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Research Article

Possible survival benefits from zoledronic acid treatment in patients with bone metastases from solid tumours and poor prognostic features—An exploratory analysis of placebo-controlled trials

Robert E. Coleman [a,*], Allan Lipton [b], Luis Costa [c], Richard J. Cook [d], Ker-Ai Lee [d], Fred Saad [e], Janet E. Brown [a,f], Evangelos Terpos [g], Pierre P. Major [h], Norio Kohno [i], Matthew Smith [j], Jean-Jacques Body [k]

[a] Department of Oncology, Cancer Clinical Trials Centre, University of Sheffield, Weston Park Hospital, Cancer Research Centre, Sheffield, UK
[b] College of Medicine, Penn State Milton S. Hershey Medical Center, Hershey, PA, USA
[c] Clinical and Translational Oncology Research Unit, Instituto de Medicina Molecular, Lisbon, Portugal
[d] Department of Statistics and Actuarial Science, University of Waterloo, Waterloo, ON, Canada
[e] Division of Urology, Centre Hospitalier de l'Université de Montréal, Hôpital Notre-Dame, Montréal, QC, Canada
[f] Department of Oncology and Clinical Research, Cancer Research UK Centre, St James's Hospital, Leeds, UK
[g] Department of Clinical Therapeutics, University of Athens School of Medicine, Athens, Greece
[h] Department of Oncology, Division of Medical Oncology, McMaster University, Juravinski Cancer Centre, Hamilton, ON, Canada
[i] Division of Breast Oncology, Tokyo Medical University, Tokyo, Japan
[j] Genitourinary Malignancies Program, Massachusetts General Hospital Cancer Center, Boston, MA, USA
[k] Department of Medicine, University Hospital Brugmann, ULB, Brussels, Belgium

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ABSTRACT

Background: Zoledronic acid (ZOL) is an important component of therapy for patients with metastatic bone disease (MBD) to reduce the risk of skeletal-related events (SREs). We evaluated overall survival (OS) in patients with MBD secondary to solid tumours included in placebocontrolled ZOL trials.
Patients and methods: Exploratory analyses were performed using databases from three randomised trials of ZOL versus placebo. 1126 patients (ZOL, $n=731$; placebo, $n=395$) with complete baseline data for 18 predefined parameters were evaluated for OS. Relative risks (RRs) with 95% confidence intervals were assessed using stratified and adjusted Cox regression models. Baseline covariates defining patient populations with significantly different effects of ZOL treatment on OS (identified by stepwise backward elimination) were included in multivariate models.
Results: Although OS was similar between the overall treatment groups, ZOL significantly improved OS in the subset of patients ($n=423$; 38%) with elevated baseline NTX (≥ 100 nmol/mmol creatinine; RR, 0.692; $P=.0028$). Notably, this effect was independent of SRE prevention. Additional covariates associated with OS benefits with ZOL (e.g., low albumin, SRE history, elevated lactate dehydrogenase, shorter cancer duration) were characteristic of advanced disease.
Conclusion: These exploratory analyses suggest a beneficial effect of ZOL on OS in patients with highly aggressive or advanced MBD.

1. Introduction

In recent years, intravenous zoledronic acid (ZOL) has become an integral component of therapy for patients with metastatic bone disease (MBD) to reduce the risk of skeletal-related events (SREs) [1]. Initially, ZOL demonstrated superiority over pamidronate (the former standard of care) for managing hypercalcaemia of malignancy (HCM) [2]. Subsequently, across a range of cancers including breast cancer (BC) [3], castration-refractory prostate cancer (CRPC) [4], non-small cell lung cancer (NSCLC), and a variety of other solid tumours (OST) metastatic to bone [5], placebo-controlled trials have shown that monthly (every 3 to 4 weeks) ZOL reduces the overall risk of SREs by 27% to 41% and extends the time to first and subsequent SREs.

Preclinical and emerging clinical data from multiple settings also suggest that ZOL has anticancer properties that may delay disease recurrence and improve survival [6–13]. Recently, ZOL was shown to improve overall survival (OS) and progression-free

* Correspondence to: Department of Oncology, Cancer Clinical Trials Centre, Academic Unit of Clinical Oncology, Weston Park Hospital, University of Sheffield, Whitham Road, Sheffield S10 2SJ, England, United Kingdom
Tel.: +44 114 2265213; fax: +44 114 2265364.
E-mail address: r.e.coleman@sheffield.ac.uk (R.E. Coleman).

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survival versus clodronate in a phase III trial in 1960 patients with multiple myeloma [10]. Furthermore, in a large, randomised trial of 1803 premenopausal patients with early endocrine-responsive BC, ZOL also reduced the risk of disease relapse by 32% versus endocrine therapy alone ($P=.009$) [8]. Together with interim results from the AZURE trial in stage II/III BC [14], these data suggest that anticancer benefits from ZOL may occur in specific patient populations, all of which are expected to have elevated osteolysis levels because of oestrogen deprivation (e.g., premenopausal patients with low-risk BC receiving goserelin, postmenopausal patients receiving letrozole, and patients with stage II/III BC with established postmenopausal status) [7,8,14].

Despite preventing $>30\%$ of SREs, some of which correlate indirectly or directly with reduced survival [15], ZOL did not significantly increase OS in three placebo-controlled phase III trials [3–5]. This may be partially attributable to the individual trials not being powered to detect OS benefit. Additionally, in many patients death may be related more to overall disease burden or complications from visceral metastases, aspects of the disease that a bone-targeted treatment are unlikely to influence.

It is now evident that overall prognosis is especially poor for patients with aggressive bone lesions (as evidenced by substantially elevated levels of the bone turnover marker *N*-telopeptide of type I collagen [NTX]) [16,17], greater extent of skeletal disease at baseline [18], or overall high burden of disease (e.g., reflected by hypoalbuminaemia, poor performance status [PS], or rapid weight loss) [19–23]. Additionally, rapid normalisation of elevated NTX levels during ZOL therapy has been associated with improved survival versus persistently elevated NTX levels [24,25]. These observations prompted us to perform exploratory analyses of the potential correlations between baseline disease characteristics, with particular focus on the rate of bone resorption and possible survival benefits with ZOL in patients with MBD from solid tumours who were included in three contemporaneous, phase III, placebo-controlled trials of ZOL.

2. Methods

2.1. Patients and treatment

Three randomised, multicentre, double-blind, placebo-controlled, phase III clinical trials evaluated the safety and efficacy of ZOL in patients with MBD from a broad range of cancers: BC, CRPC, or NSCLC and OST [3–5]. These studies were selected for inclusion because they were contemporaneous trials with substantial similarity in study designs, endpoints, treatments, schedules for assessments, and types of data collected (including bone marker estimations). In all three studies, patients had radiographically confirmed MBD, Eastern Cooperative Oncology Group (ECOG) PS ≤ 2, serum creatinine (Cr) ≤ 3 mg/dL (265 μmol/L), and provided written informed consent. Additionally the CRPC study required disease progression despite serum testosterone <50 ng/dL, but without bone pain requiring strong opioid therapy [4]. All patients received standard therapies (cancer-specific and supportive care), calcium, and vitamin D throughout the course of the studies.

The BC study randomised patients to placebo or 4 mg ZOL monthly, whereas the other two studies randomised patients to placebo, 4 mg ZOL monthly, or 8 mg ZOL monthly [3–5]. Following recommendations from a renal safety monitoring committee, the 8-mg ZOL dose was reduced to 4 mg (subsequently referred to as the 8/4-mg arm) [4,5]. Study treatments were administered for up to 24 months (CRPC), 21 months (OST), or 12 months (BC) [3–5]. Treatment outcomes were similar between the 4- and 8/4-mg ZOL groups, and results were pooled as in earlier analyses.

2.2. Patient evaluation

All trials evaluated SRE incidence (pathologic fracture, surgery to bone to treat or prevent an impending fracture, palliative radiotherapy to bone, spinal cord compression, and HCM; for patients with CRPC, SREs also included change in antineoplastic therapy primarily to alleviate bone pain) and collected mortality data.

Biochemical markers of bone metabolism (serum bone-specific alkaline phosphatase [BALP] and NTX) were assessed at baseline and at defined timepoints during the first 12 months on study in five central reference laboratories in the United States, Belgium, Argentina, Brazil, and Japan. Urinary NTX (measured in a morning second-void sample) was standardised to the level of urinary Cr and expressed as nmol/mmol Cr. Serum BALP was measured in International Units (IU)/L in the CRPC and OST studies and in Units (U)/L in the Japanese BC study. For Japanese patients, the reference upper limit of normal (ULN) for BALP provided by the laboratories was 40 U/L, whereas other sites reported a ULN of 146 IU/L.

Patients were assessed for cancer-specific and overall health parameters at baseline, including extent of MBD, ECOG PS, haematologic and nutritional parameters, and bone marker levels. The current exploratory analyses are limited to patients with complete data for all baseline assessments (18 predefined parameters), including bone markers.

2.3. Statistical methods

The primary outcome of these exploratory analyses was OS (defined as the interval from study entry to death). In patients who survived beyond the end of their follow-up (up to 24 months (CRPC), 21 months (OST), or 12 months (BC) [3–5]), survival time was censored at the time of study completion. For patients who prematurely withdrew from the trials, survival time was censored at the time of withdrawal from the trial.

Earlier studies identified NTX as prognostic in the bone metastasis setting [16,17]; therefore, models were developed with baseline urinary NTX categorised based on the ULN in postmenopausal women (64 nmol/mmol Cr) or a cutoff value previously associated with pathologic bone turnover (100 nmol/mmol Cr) [17]. Parameters such as age, weight, pain, and haemoglobin level were dichotomised using the median for each study as the cutpoint.

Biochemical parameters were dichotomised using their respective established ULNs. Because limits for albumin and lymphocyte count established in healthy people might not be relevant for heavily pretreated patients with advanced cancers, we used different methods to analyse these variables. Baseline lymphocytes (measured as percentage of total white blood cells) were dichotomised around the median or characterised using common quartiles across the three trials. Serum albumin and creatinine were characterised using quartiles (either study-specific or common, depending on the analytic model).

2.4. Assessment of potential treatment modifiers

Relative risks (RRs) and 95% confidence intervals (CIs) for death in ZOL- versus placebo-treated patients were obtained via Cox regression models [26–28], stratified by cancer type, and adjusted for ongoing chemotherapy and baseline calcium levels. Homogeneity tests were performed to validate the assumption that treatment effects were common across study populations. Tests were also conducted to assess treatment-by-covariate interactions, which would indicate a significantly different magnitude of treatment benefit for the different subgroups of patients