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Prostate Cancer

Prostate-Specific Antigen Kinetics and Outcomes in Patients with Bone Metastases from Castration-Resistant Prostate Cancer Treated with or Without Zoledronic Acid

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Abstract

Background: Zoledronic acid (ZOL) is a standard therapy for the prevention of skeletal-related events (SREs) in patients with castration-resistant prostate cancer (CRPC). Although prostate-specific antigen (PSA) is an established marker for monitoring prostate cancer patients, correlations between PSA and disease outcomes during ZOL therapy are unclear.
Objective: To evaluate the relationships among PSA kinetics, bone-directed therapy with ZOL, and clinical outcomes in men with bone metastases from CRPC using a ZOL phase 3 trial database.
Design, setting, and participants: Exploratory analyses from a phase 3 trial in men with bone metastases from CRPC ($n = 643$) randomized to ZOL or placebo every 3 wk.
Outcome measurements and statistical analysis: PSA levels during the first 3 mo of the study were evaluated in linear and logarithmic (log) models stratified using prognostic factors established in a ZOL phase 3 trial and a CRPC nomogram. Relative risks of SREs, bone disease progression (BDP), and death were calculated per 1 log (nanograms per milliliter) PSA increase. Baseline PSA models used the study median (PSA: 77.3 ng/ml) as the high/low cut-off point.
Results and limitations: A total of 202 placebo- and 434 ZOL-treated patients were assessable. In both groups, PSA increases correlated with significantly increased risks of death, BDP, and first SRE. In the placebo and ZOL groups, associated increases in risk per 1 log (nanograms per milliliter) PSA increase were 29% ($p < 0.0001$) and 10% ($p < 0.0074$), respectively, for BDP, and 24% ($p = 0.0010$) and 13% ($p = 0.0079$), respectively, for first SRE. Limitations include the retrospective nature of these analyses and the potential confounding effects of concurrent antineoplastic therapies.
Conclusions: PSA is an important prognostic tool for survival in patients with bone metastases from CRPC, and these analyses show that PSA is also prognostic for BDP and SREs regardless of bone-targeted therapy.

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1. Introduction

Serum prostate-specific antigen (PSA) levels and PSA kinetics (eg, PSA velocity and PSA doubling time) are established prognostic indicators in men with newly diagnosed prostate cancer and prostate cancer that recurs after initial therapy [1–3]. In addition, both parameters have prognostic value in men with progressive, nonmetastatic, castration-resistant prostate cancer (CRPC) [4,5]. However, in men with metastatic CRPC, PSA has been identified as a prognostic factor in only one survival model [6].

Approximately 70% of patients with CRPC develop bone metastases during the course of their disease, and they are at high risk for developing potentially debilitating skeletal-related events (SREs) including pathologic fracture, spinal cord compression, and the requirement for surgery or radiotherapy to bone [7]. Bone-targeted agents such as bisphosphonates and denosumab, the recently approved monoclonal antibody against the receptor activator of nuclear factor-κB ligand, have been shown to prevent SREs in patients with malignant bone disease [8,9].

The bisphosphonate zoledronic acid (ZOL) is an established treatment that has demonstrated significant and long-term reductions in the risk of SREs in patients with bone metastases from CRPC [10]. In patients with bone metastases from CRPC, levels of biochemical markers of bone turnover (eg, N-telopeptide of type I collagen [NTX] and bone-specific alkaline phosphatase [BALP]) correlate with survival and SRE risk. In most patients, ZOL effectively lowers NTX level, which has been associated with reduced risk of SREs and improved survival [11]. Risks of SREs and death were significantly lower in men whose NTX levels normalized within 3 mo of ZOL initiation versus men with persistently elevated NTX levels [12,13].

Currently, the real-world utilization of bone-directed therapies such as ZOL and their impact on PSA kinetics and clinical outcomes in men with bone metastases from CRPC have yet to be elucidated. Therefore, retrospective exploratory analyses were performed to evaluate potential correlations between baseline serum PSA levels or PSA kinetics and clinical outcomes (survival, bone disease progression [BDP], and risk of SREs) in men with bone metastases from CRPC who were enrolled in a large phase 3 trial of ZOL [10,11].

2. Patients and methods

2.1. Patients

This was a retrospective, exploratory analysis of data from a completed multicenter, randomized, double-blind phase 3 trial of ZOL that enrolled patients with bone metastases from CRPC ($n = 643$) [10,11] (Fig. 1). Key inclusion criteria were documented history of bone metastases; serum

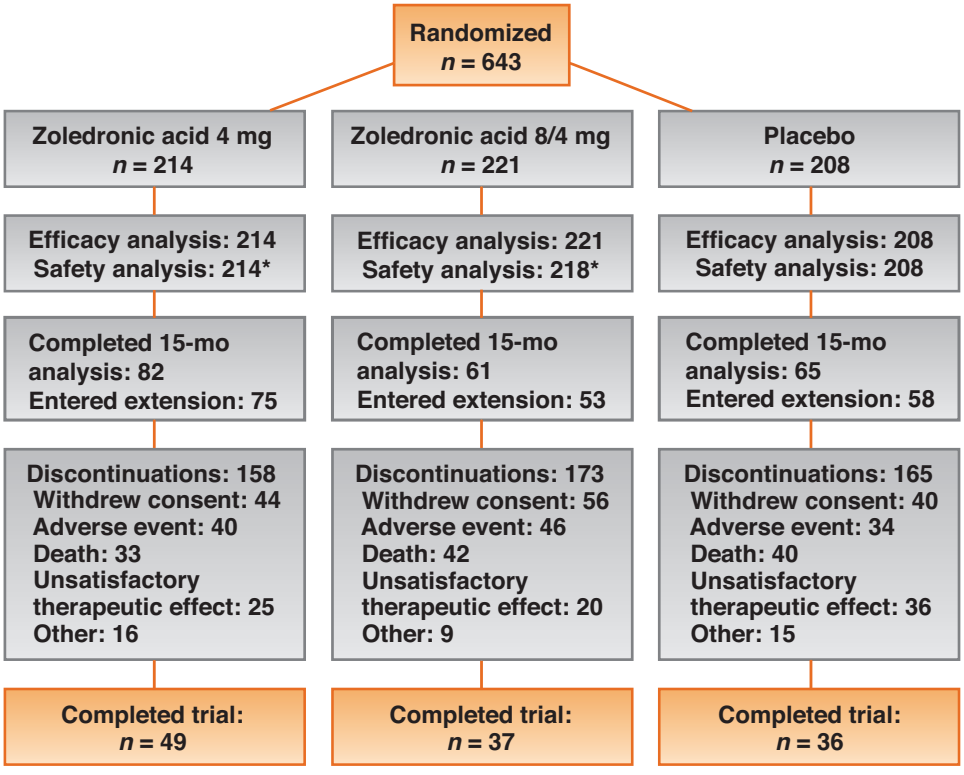

Fig. 1 – Trial registration and Consolidated Standards of Reporting Trials (CONSORT) information. The phase 3 trial has no trial registry name, number, or URL. Patient enrollment and study treatment took place between June 1998 and January 2001. Results for the phase 3 trial were published in 2002 [11] and 2004 [10]. The CONSORT diagram was originally published in 2004 [10].

*** Three patients, one randomly assigned to receive zoledronic acid 4 mg and two randomly assigned to receive zoledronic acid at 8/4 mg, never received the study drug and were not included in the safety analysis. One patient randomly assigned to receive zoledronic acid at 8/4 mg incorrectly received 4 mg; this patient was included in the 8/4-mg group for efficacy and in the 4-mg group for safety analysis.**