

The Effect of Radium-223 Therapy in Agent Orange-Related Prostate Carcinoma

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Background: Radium-223 (Ra-223) radioisotope has been reported to increase median survival in bone metastatic prostate carcinoma. The addition of Ra-223 to abiraterone was associated with an increased risk of bone fractures. There has been no comprehensive data for using Ra-223 in veterans who were exposed to Agent Orange (AO+).

Methods: We present a retrospective study of veterans with bone metastatic castration-resistant prostate cancer (CRPC) who received standard doses of Ra-223 and other sequential therapies at US Department of Veterans Affairs Pittsburgh Healthcare System in Pennsylvania from January 2014 to January 2019. Veterans were divided into 2 groups: those who were exposed to Agent Orange (AO+) and those who had no exposure (AO-). Time to study was calculated from the initiation of Ra-223. Time to skeletal-related events (SRE), progression of prostate specific antigen (PSA), bone metastasis, and alkaline phosphatase (ALP) were calculated in months using unpaired t test with 2-tailed *P* values. Median survival was calculated by Kaplan Meier R log-rank test.

Results: There were 34 veterans with bone metastatic CRPC: 17 veterans (50%) were AO+ and 17 veterans (50%) were AO-. The mean age of diagnosis of AO+ veterans was 62 years and

69 years (*P* = .005) for AO- veterans (the mean Gleason score 8.2 and 8.0, respectively [*P* = .71]). The median number of Ra-223 cycles was 6 (60%). Ten veterans received Ra-223 as first line (29%) and 24 veterans received Ra-223 later (71%). There were 12 SREs with median survival of 15 months. There was no difference in mean time to SRE between AO+ (8 veterans, 10.6 months) and AO- (4 veterans, 10.3 months) (*P* = .93). The mean time to PSA progression for AO+ was 5.4 months and AO- was 6.8 months (*P* = .28). Mean time to bone progression for AO+ was 7.6 months and AO- was 10.1 months (*P* = .16). Mean time to ALP progression for AO+ and AO- was 6.3 months and 8.7 months, respectively (*P* = .05). Twenty veterans (58%) had died. Median survival for Ra-223 first was 32 months and for Ra-223 later was 15 months (*P* = .14; hazard ratio [HR] 0.48; 95% CI, 0.17- 1.3). Median survival for AO+ and AO- veterans was 12 months and 18 months, respectively (*P* = .15; HR, 2.0; 95% CI, 0.77-5.0).

Conclusions: There was no statistical difference between AO+ and AO- veterans in terms of time to SRE, PSA, bone and ALP progression, even though there was a trend of shorter duration in AO+ veterans. There was no median survival difference between Ra-223 first vs Ra-223 later as well as between AO+ and AO- but there is a trend of worse survival in AO+ veterans.

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Patients with metastatic castrate resistant prostate carcinoma (CRPC) have several treatment options, including radium-223 dichloride (Ra-223) radionuclide therapy, abiraterone, enzalutamide, and cabazitaxel. Ra-223 therapy has been reported to increase median survival in patients with bone metastatic prostate carcinoma.^{1,2} However, ERA 223 trial data showed an increase of bone fractures with combination of Ra-223 and abiraterone.³

Agent Orange (AO) exposure has been studied as a potential risk factor for development of prostate carcinoma. AO was a commercially manufactured defoliate that was sprayed extensively during the Vietnam War. Due to a side product of chemical manufacturing, AO was contaminated with the toxin 2,3,7,8-tetrachlorodibenzo-p-dioxin, a putative carcinogen. These dioxins can enter the food chain through soil contamination. There is enough evidence to link AO to hematologic malignancies and several solid tumors, including prostate carcinoma.⁴ Although no real estimates exist for what percentage of Vietnam veterans experienced AO exposure, Sur-

veillance, Epidemiology, and End Results data showed that about 3 million veterans served in Southeast Asia where AO was used extensively in the combat theater. AO has been reported to be positively associated with a 52% increase in risk of prostate carcinoma detection at initial prostate biopsy.⁵

There has been no reported study of treatment efficacy in veterans with AO-related prostate carcinoma. We present a retrospective study of Ra-223 and other therapies in metastatic CRPC. The purpose of this study was to compare response to therapy and survival in veterans exposed to agent orange (AO+) vs veterans who were not exposed to (AO-) in a single US Department of Veteran Affairs (VA) medical center.

METHODS

This was a retrospective study of veterans with metastatic CRPC to bones who received Ra-223 radionuclide therapy with standard dose of 50 kBq per kg of body weight and other sequential therapies at VA Pittsburgh Healthcare System (VAPHS) from January 2014 to January 2019. The

purpose of this study was to measure difference in treatment outcome between AO+ veterans and AO- veterans.

Eligibility Criteria

All veterans had a history that included bone metastasis CRPC. They could have 2 to 3 small lymphadenopathies but not visceral metastasis. They received a minimum of 3 cycles and a maximum of 6 cycles of Ra-223 therapy, which was given in 4-week intervals. Pretreatment criteria was hemoglobin > 10 g/dL, platelet > 100 × 10⁹/L, and absolute neutrophil counts > 1.5 × 10⁹/L. Other therapies, such as abiraterone, enzalutamide, docetaxel, and cabazitaxel, were administered either after Ra-223 (Ra first) or before Ra-223 therapy (Ra later). Veterans also received androgen deprivation therapy (ADT) with luteinizing hormone releasing hormone (LHRH) agonist (leuprolide acetate) to maintain castrate level of testosterone and bisphosphonates for bone metastasis. Eligible veterans were divided into 2 groups: AO+ and AO-. AO+ veterans are those that were proven to be physically active during the Vietnam War and have been determined by the US government to receive service-connected compensation from the VA. AO- veterans were those who were not exposed to AO.

Statistics

Time to study was calculated from Ra-223 therapy initiation. Time to skeletal-related events (SRE), progression of prostate specific antigen (PSA), bone metastasis, and alkaline phosphatase (ALP) were calculated in months, using unpaired *t* test with 2-tailed *P* value. Median survival was calculated in months by Kaplan Meier R log-rank test (without definition).

RESULTS

Forty-eight veterans with bone metastasis CRPC received Ra-223 therapy. Of those, 34 veterans were eligible for this retrospective study: 17 AO+ veterans and 17 AO- veterans. Mean age of diagnosis was 62 years (AO+) and 69 years (AO-) (*P* = .005). Mean Gleason score was 8.2 (AO+) and 8.0 (AO-) (*P* = .71). Veterans received initial therapy at diagnosis of prostate carcinoma, including radical prostatectomy (6 AO+ and 3 AO-), localized radiation therapy (3 AO+ and

DEFINITIONS

Time to skeletal-related event: Use of radiation therapy to relieve skeletal symptoms, development of pathologic bone fractures, spinal cord compression, or tumor-related orthopedic surgical intervention.

Progression of prostate-specific antigen (PSA): Increase of ≥ 25% from the baseline level and an absolute increase of ≥ 2 ng/mL (for PSA) at ≥ 12 weeks.

Progression of alkaline phosphatase: Increase of ≥ 25% from the baseline level.

Progression of bone metastasis: New bone lesions (at least 2) and confirmed 12 weeks later with a follow-up bone scan.

TABLE 1 Demographics for Study Participants Receiving Ra-223

| Characteristics | AO+ (n = 17) | AO- (n = 17) | P Value |
|--|----------------|-----------------|---------|
| Age of diagnosis, mean, y | 62 | 69 | .005 |
| Gleason score, mean | 8.2 | 8.0 | .70 |
| PSA at starting Ra-223 (mean) | 2.0-551 (92.8) | 4.0-639 (102.3) | .86 |
| Ra-223 dose/cycle (minimum 3), mean, uCi | 157 | 113 | |
| ADT leuprolide acetate, No. | 17 | 17 | |
| Bisphosphonate (ZA or denosumab), No. | 16 | 14 | |
| Ra-223 first line, No. | 4 | 6 | |
| Ra-223 after other therapies, No. | 13 | 11 | |
| Previous therapies, No. | | | |
| Prostatectomy | 6 | 3 | |
| Radiation therapy | 3 | 5 | |
| ADT only, No. | 8 | 9 | |

Abbreviations: ADT, androgen deprivation therapy; AO+, veterans who were exposed to Agent Orange; AO-, veterans who were not exposed to Agent Orange; PSA, prostate specific antigen, Ra-223, radium-223; ZA, zoledronic acid.

5 AO-), and ADT (8 AO+ and 9 AO-) (Table 1).

Mean PSA at the initiation of Ra-223 therapy for AO+ was 92.8 (range, 2-551) and for AO- was 102.3 (range, 4-639; *P* = .86). Mean Ra-223 dose per cycle for AO+ and AO- was 157 uCi and 113 uCi, respectively. All 34 veterans received ADT (leuprolide acetate), and 30 veterans (16 AO+ and 14 AO-) received bisphosphonates (zoledronic acid or denosumab). A total of 10 veterans (29%) received Ra-223 as a first-line therapy (4 AO+ and 6 AO-), and 24 veterans (71%) received Ra-223 after hormonal or chemotherapy (13 AO+ and 11 AO-).

There were 12 SRE (8 AO+ and 4 AO-). Mean time to SRE for AO+ was 10.6 months and AO- was 10.3 months (*P* = .93). Three veterans received concurrent Ra-223 and abiraterone (participated in ERA 223 trial). Two AO+ veterans experienced SRE at 7 months and 11 months, respectively. Mean time to

TABLE 2 Median Survival and Time to Progression Comparisons

| Comparisons | AO+, Mo (n = 17) | AO-, Mo (n = 17) | P Value |
|--------------------------------|--------------------------------------|--------------------------------------|-----------------------------------|
| Time to SRE, mean | 10.6 | 10.3 | .93 |
| Time to PSA progression, mean | 5.4 | 6.8 | .28 |
| Time to bone progression, mean | 7.6 | 10.1 | .16 |
| Time to ALP progression, mean | 6.3 | 8.7 | .05 |
| Survival, median | 12.0 | 18.0 | .15, HR 2.0 (95% CI 0.77-5.0) |
| | Ra-223 first, Mo (n = 10) | Ra-223 later, Mo (n = 24) | |
| Survival, median | 32.0 | 15.0 | .14, HR 0.48 (95% CI 0.17-1.3) |

Abbreviations: ALP, alkaline phosphatase; AO+, veterans who were exposed to Agent Orange; AO-, veterans who were not exposed to Agent Orange; CI, confidence interval; HR, hazard ratio; PSA, prostate specific antigen, Ra-223, Radium-223; SRE, skeletal related events.

PSA progression for AO+ was 5.4 months and for AO- was 6.8 months ($P = .28$). Mean time to bone progression for AO+ and for AO- were 7.6 months and 10.1 months, respectively ($P = .16$). Mean time to ALP progression for AO+ and AO- were 6.3 months and 8.7 months, respectively ($P = .05$). (Table 2). The treatment pattern of AO+ and AO- is depicted on a swimmer plot (Figures 1 and 2).

Twenty veterans (58%) had died: 13 AO+ and 7 AO- veterans. Median survival for Ra-223 first and Ra-223 later was 32 months and 15 months, respectively ($P = .14$; hazard ratio [HR], 0.48). Overall median survival for AO+ veterans and AO- veterans were 12 months and 18 months, respectively ($P = .15$; HR, 2.0) (Figures 3 and 4).

DISCUSSION

There has been no reported VA study of using Ra-223 and other therapies (hormonal and chemotherapy) in veterans exposed to AO. This is the first retrospective study to compare the response and survival between AO+ and AO- veterans. Even though this study featured a small sample, it is interesting to note the difference between those 2 populations. There was 1 prior study in veterans with prostate carcinoma using radiotherapy (brachytherapy) in early-stage disease. Everly and colleagues reported that AO+ veterans were less likely to remain biochemically controlled compared with AO- and nonveteran patients with prostate carcinoma.⁴

Ansbaugh and colleagues reported that AO was associated with a 75% increase in the risk of Gleason ≥ 7 and a 110% increase in Gleason ≥ 8 . AO+ veterans are at risk for the detection of high-grade prostate carcinoma. They also tend to have an average age of diagnosis that is 4 to 5 years younger than AO- veterans.⁶

Our study revealed that AO+ veterans were diagnosed at a younger age (mean 62 years) compared with that of AO- veterans (mean 69 years, $P = .005$). We also proved that AO veterans have a higher mean Gleason score (8.2) compared with that of AO- veterans (8.0). Veterans received therapy at the time of diagnosis of prostate carcinoma with either radical prostatectomy, radiation therapy, or ADT with leuprolide acetate. Mean PSA at the start of Ra-223 therapy for AO+ was 92.8 (range, 2-551); for AO- was 102.3 (range, 4-639), which is not statistically significant.

Ra-223, an α -emitting radiopharmaceutical, mimics calcium in forming complexes with the bone mineral hydroxyapatite, which specifically targets bone metastases. Ra-223 preferentially targets new bone growth surrounding bone metastases while emitting α particles within the tumor microenvironment. α particles have high linear energy transfer with enhanced ability to induce lethal double-stranded DNA breaks, thus eliciting greater cytotoxic effects on bone-metastatic tumor sites.⁷

In a phase 3, randomized, double-blind, placebo-controlled study by Parker and colleagues (ALSYMPCA study), 921 patients who had received, were not eligible to receive, or declined docetaxel, in a 2:1 ratio, were randomized to receive 6 injections of Ra-223 or matching placebo.² Ra-223 significantly improved overall survival (OS) (median, 14.9 months vs 11.3 months) compared with that of placebo. Ra-223 also prolonged the time to the first symptomatic SRE (median, 15.6 months vs 9.8 months), the time to an increase in the total ALP level (median 7.4 months vs 3.8 months), and the time to an increase in the PSA level (median 3.6 months vs 3.4 months).²

In our study, the mean time to SRE for AO+ was 10.6 months and AO- was 10.3 months ($P = .93$). Mean time to PSA progression for AO+ was 5.4 months and for

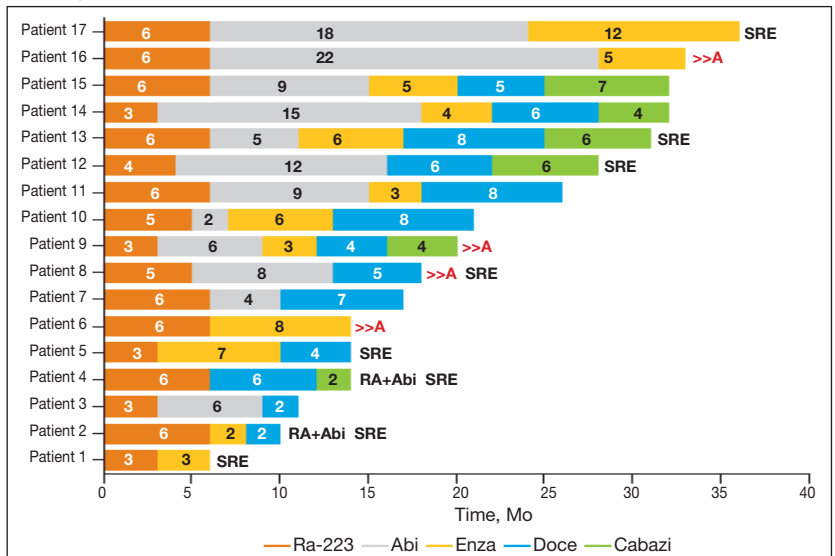
AO- was 6.8 months ($P = .28$). Mean time to bone progression for AO+ and for AO- were 7.6 months and 10.1 months respectively ($P = .16$). Mean time to ALP progression for AO+ and AO- were 6.3 months and 8.7 months respectively ($P = .05$). There is a trend of shorter PSA progression, bone progression, and ALP progression in AO+ veterans, though these were not statistically significant. The median survival for AO- was 18 months and for AO+ was 12 months, which is comparable with median survival of 14.9 months from the ALSYMPCA study.

Twelve veterans developed SREs. All received radiation therapy due to bone progression or impending fracture. AO+ veterans developed more SREs ($n = 8$) than did AO- veterans ($n = 4$). There were more AO- veterans alive ($n = 10$) than there were AO+ veterans ($n = 4$). The plausible explanation of this may be due to the aggressive pattern of prostate carcinoma in AO+ veterans (younger age and higher Gleason score).

VAPHS participated in the ERA trial between 2014 and 2016. The trial enrolled 806 patients who were randomly assigned to receive first-line Ra-223 or placebo in addition to abiraterone acetate plus prednisone.³ The study was unblinded prematurely after more fractures and deaths were noted in the Ra-223 and abiraterone group than there were in the placebo and abiraterone group. Median symptomatic SRE was 22.3 months in the Ra-223 group and 26.0 months in the placebo group. Fractures (any grade) occurred in 29% in the Ra-223 group and 11% in the placebo group. It was suggested that Ra-223 could contribute to the risk of osteoporotic fractures in patients with bone metastatic prostate carcinoma. Median OS was 30.7 months in the Ra-223 group and 33.3 months in the placebo group.³

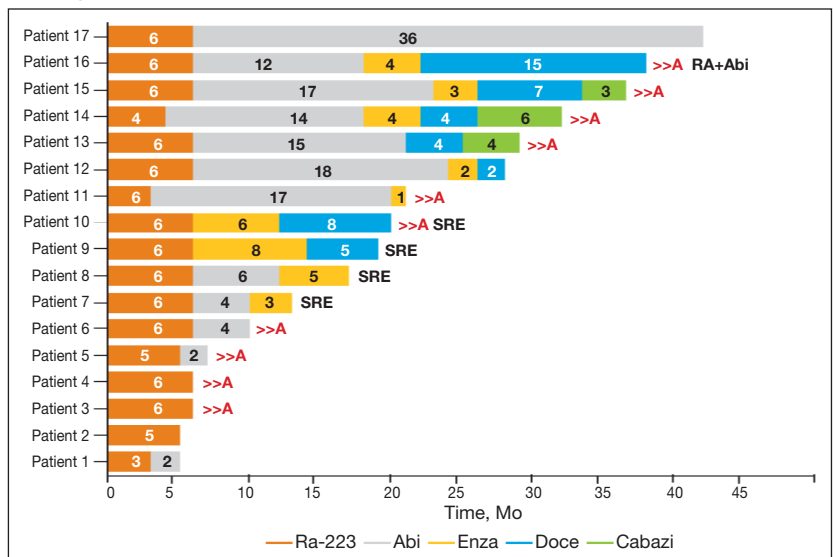
We enrolled 3 veterans in the ERA clinical trial. Two AO+ veterans had SREs at 7 months and 11 months. In our study, the median OS for Ra-223 first line was 32 months, which is comparable with median survival of 30.7 months from ERA-223 study. Median survival for Ra-223 later was

FIGURE 1 Treatment Pattern of 17 Veterans With Agent Orange Exposure



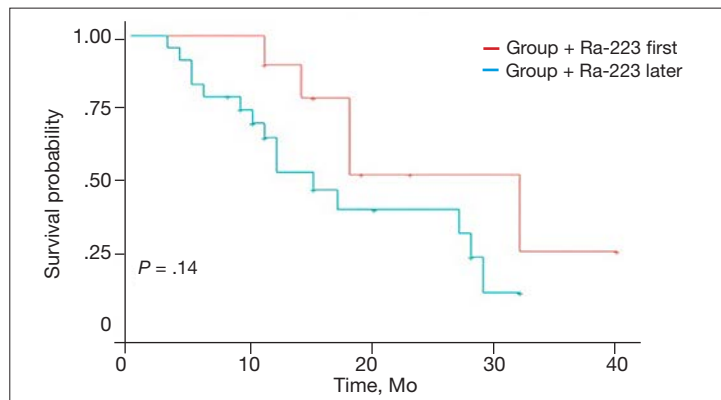
Abbreviations: >>A, alive; abi, abiraterone; Cabazi, cabazitaxel; Doce, docetaxel; Enza, enzalutamide; Ra-223, radium-223; SRE, skeletal-related event, Ra+Abi, veterans participated in ERA trial.

FIGURE 2 Treatment Pattern of 17 Veterans With No Agent Orange Exposure

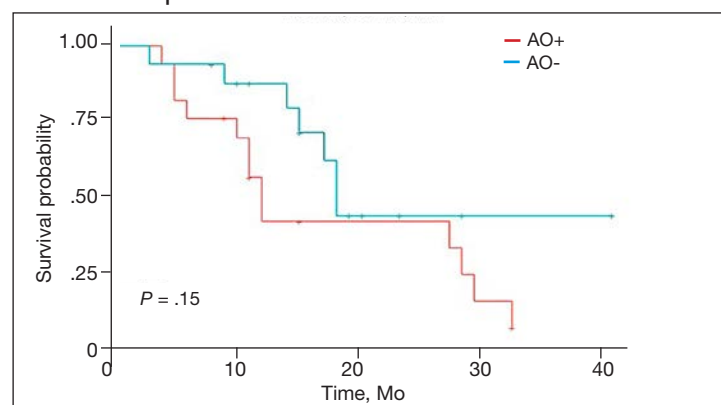


Abbreviations: >>A, alive; abi, abiraterone; Cabazi, cabazitaxel; Doce, docetaxel; Enza, enzalutamide; Ra-223, radium-223; SRE, skeletal-related event, Ra+Abi, veterans participated in ERA trial.

only 15 months. We recommend veterans with at least 2 to 3-bone metastasis receive Ra-223 in the first-line setting rather than second- or third-line setting. In this retrospective study with Ra-223 and other therapies, we proved that AO+ veterans have a worse response and OS when compared with that of AO- veterans.

FIGURE 3 Kaplan Meier Median Survival Ra-223 First vs Ra-223 Later

Abbreviation: Ra-223, radium-223.

FIGURE 4 Kaplan Meier Median Survival for AO+ vs AO-

Abbreviations: AO+, exposed to Agent Orange; AO-, not exposed to Agent Orange.

CONCLUSIONS

This is the first VA study to compare the efficacy of Ra-223 and other therapies in metastatic CRPC between AO+ and AO- veterans. AO+ veterans were diagnosed at a younger age and had higher Gleason scores. There was no statistical difference between AO+ and AO- veterans in terms of time to SRE, PSA progression, and bone and ALP progression even though there was a trend of shorter duration in AO+ veterans. There was no median survival difference between veterans who received Ra-223 first vs Ra-223 later as well as between AO+ and AO- veterans, but there was a trend of worse survival in veteran who received Ra-223 later and AO+ veterans.

This study showed that AO+ veterans have a shorter duration of response to therapy and shorter median survival compared with that of AO- veterans. We recommend that veterans should get Ra-223 in the first-line setting rather

than after hormonal therapy and chemotherapy because their marrows are still intact. We need to investigate further whether veterans that exposed to carcinogen 2,3,7,8-tetrachlorodibenzo-p-dioxin may have different molecular biology and as such may cause inferior efficacy in the treatment of prostate carcinoma.

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