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A Randomized, Double-Blind, Dose-Finding, Multicenter, Phase 2 Study of Radium Chloride (Ra 223) in Patients with Bone Metastases and Castration-Resistant Prostate Cancer

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Abstract

Background: Patients with castration-resistant prostate cancer (CRPC) and bone metastases have an unmet clinical need for effective treatments that improve quality of life and survival with a favorable safety profile.
Objective: To prospectively evaluate the efficacy and safety of three different doses of radium chloride (Ra 223) in patients with CRPC and bone metastases.
Design, setting, and participants: In this phase 2 double-blind multicenter study, 122 patients were randomized to receive three injections of Ra 223 at 6-wk intervals, at doses of 25 kBq/kg ($n = 41$), 50 kBq/kg ($n = 39$), or 80 kBq/kg ($n = 42$). The study compared the proportion of patients in each dose group who had a confirmed decrease of ≥50% in baseline prostate-specific antigen (PSA) levels.
Outcome measurements and statistical analysis: Efficacy was evaluated using blood samples to measure PSA and other tumor markers, recorded skeletal-related events, and pain assessments. Safety was evaluated using adverse events (AEs), physical examination, and clinical laboratory tests. The Jonckheere-Terpstra test assessed trends between groups.
Results and limitations: The study met its primary end point with a statistically significant dose–response relationship in confirmed ≥50% PSA declines for no patients (0%) in the 25-kBq/kg dose group, two patients (6%) in the 50-kBq/kg dose group, and five patients (13%) in the 80-kBq/kg dose group ($p = 0.0297$). A ≥50% decrease in bone alkaline phosphatase levels was identified in six patients (16%), 24 patients (67%), and 25 patients (66%) in the 25-, 50-, and 80-kBq/kg dose groups, respectively ($p < 0.0001$). The most common treatment-related AEs (≥10%) occurring up to week 24 across all dose groups were diarrhea (21%), nausea (16%), and anemia (14%). No difference in incidence of hematologic events was seen among dose groups. Potential limitations include small patient numbers and differences among dose groups at baseline.
Conclusions: Ra 223 had a dose-dependent effect on serum markers of CRPC activity, suggesting that control of bone disease with Ra 223 may affect cancer-related outcomes. Ra 223 was well tolerated at all doses.
Trial registration: ClinicalTrials.gov: NCT00337155.

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1. Introduction

Bone metastases, a major cause of morbidity and mortality in patients with castration-resistant prostate cancer (CRPC) [1], are associated with pain, pathologic fracture, spinal cord compression, and decreased survival [2,3]. Current bone-targeted therapies (eg, bisphosphonates, denosumab) are primarily limited to delaying skeletal-related events (SREs), with no improvement in survival or quality of life [4–6].

Radium chloride Ra 223, a targeted α-emitter, is a calcium-mimetic, bone-seeking agent [7,8] that generates highly localized radiation zones to induce nonrepairable, double-stranded DNA breaks in metastatic cells [9–11], with minimal effects on normal tissue [12–14]. Ra 223 has demonstrated a favorable safety profile [15–17] and consistent improvement in serum biomarkers, pain, and overall survival (OS) in patients with CRPC and bone metastases [16–18]. In a phase 2 study ($n = 64$), Ra 223 significantly improved OS compared with placebo and increased prostate-specific antigen (PSA) and bone alkaline phosphatase (ALP) response rates [16,19]. In a phase 3 study ($n = 921$), Ra 223 significantly improved OS, time to first SRE, and time to PSA progression compared with placebo [18].

The current prospective study compares proportions of patients with CRPC and bone metastases showing a ≥50% PSA response across three Ra 223 doses in order to inform the dose choice for subsequent trials.

2. Patients and methods

2.1. Patients

Eligible patients had castration-resistant (hormone-refractory) prostate adenocarcinoma with serum testosterone levels ≤50 ng/dl after orchiectomy or while maintained on androgen ablation therapy. Eligibility required a baseline PSA ≥10 ng/ml with progressively rising PSA values (two consecutive increases over previous reference value), multifocal bone metastases, Eastern Cooperative Oncology Group score 0–2, life expectancy ≥6 mo, and adequate hematologic and hepatic function. Patients who received prior hormonal drug therapy had to stop flutamide, nilutamide, or cyproterone acetate ≥4 wk, and bicalutamide ≥6 wk, before Ra 223 injection, with subsequent disease progression.

Patients were excluded if they had received chemotherapy, immunotherapy, external-beam radiation therapy (EBRT), or investigational drugs within the previous 4 wk, had received systemic radiotherapy within the last year, or had visceral metastases from prostate cancer (PCa). Abdominal or pelvic lymph node involvement (≤1 cm in the short-axis diameter) was permitted. All patients provided written informed consent.

2.2. Study design

This randomized, double-blind, multicenter, phase 2 study evaluated the efficacy and safety of three Ra 223 dose regimens in patients with CRPC and bone metastases (Fig. 1). Patients were randomized with equal probability to receive three intravenous injections of Ra 223 (25, 50, or 80 kBq/kg) at 6-wk intervals. The study was unblinded after the last patient completed the week 24 assessment; follow-up visits assessed efficacy, long-term safety, and survival.

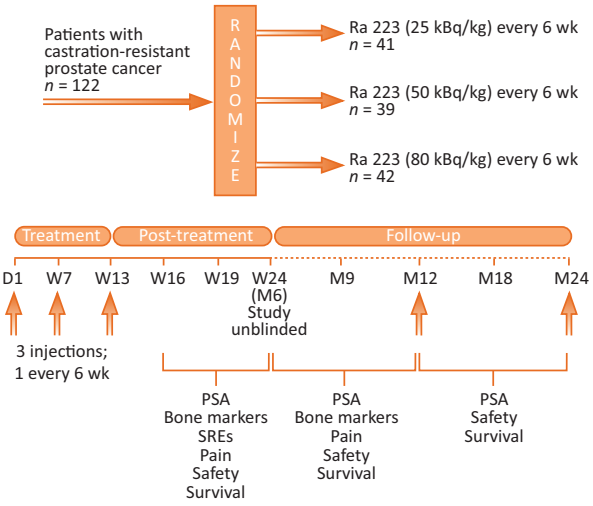

Fig. 1 – Study design. PSA = prostate-specific antigen; SRE = skeletal-related event; D = day; W = week; M = month.

The primary objective was to compare proportions of patients showing PSA response (≥50% decrease from baseline, confirmed by a second measurement ≥19 d later) on the three Ra 223 dose regimens. Secondary objectives included evaluating the effects of these regimens on bone ALP and serum C-terminal cross-linking telopeptide of type I collagen (s-CTX-I); maximum percentage of PSA decrease from baseline; time to first SREs; pain response; correlation between bone ALP and PSA and s-CTX-I and PSA; and safety, tolerability, long-term safety, and OS.

The study was conducted in accordance with the Declaration of Helsinki and good clinical practices guidelines. The protocol was approved by an independent ethics committee at each center.

2.3. Assessments

Efficacy was evaluated on measurements made during the 24-wk blinded study period, with blood samples measuring PSA, bone ALP, and s-CTX–I evaluated in a central laboratory. Pain was measured with an index based on average pain in the last week (item 3 score on the Brief Pain Inventory [BPI] [20]) and analgesic consumption categorized using the World Health Organization analgesic ladder [21]. An adjudication committee performed pain classification before blinding was broken. SREs were defined as an increase in average pain or analgesic consumption, presence of neurologic symptoms, new pathologic bone fractures, tumor-related orthopedic surgery, EBRT or corticosteroids to relieve pain, radioisotopes to relieve new skeletal-related symptoms, chemotherapy or hormones for disease progression in the skeleton, or bisphosphonates for pain or skeletal disease progression. Survival was assessed throughout the study. Information on pain and SREs was additionally collected up to the month 12 visit (BPI) or month 24 visit (SREs).

Safety evaluations used adverse events (AEs), physical examination, and clinical laboratory tests. All AEs occurring before week 24 were reported; subsequent AEs were reported only if they were treatment-related (per investigator). AEs were graded according to Common Terminology Criteria for Adverse Events v.3.0. Long-term safety was assessed up to 24 mo.

The per-protocol (PP) population included all patients who received two or more Ra 223 injections at an interval of 6 wk ± 10 d and had two or more postbaseline PSA measurements separated by ≥19 d. Except for survival, all efficacy analyses performed on data to week 24 used the PP population. Analyses of survival and safety data, as well as of all data