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Review of Palliative Radium 223 (223Ra) in metastatic castration resistant prostate cancer (mCRPC): Experience at West Virginia University (WVU) Cancer Center

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ABSTRACT

BACKGROUND

The ALSYMPCA trial of α-emitter 223Ra in symptomatic bone predominant mCRPC reported 223Ra median overall survival (OS) of 14.9 months versus 11.3 months OS for placebo. However, subsequently reported "real world" experience with 223Ra in smaller mCRPC patient cohorts has appeared less successful. We performed a retrospective observational study to review our own 223Ra experience at WVU.

METHODS

Demographic, clinical, laboratory and imaging data were reviewed in all bone predominant mCRPC patients treated with 223Ra at WVU, from 2014 to 2019. The number of bone metastases per patient at start of treatment with 223Ra was quantified via nuclear bone scans (12; 5 of which also had SPECT/CT), body CT scans (8), and PET/CT scans (4). Standard descriptive statistics were used to study IRB-exempt, de-identified patient data. Median survival in ALSYMPCA and WVU patients was compare using a two-sided one-sample log-rank test based on the exponential distributions. The primary end-point was patient overall survival (OS) after initiating 223Ra.

RESULTS

Twenty four men received 98 infusions of 223Ra; 83% of these men were referred from outside WVU. Prior to first infusion, all 24 had received androgen deprivation therapy (ADT). These 24 men received a total of 73 sequential combinations of ADT, 68 of which (93%)

preceded the first 223Ra infusion. Also, before 223Ra, 19 (79%) had received docetaxel and 19 (79%) had received 33 courses of radiation, 24 of which targeted non-prostate sites.

Eleven men (46%) completed all six planned 223Ra infusions; 13 (54%) stopped early because of clinical deterioration. As of August 2020, only one patient remains alive after completing 6 cycles of 223Ra. Median OS from first 223Ra infusion to last follow-up or death was 8.3 months (range 0-44 mos.) -- nearly 50% less than the ALSYMPCA median survival of 14.9 months (P 0.01). Compared to ALSYMPCA, more WVU patients had received bisphosphonates and docetaxel, more had ECOG PS $\geq$2, more used opiates for pain, more had greater bone metastases burden by imaging, and more had lower hemoglobin, albumin, alkaline phosphatase, and PSA levels.

CONCLUSIONS

While the science supporting the development and clinical use of 223Ra is compelling, optimal clinical benefit will likely require earlier referral for 223Ra, before patients have exhausted most conventional therapies. At WVU, we found that our referred patients had practically all ADT, radiation, and cytotoxic therapy before starting 223Ra. We continue to offer 223Ra therapy to men with symptomatic bone-predominant CRPC, but are encouraging earlier patient referral.

KEYWORDS: Metastatic, Castration resistant, Prostate Cancer, Radium 223

INTRODUCTION

Prostate cancer (PC) is the second commonest cancer in men, with an estimated 174,650 new cases and 31,620 deaths in 2019 in the United States *(1).* PC patients with bone metastasis frequently experience skeletal-related events (SREs), including pathological fractures, hypercalcemia, spinal cord compromise, and pain requiring surgery, radiotherapy and other interventions *(2).*

A large, multicenter, randomized, placebo-controlled, phase 3 trial of 223Ra in mCRPC (ALSYMPCA trial) with positive results led to subsequent approval of 223Ra by the United States Food and Drug Administration (FDA) to treat symptomatic bone metastasis in patients with mCRPC with no known visceral metastasis *(3).* The median overall survival was 14.9 months in patients who received 223Ra versus 11.3 months in those receiving placebo, a 30% reduction in the risk of death in 223Ra patients versus placebo. Also, the time to the first symptomatic SRE was significantly prolonged in patients receiving 223Ra *(3).*

However, post-approval "real world" experience with 223Ra in mCRPC has often found shorter median survival and greater complication rates than reported by the ALSYMPCA trial *(4-19).*

We decided to perform our own retrospective observational study of our clinical experience with 223Ra in mCRPC patients referred to the West Virginia University Cancer Center.

PATIENTS AND METHODS

Demographic, clinical and laboratory data was collected from electronic medical records (Epic) for every man with prostate cancer who received 223Ra during a five-year period beginning in 2014. No patient who received any 223Ra at WVU during this period was excluded. Several outside laboratory results in one patient could not be retrieved, so laboratory data on 23 patients was analyzed. A nuclear radiologist who administered the 223Ra reviewed nuclear bone scans, nuclear SPECT/CT scans, and PET scans to quantify the number of bone metastases in each patient at start of 223Ra. Imaging included 12 nuclear bone scans (5 of which also had SPECT/CT), 8 body CT scans, and 4 PET/CT scans. Patient parameters were compared to those published from the ALSYMPCA trial patients who received 223Ra[3]. (Tables 1-3)

Standard descriptive statistics (mean, median, min, max, range) were used to study IRB-exempted, de-identified patient data. Median survival in ALSYMPCA and WVU patients was compare using a two-sided one-sample log-rank test based on exponential distributions. The primary end-point was WVU patient survival from the start of the 223Ra infusions, calculated using the Kaplan-Meir method. (Figure 1).

RESULTS

Over a 5-year period, 24 patients received 98 total monthly infusions of 223Ra. All patients resided in West Virginia and 83% were referred from oncology practices outside of WVU.

At initial cancer diagnosis, prior to 223Ra, only 4 patients (17%) had disease localized to the prostate and 12 (50%) were TNM classification M1/stage 4. At time of first 223Ra infusion, median age (range) was 68 (54-89) years and median PSA value (range) was 75.4 (1.5 to 928.1) ng/mL.

The 24 mCRPC patients received, in total, 73 sequential combinations of androgen deprivation therapy (ADT), including abiraterone (with prednisone), bicalutamide, degarelix, finasteride, leuprolide, megesterol, enzalutamide, or estrogen patches. All 24 patients received one (100%), 22 received two (92%), 17 received three (71%), and 10 received four or more trials of various ADT (42%). Given all of the different types of ADT administered, 93% of all ADT preceded the first infusion of 223Ra.

Eighteen patients (75%) received docetaxel chemotherapy prior to 223Ra, and eight of these had two or more chemotherapy agents before 223Ra. Nineteen patients (79%) received a total of 33 courses of radiation therapy; 9 courses targeted the prostate, 24 courses targeted other palliative sites. For 18 of the 19 radiation therapy patients (95%), radiation preceded the first infusion of 223Ra.

All 24 men (100%) received a first infusion of 223Ra; 21 (88%) a second; 16 (67%) a third; 13 (54%) a fourth; 13(54%) a fifth; and 11(46%) received all six planned infusions. Thus, 13 men (54%) did not complete all six planned infusions of 223Ra, stopping because of clinical deterioration. The median overall survival in the 24 men, from first 223Ra infusion to last

follow-up (August 2020) was 8.3 months (range 0-44), P 0.01 versus the ALSYMPCA median survival (Tables 1-3). One of the 24 patients currently remains alive with disease, having completed 6 cycles of 223Ra.

DISCUSSION:

The science supporting the development and clinical use of 223Ra is compelling. An α-emitter, Radium-223 dichloride (223Ra) is bone-seeking and complexes with hydroxyapatite, releasing short range (<100 μm) high-energy particles that exert a selective anti-tumor effect *(20).* Areas of active bone remodeling and bone vascular supply are the main target sites for 223Ra localization *(21).* In mouse models, 223Ra inhibits tumor-induced pathological bone formation in the tumor microenvironment adjacent to tumor foci *(22).*

Pre-clinical work with mice confirmed that 223Ra selectively accumulates in the bone with only minute amounts of daughter radionuclides released from skeletal sites of 223Ra decay[23]. Moreover, dosimetry studies showed that short-range alpha radiation from 223Ra substantially spares bone marrow, with relatively less toxicity as compared to beta-emitting Strontium-89 *(23).*

A Phase 1 clinical trial demonstrated that 223Ra preferentially targets bone metastases rather than diffusely targeting healthy bone tissue *(24)*. A randomized, multicenter, placebo-controlled, Phase 2 trial, assigned patients receiving external beam radiation therapy (EBRT) for pain control, to receive either four 223Ra injections (50 $kBq\ kg^{-1}$) at 4-week intervals or placebo on the same schedule. The group receiving 223Ra demonstrated significant decline in alkaline phosphatase levels, delay in time to PSA progression, and a trend towards reduced skeletal related events and improved overall survival. The safety profile was acceptable, hematologic toxicity was not significantly different between the two groups, and no patient discontinued 223Ra due to treatment-related toxicity *(25).*

Parker et al reported the pivotal phase III study of 223Ra, involving 614 223Ra treated patients versus 307 in a placebo group, treated at 136 centers in 19 countries *(3).* At time of publication, 532 of 921 patients (58%) had received all six injections of 223Ra. The median overall survival was 14.9 months in the 223Ra group and 11.3 months in the placebo group. Radium 223 was associated with a 30% reduction in the risk of death versus placebo. The effect of 223Ra on overall survival was consistent across all subgroups, and 223Ra was not associated with significantly more grade 3 or 4 toxic effects than placebo.

However, subsequent to 223Ra approval and widespread use in the United States, multiple reports raised caveats concerning patient selection for 223Ra, finding shorter overall survival and more adverse events than reported by ALSYMPCA. The majority of these have been smaller cohorts in both single institutions as well as a few multi-center experiences. Stolen et al and Vogelzang et al both looked at outcomes of patients receiving the full 6 cycles versus those who could not complete treatment. The cohorts had 55-184 patients and OS favored those who completed all 6 cycles of therapy (16 mo vs 4 mo in Stolen et al cohort, 17 mo in Vogelzang cohort) *(4-5).*

Etchebehere et al reported 41 men with metastatic PC treated at MD Anderson Cancer Center who had fluoride PET/CT prior to 223Ra *(26).* They defined bone marrow failure (BMF) as World Health Organization (WHO) grade 3 hematologic toxicity with no recovery after 6 weeks, or recorded death due to bone marrow failure. BMF correlated with tumor burden on imaging, which by multi-variable analysis, was the only independent predictor for bone marrow failure. Another report by Etchebehere et al on 110 223Ra treated patients noted that improving alkaline phosphatase levels and pain scores were associated with improved outcomes *(6).*

Additionally there have also been multiple reports showing better outcomes when using 223Ra earlier in the course of disease. Hague et al, Saad et al, Baldari et al, Wong et al and Sartor et al all found this to be the case within their respective studies *(27-29, 8).* Specifically Saad et al had the largest cohort of these and reported on the "early access" program after the ALSYMPCA study and before regulatory approval of 223Ra in 2013. 839 patients were enrolled from 113 sites in 14 countries; 696 patients received one or more doses of 223Ra; 403 (58%) had all 6 planned injections *(28).*

Finally Sartor et al reported the U.S. experience from the expanded access, phase II, open label, single arm, multi-center trial. Those with more advanced disease were less likely to benefit from the isotope. The median overall survival in those receiving 5-6 injections was not reached, while the median survival in those with fewer than 5 injections was 7.5 months *(12).*

In July 2018, the European Medicines Agency (EMA) safety committee, Pharmacovigilance Risk Assessment Committee (PRAC), recommended restricting the use of radium-223 dichloride to patients who have had only two previous treatments for metastatic prostate cancer or who cannot receive other treatments *(13, 14).* PRAC recommended that 223Ra should not be used with: 1) abiraterone plus corticosteroid, 2) other systemic cancer therapies except for hormonal therapy, and 3) in asymptomatic patients or those with few osteoblastic bone metastases. PRAC further suggested that patients be carefully assessed for fracture risk, and use of bisphosphonates or RANKL inhibitors should be considered to increase bone strength before 223Ra. While O'Sullivan et al made a case against these PRAC restrictive recommendations, Leibowitz-Amit countered that the EMA recommendations were not only because of detrimental effects on bone fractures when used with abiraterone, but also because of risk of lymph node or visceral progression during 223Ra bone-focussed treatment *(30, 31).*

Of interest, one study has looked at possible predictive measures of survival in patients receiving 223Ra. Dittman et al used quantitative bone SPECT/CT scanning prior to 223Ra in 60 patients with mCRPC, and found that isotope uptake in the central skeleton varied from 11-56% of the injected dose. After 223Ra, median overall survival (OS) in all 60 patients was 15.2 months. When skeletal uptake was 26% or more, median OS was 7.3 months; when skeletal uptake was < 26%, median OS was 30.8 months *(17).* The authors concluded that initial quantitative SPECT/CT bone scanning could predict subsequent patient survival after treatment with 223Ra. This finding may be of interest in future, once more data becomes available.

After reviewing our own patient experience, we identified certain factors likely contributing to our patients' shorter than expected median overall survival. Practically all androgen deprivation, radiation, and cytotoxic therapy was given prior to referral to WVU for 223Ra. Although most referred patients initially seemed eligible for 223Ra based on performance status and usual laboratory parameters, many appeared to receive only minor benefit from 223Ra as administered. When compared to the original ALSYMPCA prostate cancer patients, more patients at WVU received bisphosphonates and docetaxel, had PS >2, took more opiates for cancer pain, had greater bone metastases burdens, and had lower hemoglobin, albumin, alkaline phosphatase, and PSA levels (Tables 1-3).

Eighty-three percent of our patients were referred from outside clinicians, and 54% of our patients could not receive the planned six infusions of 223Ra, stopping because of clinical deterioration. The median overall survival in the 24 men, from first 223Ra infusion to last follow-up (August 2020) was 8.3 months (range 0-44), inferior to the ALSYMPCA median survival (P 0.01, Table 1). One of the 24 patients currently remains alive with disease, having completed 6 cycles of 223Ra.

Potential limitations of our study are that it was observational and retrospective, and our Appalachian referral patient results may be hard to extrapolate to other practice settings. The ALSYMPCA trial was multi-centered, multi-national, and prospective, while our WVU data was from a single referral center. The number of 223Ra treated patients studied in the two trials differed by over 25-fold, as we had a relatively small number of patients in our data set (the last patient reported here started 223Ra in Oct 2018). Also, data collection time frames of the two studies differed by more than five years. Imaging in our patients included 12 nuclear bone scans (5 of which also had SPECT/CT), 8 body CT scans, and 4 PET/CT scans. Thus, only 7 patients had only a nuclear bone scan, and use of higher resolution imaging in the other 17 might have increased our detection of the number of bone lesions versus earlier studies using only conventional nuclear bone scans *(17).* Despite these issues, our report adds to the growing amount of "real world" data concerning use of 223Ra, which will hopefully guide the future clinical application of this promising isotope.

In conclusion, we think that our initial referral pattern resulted in more heavily pre-treated cancer patients receiving 223Ra, with suboptimal results versus ALSYMPCA. Hopefully, this will improve as patients become more aware of 223Ra availability and use, with earlier patient demand and earlier referral for 223Ra. Currently, 223Ra appears to be an evolving and promising treatment for bone predominant metastatic prostate cancer and potentially for other osteoblastic tumors, including metastatic breast cancer, differentiated thyroid cancer, and renal cell carcinoma *(32).* However, treatment benefit will likely be optimal when 223Ra is given earlier, targeted to patients who have not already exhausted most conventional therapies. Going forward, we are continuing to offering 223Ra isotope therapy for men with symptomatic bone predominant castrate-resistant prostate cancer but emphasize earlier referral to our center.

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Table 1: Baseline 223Ra prostate cancer patient characteristics: ALSYMPCA Trial (NEJM 2013; 369:213-223) versus WVU 223Ra patients

223Ra Treatment Group	ALSYMPCA	WVUH
Number of patients	614	24
Survival, median months	14.9	8.3 (P 0.01)
Median Age, years (range)	71 (49-90)	68 (54-89)
>75 years old	171 (28%)	4 (17%)
Caucasian	575 (94%)	24 (100%)
Current bisphosphonates, Yes	250 (41%)	15 (63%)
Current bisphosphonates, No	364 (59%)	9 (37%)
Any Prior docetaxel, Yes	352 (57%)	17 (71%)
Any Prior docetaxel, No	262 (43%)	7 (29%)
ECOG performance status 0	165 (27%)	1 (4%)
ECOG performance status 1	371 (60%)	14 (58%)
ECOG performance status 2+	77 (13%)	9 (38%)
WHO ladder for cancer pain 0		3 (13%)
WHO ladder for cancer pain 1	257 (42%)	3 (13%)
WHO ladder for cancer pain 2	151 (25%)	7 (29%)
WHO ladder for cancer pain 3	194 (32%)	11 (46%)

Table 2: Baseline 223Ra prostate cancer patient characteristics (laboratory data): ALSYMPCA Trial (NEJM 2013; 369:213-223) versus WVU 223Ra patients

223Ra Treatment Group	ALSYMPCA	WVUH
Median Biochemical Values, (range)	N = 614 pts	N = 23 pts
Total Alkaline Phosphatase <220 U/L	348 (57%)	18/23 (78%)
Total Alkaline Phosphatase >220 U/L	266 (43%)	5/23 (22%)
Hemoglobin g/dL	12.2 (8.5-15.7)	11.5 (8.6-15.3)
Albumin g/L	40 (24-53)	33.5 (17-39)
Total Alkaline Phosphatase, U/L	211 (32-6431)	115 (68-820)
Lactate dehydrogenase U/L	315 (76-2171)	274 (118-809)
PSA microgm/L	146 (3.8-6026)	75.4 (1.5-928)

Table 3: Baseline 223Ra prostate cancer patient characteristics (bone metastasis and radiation): ALSYMPCA Trial (NEJM 2013; 369:213-223) versus WVU 223Ra patients

223Ra Treatment Group	ALSYMPCA	WVUH
Bone Metastases <6	100 (16%)	3/23 (13%)
Bone Metastases 6-20	262 (43%)	5/23 (22%)
Bone Metastases >20	195 (32%)	14/23 (61%)
Bone Metastases “Super Scan”	54 (9%)	1/23 (4%)
Radiation <12 weeks from screening, Yes	99 (16%)	3 (13%)
Radiation <12 weeks from screening, No	515 (84%)	21 (87%)

Figure 1: Kaplan-Meier overall survival (OS) of 24 WVUH prostate cancer patients from time of first Radium-223 isotope infusion.