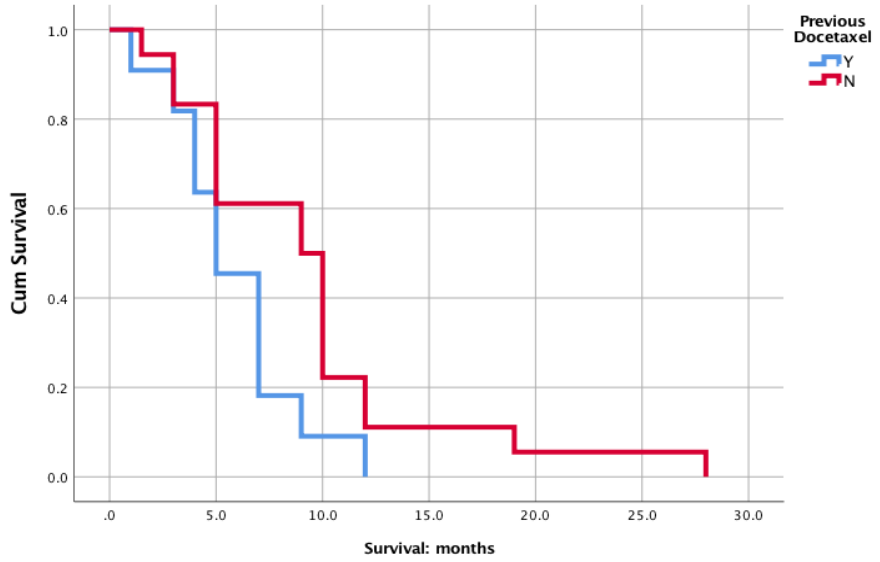
At a median follow up of 13 months, 41% (n=21) of patients were alive. The median overall survival (OS) for the entire group was 7 months. Further subgroup survival analysis was performed using a number of variables including the number of cycles of Ra-223 completed, Docetaxel naivety and number of prior treatments in mCRPC. A statistically significant difference was seen in the OS between those who had completed 5-6 cycles of Ra-223 versus those who had completed 1-4 cycles of treatment, median OS 10 months versus 5 months, p=0.01. (Fig.1)

Figure 2: Overall Survival: Number of Cycles of Radium 223.



Additionally, a statistically significant difference in OS was seen between patients who had Docetaxel pretreatment and those who were Docetaxel naïve: 5.1 months versus 10 months p=0.025. (Fig. 2). Patients who had normalisation of alkaline phosphatase had median OS of 10 months compared with patients who had a rise in alkaline phosphatase who had a median OS of 3 months. Of note, those who completed between 5 and 6 cycles of Ra-223 and had a normalisation of alkaline phosphatase (n=10) had the longest median OS of all subgroups at 12 months. Cox regression analysis identified the presence of lymphnode disease, a superscan appearance on bone scan and an ECOG performance status of 2 to be associated with poorer overall survival.

Figure 2: Overall Survival: Previous Docetaxel.



Discussion

This real world study demonstrated that over the past four years in Ireland, Ra-223 has been successfully utilised in the treatment of mCRPC. Ra-223 was relatively well tolerated amongst our cohort of patients, with limited grade 3 toxicities experienced. Despite this, just over a third of patients (37%) completed all six cycles of treatment compared to 58% of those on the ALSYMPCA trial. Furthermore, median overall survival amongst our cohort was inferior to both the treatment and placebo arm of the initial Phase 3 trial and indeed other real world settings. [2,8,9] The median overall survival for our cohort was 7 months compared to 11.2 months for the placebo arm and 14 months for the treatment arm in the Phase 3 ALYSMPCA trial.[2] We postulate a number of reasons for this. Firstly, the median age of our cohort was significantly older than that of the ALSYMPCA trial with over 85% (n=46) of our cohort aged over 75 years of age, compared to 23% of the cohort in the Phase III trial.[2] Secondly, our cohort had undergone significant pretreatment with the median number of prior treatments in the mCRPC setting alone being 2 versus median of 1 in the ALSYMPCA trial. Additionally, concurrent co-morbid conditions were common in our cohort and likely contributed to overall decline in ECOG performance status which led to early termination of treatment for many. Early termination of treatment has been linked to a poorer overall survival in not only our study, but also in previously published real world studies.[8]

Radium 223 appeared to offer the largest benefit in those who were chemotherapy naive and had completion or near completion of all cycles (5-6). Rad-223 represented the last line of treatment for the majority of our heavily pretreated patients. This likely contributed to its relatively modest tolerability amongst the Irish population. Future utilisation of Ra-223 in Ireland at an earlier time point in the treatment paradigm of mCRPC- as is being trialed in the PEACE III trial -may confer an improvement in tolerability, higher rates of completion of treatment and subsequent improved efficacy amongst the Irish and global population.[10] Our study is limited by its small sample size, further collaboration with other tertiary centres to establish an all-Ireland overview of Ra-223 in the real world setting would be useful.

Our study demonstrates that Ra-223 is a tolerable and efficacious treatment in a cohort of patients with advanced mCRPC, however in patients with a baseline ECOG performance status of 2, extensive bone disease and lymphnode disease, its benefit may be limited.

Declaration of Conflicts of Interest:
I can declare that there are no conflicts of interest for this article.

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