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Research Article

The ZOTECT study: Effect of zoledronic acid on bone metabolism in patients with bone metastases from prostate or breast cancer

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ABSTRACT

Purpose: The ZOTECT study assesses the effect of zoledronic acid (ZOL) on bone-marker levels and potential correlations with disease outcomes in bisphosphonate-naive patients.
Methods: This prospective, single-arm, open-label study in bisphosphonate-naive (≥ 6 months) patients with bone metastases from prostate cancer (PC; $n=301$) or breast cancer (BC; $n=99$) enrolled at 98 German sites (May 2006 to July 2008) investigated the effect of ZOL (4 mg intravenously every 4 weeks × 4 months, with a final follow-up at 12 months) on bone-marker levels. Secondary assessments: skeletal-related event (SRE) rate, pain, quality of life (QoL), and prostate-specific antigen levels. Endpoints were assessed using summary statistics by visit/tumor type and Kaplan–Meier analyses.
Results: ZOL treatment significantly decreased bone-marker levels (amino-terminal propeptide of type I collagen [P1NP], C-terminal cross-linking telopeptide of type I collagen [CTX]; $P<0.0001$), and this decrease was maintained through the final 1-year follow-up visit. Baseline P1NP and CTX levels correlated with extent of bone disease ($P<0.0001$, each) and on-treatment decreases in marker levels. Skeletal disease burden and bone-marker levels were similar between PC and BC patients, and ZOL did not significantly influence osteoprotegerin/receptor activator of nuclear factor-κB ligand levels. Only 13 SREs occurred in 11 patients, supporting the known ZOL-mediated reduction in SREs. On-treatment bone-marker level changes did not correlate with SRE rate, pain scores, or QoL. Generally, ZOL was well tolerated and adverse events were consistent with its known safety profile.
Conclusions: This study confirms that ZOL therapy significantly reduces bone turnover (measured as P1NP and CTX levels) in patients with bone metastases from PC or BC.

1. Introduction

Up to 75% of patients with advanced prostate cancer (PC) or breast cancer (BC) will develop bone metastases, which dysregulate normal bone metabolism [1]. Without antiresorptive therapies, most patients with bone metastases will experience potentially debilitating skeletal-related events (SREs: pathologic fractures, spinal cord compression, hypercalcemia, the need for surgery to bone, or severe bone pain requiring palliative radiotherapy) [1,2]. Zoledronic acid (ZOL) is a nitrogen-containing bisphosphonate and potent osteoclast inhibitor. Treatment with ZOL reduces the risk of SREs and suppresses pathologic bone turnover in patients with multiple myeloma or bone metastases from solid tumors, including PC and BC [3–5].

Abbreviations: AE, adverse events; BC, breast cancer; CrCl, creatinine clearance; CTX, C-terminal cross-linking telopeptide of type I collagen; ECOG, Eastern Cooperative Oncology Group; EORTC, European Organisation for Research and Treatment of Cancer; ITT, intent-to-treat; NTX, urinary N-telopeptide; OPG, osteoprotegerin; P1NP, amino-terminal propeptide of type I collagen; PC, prostate cancer; PSA, prostate-specific antigen; QoL, quality of life; RANKL, receptor activator of nuclear factor-κB ligand; SRE, skeletal-related event; ULN, upper limit of normal; VAS, visual analogue scale; ZOL, zoledronic acid

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Biochemical markers of bone turnover include enzymes and peptides released during the bone remodeling process, which can be measured in the urine or blood and are potentially useful for assessing the overall state of bone turnover [6]. For example, amino-terminal propeptide of type I collagen (P1NP), serum C-terminal cross-linking telopeptide of type I collagen (CTX), and urinary N-telopeptide (NTX) is physiologic byproducts of bone remodeling. Elevated levels of CTX or NTX are common in patients with osteolytic bone lesions; thus, these markers may reflect increased osteolysis (osteoclast-mediated bone resorption), which is more pronounced in BC. The bone formation marker P1NP is elevated in osteoblastic or mixed osteolytic–osteoblastic lesions, as occurs with PC. Other important markers of bone turnover include modulators of osteoclast activity, such as the receptor activator of nuclear factor-κB ligand (RANKL) and osteoprotegerin (OPG). Osteoprotegerin is a physiologic inhibitor of RANKL, an inducer of osteoclast activity.

Elevated levels of bone turnover markers (e.g., NTX and CTX) have been associated with poor clinical outcomes in patients with cancer [7–9], including increased SRE risk [7,8]. Moreover, antiresorptive therapies have been shown to reduce bone turnover marker levels in patients with cancer [10,11]. Retrospective analyses of data from phase 3 trials of ZOL versus control (i.e., placebo for PC, pamidronate for BC) in patients with bone metastases from castration-resistant PC ($N=314$) or BC ($N=379$) showed that ZOL normalized NTX levels within 3 months in most patients (70% PC, 81% BC) who had high baseline NTX levels (PC, $n=193$; BC, $n=220$) [11]. Moreover, ZOL-mediated normalization of NTX levels within 3 months of treatment was associated with decreased risks of first SRE (40% decrease; $P\leq 0.04$) and death (PC, 59% decrease; $P<0.0001$) versus persistently increased NTX levels [11]. Further retrospective analyses of this trial database also showed that ZOL therapy was associated with improved survival in patients with aggressive bone disease [12]. Thus, modulating bone turnover with ZOL may improve clinical outcomes in patients with advanced cancer. Here we present results from the ZOTECT study (NCT00334139), which assessed the effect of ZOL therapy on bone turnover and potential correlations with disease outcomes.

2. Patients and methods

2.1. Study design and treatment

This prospective, single-arm, open-label study examined the effect of ZOL on bone turnover marker levels in patients who were bisphosphonate naive for at least 6 months with bone metastases from PC or BC recruited between May 2006 and July 2008. The patients received four doses of ZOL (4 mg every 4 weeks); continued treatment with ZOL was recommended (but not mandatory) afterward. All patients were advised to take 500-mg calcium supplements and a multivitamin tablet daily. Patients also received concomitant anticancer therapy as determined by the treating physician.

Bone turnover markers (CTX, P1NP, RANKL, and OPG) and prostate-specific antigen (PSA) levels were measured at baseline, monthly through 120 days (study end), and at the final 1-year follow-up visit (360 days; Fig. 1). No data were systematically collected between the 120-day visit and the 1-year follow-up (360-day visit). Laboratory measurements (PSA [patients with PC] and bone markers [all patients]) were performed at a single laboratory (Marburg, Germany). Bone scans were performed at baseline to determine the extent of bone disease, and SREs were assessed at baseline, on-study (visits 2–5), and at study end (visit 6). Pain was evaluated using visual analogue scale (VAS) and analgesic scores. Quality of life (QoL) was measured using the European Organisation for Research and Treatment of Cancer (EORTC) C-30 and BR-23 modules.

2.2. Patients

2.2.1. Inclusion criteria

All patients had histologically proven PC or BC with one or more cancer-related bone lesions, with or without hormonal therapy. Standard concomitant anticancer therapy was allowed, including prior surgery, chemotherapy, and radiotherapy (completed ≥ 4 weeks before enrollment). Additional requirements included Eastern Cooperative Oncology Group (ECOG) performance status of 0–2, normal cardiac function, life expectancy of ≥ 6 months, total bilirubin ≤ 2.5 times the upper limit of normal (ULN), normal serum glutamic pyruvic transaminase, serum glutamic-oxaloacetic transaminase ≤ 2.5 times the ULN, and creatinine clearance (CrCl) ≥ 30 mL/min (Cockcroft–Gault formula). A negative pregnancy test at screening was required for women of childbearing potential. All patients were ≥ 18 years of age at study entry, signed informed consent before study entry, and were accessible for treatment during the study.

This clinical study was designed, implemented, and reported in accordance with the International Conference on Harmonisation's Harmonised Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/83/EC and US Code of Federal Regulations Part 21), and with the ethical principles laid down in the Declaration of Helsinki.

2.2.2. Exclusion criteria

Patients with prior bisphosphonate therapy within 6 months of enrollment, known hypersensitivity to ZOL or other bisphosphonates, or previous radiation therapy to bone (including therapeutic radioisotopes such as strontium-89) within 1 month were excluded. To reduce the risk of osteonecrosis of the jaw, patients with current or active dental problems or recent/planned dental surgery were excluded. Other exclusion criteria included no detectable cancer-related bone lesions (bone radiographs or bone scan) or the presence of symptomatic brain metastases, renal impairment (CrCl <30 mL/min), abnormal calcium levels (corrected serum calcium <8.0 mg/dL or ≥ 12.0 mg/dL), history of diseases that influence bone metabolism (e.g., Paget's disease, primary hyperparathyroidism), or osteoporosis (T-score ≤ -2.5) requiring antiresorptive therapy. Exclusions specific to women included breastfeeding, pregnancy, or failure to use at least one medically acceptable contraception method.

2.3. Key endpoints

The primary endpoint of this trial was the course of changes in bone turnover marker levels (CTX, P1NP, RANKL, OPG) during and after ZOL therapy. Secondary endpoints included pain (VAS and analgesic scores), rate of SREs (excluding hypocalcemia), PSA course (PC cohort), QoL, safety, tolerability, and potential relationships between baseline bone marker levels and clinical disease parameters (extent of disease, pain, and SREs).

2.4. Statistical analyses

Analyses of these data were exploratory (i.e., hypothesis generating rather than hypothesis confirming). Summary statistics (intent-to-treat [ITT] and per-protocol populations) for absolute values and changes from baseline were calculated by visit and tumor type. Data were transformed using natural log (original value $+1$) to adjust for skewed distributions. Time-to-event variables (time to first SRE and overall survival) were analyzed