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Original Article

Real-world Outcomes and Factors Predicting Survival and Completion of Radium 223 in Metastatic Castrate-resistant Prostate Cancer

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Abstract

Aims: To analyse outcomes in metastatic castrate-resistant prostate cancer (mCRPC) patients treated with radium 223 (Ra-223) across the Yorkshire and Humber Cancer Network.
Materials and methods: A regional, multicentre, retrospective cohort study of 189 men undergoing Ra-223 for mCRPC between March 2014 and April 2017 was undertaken. Factors predicting overall survival and completion of planned treatment were assessed.
Results: The median overall survival for the entire cohort was 10.5 months. Those completing five to six cycles of Ra-223 had a higher overall survival of 18.6 months. On multivariable analysis, four factors remained independent significant predictors of overall survival: age ($P = 0.005$, hazard ratio 1.07 [1.02–1.12]); number of cycles of Ra-223: 5–6 versus 1–4 ($P \leq 0.001$, hazard ratio 0.10 [0.005–0.20]); baseline alkaline phosphatase ($P = 0.044$, hazard ratio 1.06 [1.002–1.12]); neutrophil-to-lymphocyte ratio ($P = 0.033$, hazard ratio 1.19 [1.01–1.40]). Baseline performance status 0 versus 2 ($P = 0.026$, odds ratio 0.080 [0.001–0.74]) and higher baseline haemoglobin ($P = 0.028$, odds ratio 1.04 [1.004–1.074]) were independent predictors of the completion of five to six cycles of Ra-223.
Conclusions: Younger age, completion of five to six cycles of Ra-223, lower alkaline phosphatase and neutrophil-to-lymphocyte ratio are predictors of overall survival. This is the first study to report neutrophil-to-lymphocyte ratio as an independent predictor of overall survival in a Ra-223 cohort. Good performance status and higher baseline haemoglobin predict the completion of five to six cycles of Ra-223.

Key words: Metastatic castrate-resistant prostate cancer; neutrophil-to-lymphocyte ratio; overall survival; radium 223

Introduction

Prostate cancer is the most common cancer diagnosed in European men, causing 72 000 deaths per year across Europe [1]. Several new systemic therapies have been shown to prolong survival in metastatic castrate-resistant prostate cancer (mCRPC) and have been approved for use, including enzalutamide, abiraterone, cabazitaxel and radium 223 (Ra-223).

Ra-223 is a novel bone-seeking alpha-particle emitter with a half-life of 11.4 days. Ra-223 mimics calcium, forming complexes with hydroxyapatite and targeting regions of high bone turnover, such as osteoblastic metastases, which are commonly seen in advanced prostate cancer. The high linear energy transfer of alpha particles induces double-strand DNA breaks, whereas the two to 10 cell width range limits toxicity to surrounding tissue and marrow [2]. Ra-223 is administered as an intravenous injection every 4 weeks for a period of 6 months.

The ALSYMPCA trial [3] randomised 921 men with predominantly bone mCRPC to six cycles of Ra-223 or placebo and showed an overall survival benefit of 3.6 months in those treated with Ra-223. Patients were required to have symptomatic bone metastatic disease, with no known

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visceral metastatic disease and no lymph node metastases larger than 3cm. An Eastern Cooperative Oncology Group (ECOG) performance status of 0–2 and a life expectancy of greater than 6 months were also required. The National Institute of Health and Care Excellence (NICE) subsequently issued technology appraisal guidance and Ra-223 is now widely available [4].

The Yorkshire and Humber Clinical Network covers a large geographical area of over 5000 square miles and delivers oncology services to a population of 5.4 million located in diverse communities ranging from dense, deprived urban areas to remote and rural communities [5]. There are three cancer centres based in Hull, Leeds and Sheffield and specialised radiation cancer services such as Ra-223 are delivered from these bases. The purpose of this regional, multicentre, retrospective audit was to analyse real-world outcomes in mCRPC patients treated with Ra-223 from the establishment of the service in 2014.

Materials and Methods

Patients

All patients with mCRPC who received at least one dose of Ra-223 since the introduction of this service in 2014 at the three treating centres in Yorkshire and Humber were included. Only patients who either completed all planned Ra-223 cycles or had discontinued Ra-223 were included; those mid-treatment at the time of analysis were excluded. The cohort was divided into two groups: patients who completed one to four cycles of Ra-223 (70 patients; group 1–4) and those who completed five to six cycles of Ra-223 (119 patients; group 5–6).

Data Collection

Retrospective data collection was completed from electronic and paper medical records. Patients routinely had full blood counts, renal and liver function tests, and prostate-specific antigen (PSA) checked before each cycle. Baseline bloods were documented. As a proportion of blood tests were performed in primary care or peripheral hospitals, not all results were retrievable for study purposes. Alkaline phosphate (ALP) response was defined as a decrease of 50% from baseline ALP levels during treatment months. Similarly, a PSA response was defined as a 50% decrease from baseline. Baseline ECOG performance status was noted.

Comorbidities were classified according to the Adult Comorbidity Evaluation (ACE-27) score [6]. Pain scores were not clearly documented in patient notes and hence excluded from the analysis.

Major adverse events, including the need for transfusions and skeletal-related events (SRE) during treatment months, were documented. SREs were defined as metastatic spinal cord compression, symptomatic pathological fracture, palliative radiotherapy to relieve symptoms or surgery to bone.

Statistics

The primary outcome measure was median overall survival. Kaplan–Meier survival curves from the start of Ra-223 to the time of death were plotted. Reverse Kaplan–Meier was used to calculate the median follow-up. Cox regression was used to identify factors predicting overall survival. The following factors were included in the univariate survival analysis: age, ACE comorbidity score, one to four versus five to six cycles of Ra-223, Gleason score, ECOG performance status, baseline bloods including haemoglobin, PSA, ALP, albumin and neutrophil-to-lymphocyte ratio (NLR), previous use of docetaxel, number of previous lines of therapy, ALP and PSA response. Logistic regression was used to identify which baseline characteristics predicted the completion of five to six cycles of Ra-223 compared with one to four cycles. All above factors, except ALP and PSA response, were used in univariate logistic regression. Factors with P-value < 0.1 on univariate analysis were carried into the multivariate analyses, which were carried out using a backwards selection method.

Results

In total, 189 patients with mCRPC underwent treatment with Ra-223 across the region between March 2014 and April 2017. The median age was 72 years (range 51–86 years). 115/189 (61%) patients died during the study period, with 74/189 (39%) remaining alive at the time of analysis. Ninety-four per cent of patients in group 1–4, but only 41% of patients in group 5–6 died during the study period; 8/189 patients died within 1 month of the last Ra-223 treatment. The median follow-up was 16.8 months.

The median overall survival for the entire cohort was 10.5 months (95% confidence interval 8.7–12.3 months).

On comparison according to number of cycles completed, group 1–4 had a median survival of 4.5 months (95% confidence interval 3.3–5.7 months) and group 5–6 had a median survival of 18.6 months (95% confidence interval 16.9–20.1 months; $P \leq 0.001$; Figure 1a).

The clinical characteristics of the entire patient group and the analysis of potential factors associated with overall survival are shown in Tables 1 and 2, respectively. Baseline blood results were available for 90% of patients, with the exception of NLR, which was available in 77% of patients, and albumin level, which was available in only 49% of patients. Sixty-eight per cent of patients had calculated ACE-27 scores (data available from only two centres). On univariate analysis the following factors were associated with poorer overall survival: increasing age, completion of only one to four cycles, poorer initial performance status, lower baseline haemoglobin, higher initial PSA, higher baseline ALP, higher NLR and poorer PSA response during treatment. On multivariable analysis, only four of these factors remained independent significant predictors of overall survival: age ($P = 0.005$, hazard ratio 1.07 [1.02–1.12]); number of cycles of Ra-223: 5–6 versus 1–4 ($P \leq 0.001$,

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