Journal of Bone Oncology 2 (2013) 70–76

Contents lists available at ScienceDirect

Journal of Bone Oncology

journal homepage: www.elsevier.com/locate/jbo

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

ARTICLE INFO

Article history:
Received 18 December 2012
Received in revised form
14 January 2013
Accepted 14 January 2013
Available online 9 February 2013

Keywords:
Breast cancer
Non-small cell lung cancer
N-telopeptide of type I collagen
Prostate cancer
Survival
Zoledronic acid

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).

2212-1374/$ - see front matter © 2013 Elsevier GmbH. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).
http://dx.doi.org/10.1016/j.jbo.2013.01.002

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

defined by the covariates. The potential treatment-effect modifiers assessed included age, weight, cancer duration, brief pain inventory composite pain score, analgesic use, ECOG PS, prior SRE (yes/no), lactate dehydrogenase (LDH), haemoglobin, lymphocyte count, serum glutamic oxaloacetic transaminase, albumin, Cr, and bone markers. These variables were selected based on assessment of the trial databases and group discussions involving all academic authors; the selection was designed to include the largest possible number of cancer-related and bone-specific variables to achieve robust analyses from the available databases. Baseline covariates associated with a significantly different probability of OS benefit from ZOL treatment (interactive P value for treatment-by-covariate interaction [P_{int}] $< .05$) were identified using stepwise backward elimination and included in a multivariate model adjusted for other significant main effects. Using different cutpoints for key covariates in various models (study-specific or common quartiles for albumin, creatinine, and lymphocytes; 64 or 100 nmol/mmol Cr for NTX, approximating the upper limit of normal for premenopausal and postmenopausal women, respectively) facilitated testing the robustness of interactions between these covariates and treatment effects. Because SREs have been associated with increased mortality [15], some of the models were adjusted for SRE incidence as a time-dependent variable.

3. Results

3.1. Baseline demographics

Three randomised trials of ZOL (4 or 8/4 mg monthly; $n=1071$) versus placebo ($n=571$) [3–5] included 1642 patients with bone metastases from solid tumours. Baseline characteristics were similar between treatment groups for the individual trials (Table 1). Complete baseline assessments including bone marker levels were available for 1126 patients (ZOL, $n=731$; placebo, $n=395$).

3.2. Overall survival

The probability of death was similar between ZOL and placebo in the intention-to-treat population (RR, 0.939; 95% CI, 0.828 to 1.064; $P=.323$), as it was for the subset with complete baseline assessments (RR, 0.952; 95% CI, 0.813 to 1.114). Median survival varied considerably between trials because of the different natural histories of the underlying malignancies; however, there was no heterogeneity of ZOL effect by study ($P_{int}=.935$). Baseline covariates associated with worse OS included cancer duration less than median, prior SRE, LDH $\geq$ ULN, and low albumin (Table 2).

3.3. Baseline variables influencing overall survival during zoledronic acid treatment

Models evaluating possible correlations between all baseline variables and the potential for OS benefit from ZOL (treatment-by-covariate interaction) were developed, typically dichotomising baseline NTX using 64 (postmenopausal ULN) or 100 nmol/mmol Cr (severely elevated pathologic bone resorption) [17] as the cutpoint. In the multivariate model (Table 2), baseline covariates associated with significantly different probability of survival benefits from ZOL treatment included analgesic use ($P_{int}=.041$), SRE history ($P_{int}=.029$), NTX level ($P_{int}=.039$ and.018 for 64 and 100 nmol/mmol Cr, respectively), and albumin level ($P_{int}=.002$).

3.4. Influence of increased bone resorption rate on treatment effect

In models using 100 nmol/mmol creatinine as a cutpoint for NTX (reflective of severe bone disease) [17] and categorising parameters reflective of overall health (e.g., albumin, Cr, lymphocytes) using study-specific percentiles, baseline NTX $\geq$ 100 nmol/mmol Cr emerged as a significant modifier of the ZOL treatment effect (consistent with earlier reports in NSCLC) [29]. In this cohort, ZOL reduced the risk of death by 31% ($P=.0028$) versus placebo, an effect significantly different from that for patients with baseline NTX $<$ 100 nmol/mmol Cr ($P_{int}=.0121$).

3.5. Additional treatment-effect modifiers

To assess additional treatment effect modifiers, we analysed reduced multivariate models that dichotomised NTX using 64-nmol/mmol Cr as cutpoint and categorised albumin, creatinine, and lymphocytes using common or study-specific quartiles. Models using common quartiles to categorise albumin, creatinine, and lymphocyte levels showed that cancer duration before study entry ($P_{int}=.0125$), and prior history of SREs ($P_{int}=.0160$) were associated with the likelihood of a survival benefit from ZOL (Fig. 1). Treatment with ZOL was associated with a 42% reduction in the risk of death in patients with a history of prior SREs and cancer duration shorter than the median (HR=0.576; 95% CI 0.433–0.767; $P=.0002$). Not surprisingly, these characteristics are consistent with aggressive, rapidly progressing MBD.

Models using study-specific quartiles to categorise albumin, creatinine, and lymphocyte levels showed age ($P_{int}=.0459$), ECOG

Table 1
Patient demographics and baseline disease characteristics.

	NSCLC/OST [5]		**Prostate cancer** [4]		**Breast cancer** [3]	
	ZOL ($n=522$)	**Placebo** ($n=250$)	**ZOL** ($n=435$)	**Placebo** ($n=208$)	**ZOL**[a] ($n=114$)	**Placebo** ($n=113$)
ECOG PS, *n* (%)						
Fully active (0)	110 (21)	50 (20)	184 (42)	93 (45)	76 (67)	74 (65)
Some impairment (1–2)	407 (79)	200 (80)	250 (58)	115 (55)	38 (33)	39 (35)
Prior SRE, *n* (%)	346 (66)	180 (72)	137 (32)	78 (38)	39 (34)	47 (42)
Baseline NTX, *n* (%)[b]						
$\geq$ 64 nmol/mmol Cr	182 (52)	94 (59)	276 (67)	135 (67)	62 (56)	59 (54)
$\geq$ 100 nmol/mmol Cr	95 (27)	49 (31)	188 (45)	94 (47)	41 (27)	33 (30)
Baseline albumin (g/L)						
Median (range)	38 (23–50)	38 (22–48)	41(20–50)	42 (27–50)	43 (26–52)	43 (28–53)

Cr, creatinine; ECOG PS, Eastern Cooperative Oncology Group performance status; NSCLC/OST, non-small cell lung cancer and other solid tumours; NTX, *N*-telopeptide of type I collagen; SRE, skeletal-related event; ZOL, zoledronic acid.
Data from Kohno et al. [3], Saad et al. [4], and Rosen et al. [5].

[a] All patients received 4 mg zoledronic acid.
[b] Data from the bone marker subset (total $n=1339$ across the three trials).

Table 2
Analyses for risk of death in zoledronic acid-treated versus placebo-treated patients (adjusted for chemotherapy and baseline calcium).

Covariate	*N*	RR	95% CI	*P* value	P_{int}
Cancer duration					.0706
< Median	538	0.798	**0.637 to 0.998**	**.048**	
≥ Median	588	1.067	0.855 to 1.332	.565	
Age					.9917
< Median	509	0.960	0.752 to 1.225	.742	
≥ Median	617	0.961	0.783 to 1.181	.707	
Weight					.4383
< Median	549	0.901	0.727 to 1.118	.346	
≥ Median	577	1.021	0.811 to 1.285	.858	
BPI composite score					.1750
< Median	542	1.047	0.828 to 1.324	.700	
≥ Median	584	0.842	0.681 to 1.040	.111	
Analgesic use					**.0411**
None	331	1.310	0.912 to 1.882	.144	
Some	795	0.861	0.723 to 1.026	.094	
ECOG PS					.0806
Fully active	450	1.168	0.875 to 1.560	0.291	
Some impairment	676	0.860	0.713 to 1.037	0.114	
Prior SRE					**.0291**
No	599	1.137	0.905 to 1.428	.271	
Yes	527	0.801	**0.644 to 0.994**	**.044**	
NTX (nmol/mmol) Cr					**.0388**
< ULN	445	1.179	0.894 to 1.555	.243	
≥ ULN	681	0.827	0.683 to 1.002	.052	
NTX (nmol/mmol) Cr					**.0178**
< 100	703	1.083	0.878 to 1.336	.457	
≥ 100	423	0.738	0.582 to 0.937	.012	
BALP[a]					.5977
< ULN	381	1.011	0.754 to 1.357	.939	
≥ ULN	745	0.921	0.921 to 1.109	.386	
LDH					.0644
< ULN	862	0.993	0.828 to 1.192	.942	
≥ ULN	264	0.707	**0.518 to 0.965**	**.029**	
Lymphocytes					.5863
≤ Median	608	0.912	0.742 to 1.122	.384	
> Median	5181	0.997	0.782 to 1.269	.978	
Haemoglobin					.1817
≤ Median	691	1.040	0.855 to 1.264	.697	
> Median	435	0.831	0.638 to 1.083	.170	
SGOT					.4257
< ULN	815	0.900	0.747 to 1.086	.273	
≥ ULN	311	1.036	0.775 to 1.386	.810	
Albumin (quartile)					**.0024**
< 1st quartile	242	0.580	**0.425 to 0.791**	**.001**	
≥ 1st but < 2nd	269	1.227	0.863 to 1.744	.254	
≥ 2nd but < 3rd	257	0.799	0.585 to 1.090	.156	
≥ 3rd quartile	358	1.182	0.873 to 1.600	.280	
Cr (quartile)					.5868
< 1st quartile	251	0.788	0.564 to 1.102	.164	
≥ 1st but < 2nd	227	0.929	0.664 to 1.300	.668	
≥ 2nd but < 3rd	298	1.075	0.784 to 1.474	.654	
≥ 3rd quartile	350	1.000	0.753 to 1.328	.999	

Bold text indicates statistically significant correlation.
BALP, bone-specific alkaline phosphatase; BPI, brief pain inventory; CI, confidence interval; Cr, creatinine; ECOG PS, Eastern Cooperative Oncology Group performance status; LDH, lactate dehydrogenase; NTX, N-telopeptide of type I collagen; P_{int}, interactive *P* value for treatment-by-covariate interaction; RR, relative risk; SGOT, serum glutamic oxaloacetic transaminase; SRE, skeletal-related event; ULN, upper limit of normal.

[a] BALP levels in the Japanese breast cancer trial were dichotomised using 40 U/L (the study-specific median) as the cutpoint because of the low BALP distribution among those patients.

PS (P_{int}=.0304), lymphocyte levels (P_{int}=.0137), and albumin levels (P_{int}=.0154) to be significantly associated with the likelihood of survival benefit from ZOL (Fig. 2). Results from this model should be interpreted with caution given the small numbers of patients in individual subgroups. Nonetheless, patients with albumin levels within the lowest quartile tended to derive a survival benefit from ZOL regardless of other factors. The potential for improved survival with ZOL was also more pronounced in patients with impaired ECOG PS. The likelihood of OS benefit with ZOL was blunted in patients with normal lymphocyte levels (i.e., in the 2nd and 3rd quartiles), possibly because these patients might have tolerated any concomitant chemotherapy better than patients with lymphopaenia.

3.6. Survival benefit from zoledronic acid treatment is not dependent on SRE prevention

To control for potential effects of SREs on survival [15], the observed OS benefit with ZOL treatment was evaluated using treatment-by-covariate interactions for the pooled patient population in models categorising albumin and Cr using study-specific quartiles, and adjusting for cumulative SRE incidence in three different waysas a linear effect, a categoric variable, or a time-dependent stratification factor. All of these models yielded highly consistent results wherein the OS benefits with ZOL were partially attenuated but always maintained in patients with high baseline NTX. In the most robust of these models, the OS benefit with ZOL in the NTX ≥ 100 nmol/mmol Cr subset remained significant after inclusion of a time-dependent covariate recording the cumulative number of SREs after randomisation as a categoric variable (Fig. 3). The effect of ZOL on OS therein was significantly different from that observed in patients with baseline NTX < 100-nmol/mmol Cr, regardless of whether the model was adjusted for time-dependent SRE incidence (P_{int}=.0159) or not (P_{int}=.0106).

4. Discussion

Bisphosphonates reduce skeletal morbidity in patients with advanced cancers involving bone and have become a recommended component of the multidisciplinary treatment of MBD [1]. However, bone-health benefits have not generally translated into significantly improved OS in phase III trials [3–5]. These individual placebo-controlled trials were not powered to evaluate OS differences and included groups of patients with low SRE rates (e.g., patients with MBD in the skull) [30] or aggressive metastases in vital organs that may have contributed substantially to mortality. A bone-targeted therapy would be less likely to influence the clinical course of disease in such patients.

In the overall phase III MBD trial population, there was only a 5% nonsignificant improvement in OS with ZOL treatment. Nonetheless, the results herein suggest a beneficial effect of ZOL on survival (up to 24 months and in addition to SRE prevention) in patients with MBD and baseline characteristics associated with aggressive disease and/or poor prognosis. These characteristics include parameters associated with aggressive bone disease – namely, high baseline NTX, prior SREs at baseline – or parameters indicating a poor overall condition (e.g., low albumin levels and impaired PS). In particular, the survival benefit in patients with high NTX was observed in multiple analytic models regardless of how other covariates were categorised, and is biologically plausible given the antiresorptive ability of bisphosphonates. Cancer-induced osteolysis is the main therapeutic target for bisphosphonates and, consistent with other targeted therapy approaches, measurement of target activity may help identify patient populations with the greatest likelihood of benefit from treatment. Furthermore, the larger survival benefit with ZOL in patients with NTX > 100 nmol/mmol Cr (versus a smaller trend in patients with NTX > 64 nmol/mmol Cr) suggests a dose-response effect.

Interestingly, several of the characteristics associated with potential OS benefits from ZOL have been also associated with poor clinical outcomes in earlier studies in patients with advanced cancers. High baseline NTX is associated with increased

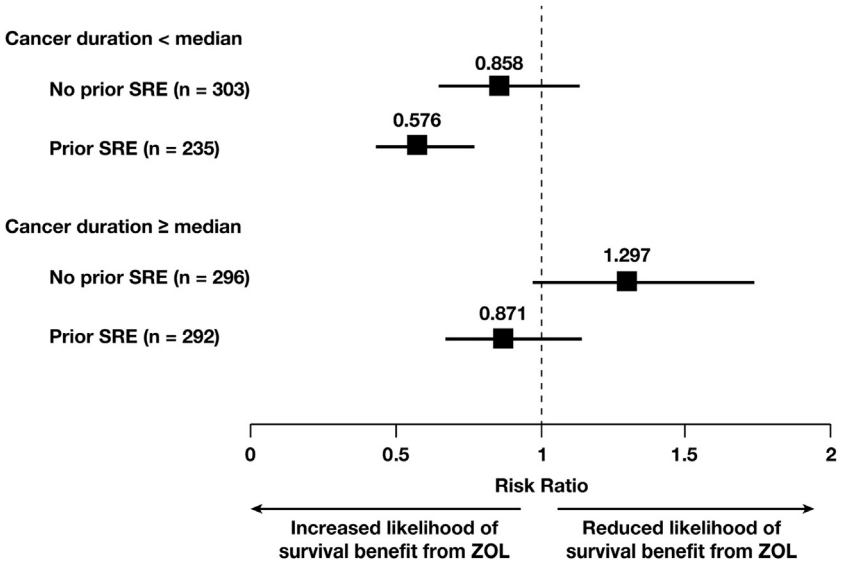

Fig. 1. Multivariate model for treatment-by-covariate effects on overall survival benefits with zoledronic acid (ZOL) in patients with complete baseline prognostic variables ($n=1126$). Model was stratified by tumour type and adjusted for prior chemotherapy status (yes vs. no) and baseline calcium levels (as a continuous variable); NTX level was dichotomized using 64 nmol/mmol creatinine as cut-point, baseline albumin, creatinine, and lymphocytes were categorized using common quartiles. ECOG PS, Eastern Cooperative Oncology Group performance status; Q1–Q4, lowest-highest quartiles; SRE, skeletal-related event; ECOG PS = 0 implies fully active; ECOG PS ≥ 1 implies some impairment.

risks of SREs and death [17], and low albumin levels have emerged as negative prognostic indicators in a variety of advanced cancers [19–23,31]. Factors such as hypoalbuminaemia and poor PS might also impact treatment decisions (e.g., by exacerbating the side effects of chemotherapy or by hindering access to in-clinic treatment), thereby influencing clinical outcomes. The strong associations between such "poor-prognosis" variables and the probability of OS benefits from ZOL suggest that bone-directed therapy continues to provide benefits even in patients with the most advanced disease; moreover, such patients might derive even greater benefits from ZOL.

Consistent with recent results from the MRC Myeloma IX trial [10], the survival benefits associated with ZOL in the present analyses appeared independently of SRE prevention. If the observed improvements in OS with ZOL treatment were completely attributable to preventing potentially life-limiting SREs [15], the survival benefits would not be sustained in models including SRE incidence as a competing time-dependent variable. The consistent maintenance of the OS benefits of ZOL in models adjusting for SREs suggests that ZOL, in addition to preventing treatment interruption and cessation because of SREs and the associated decreases in PS, may exert anticancer effects in some patient subsets. Of note, the survival impact is greatest in those patients with NSCLC and OST, whose survival is typically short and for whom a delay in anticancer treatment of a few weeks may have more bearing on subsequent outcome.

This study has some limitations. First, it is a retrospective evaluation of prospectively collected information, and as such must be considered exploratory. However, the relationships between osteolysis rate and other modifiers of the effect of ZOL on survival make clinical and biologic sense. Second, only 69% of patients had complete baseline assessments; however, a dataset of 1100 patients with MBD is one of the largest populations ever evaluated for prognostic factors. Third, survival information is only available for the duration of the respective periods of extended follow-up (24 months for CRPC, 21 months for NSCLC and OST, or 12 months for BC) and as a result only a few breast cancer events contribute to the findings. Finally, the effect of new bone-directed therapies on survival remains a topic for investigation.

Denosumab, an inhibitor of receptor activator of nuclear factor kappa-B ligand (RANKL), has demonstrated comparable or superior efficacy versus ZOL for reducing SREs in head-to-head clinical trials in patients with MBD from solid tumours [32–34]. Nonetheless, OS was similar between treatment arms [32–34], suggesting that SRE prevention alone may be insufficient to alter survival. Although correlative analyses are yet to be reported, these trials prospectively collected bone marker data at baseline and 13 weeks, and present an opportunity to investigate whether the correlations between elevated osteolysis levels and survival benefits with antiresorptives are generally applicable.

5. Conclusion

Our findings may help physicians in selecting high-priority patients for bisphosphonate treatment. Zoledronic acid is indicated for treating patients with MBD from any malignancy [1,35]; however, many patients do not receive treatment (especially in NSCLC and CRPC). Although it may not be cost-effective to treat all, assessing NTX or a similar osteolysis marker could help identify patients who both have a higher risk of SREs (which can be reduced with ZOL treatment) and who may also derive a worthwhile OS benefit from this relatively simple and well-tolerated intervention. Overall, our models suggest that patients with poor overall prognosis are more likely to derive OS benefits from ZOL, indicating that aggressive disease or impaired PS should not preclude ZOL treatment.

Funding

This work was supported by Novartis Pharmaceuticals Corporation. As the sponsor of the studies included in the meta-analysis, Novartis made the data available to the authors. All analyses were conducted by the independent statistician (RJC). The corresponding author initiated and directed all analyses, had access to all data in the study, and took final responsibility for the decision to submit for publication. All authors were responsible for the content of this review.

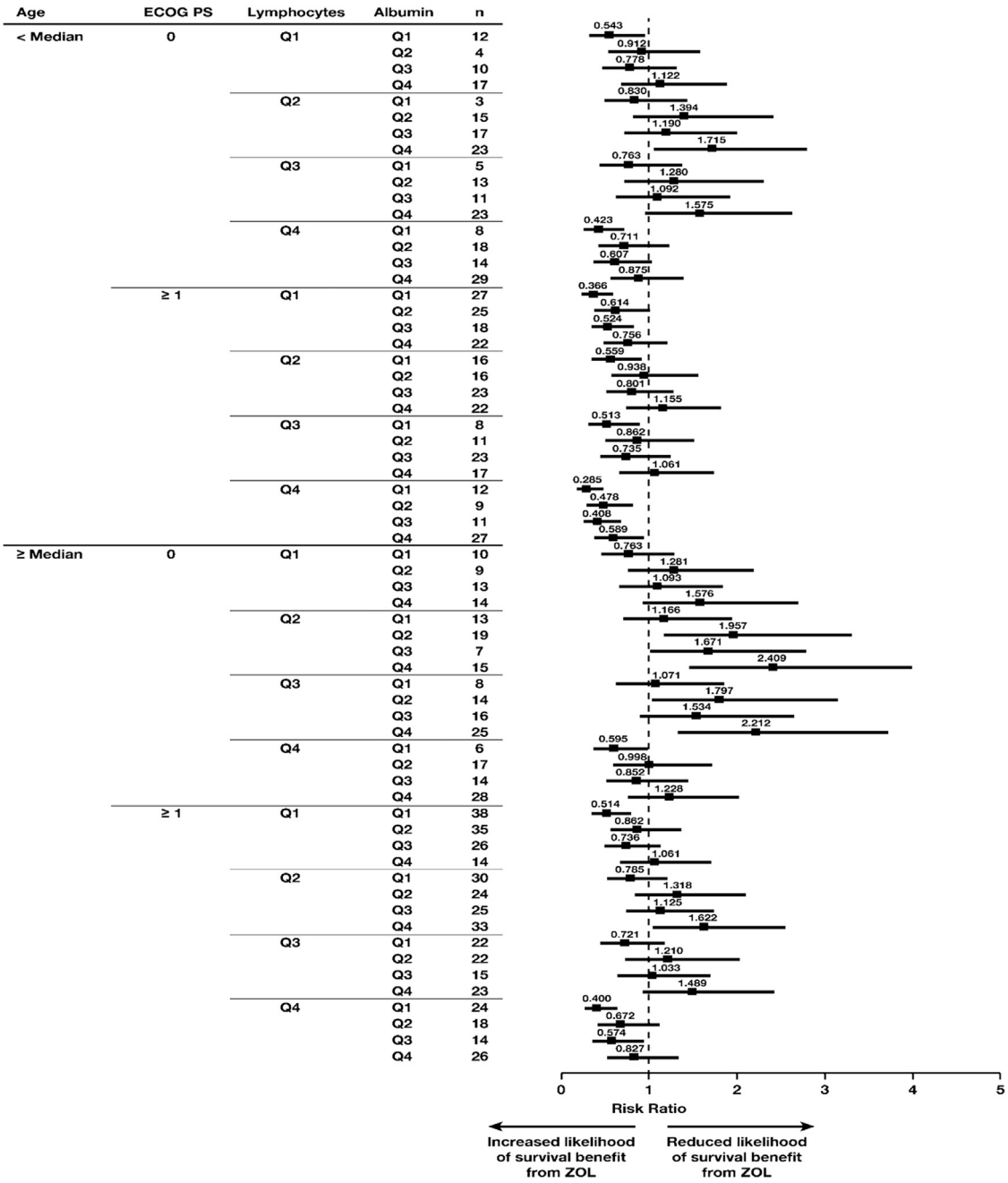

Fig. 2. Multivariate model for treatment-by-covariate effects on overall survival benefits with zoledronic acid (ZOL) in patients with complete baseline prognostic variables ($n=1126$). Model was stratified by tumour type and adjusted for prior chemotherapy status (yes vs. no) and baseline calcium levels (as a continuous variable); NTX level was dichotomized using 64 nmol/mmol creatinine as cut-point, baseline albumin, creatinine, and lymphocytes were categorized using study-specific quartiles. ECOG PS, Eastern Cooperative Oncology Group performance status; Q1–Q4, lowest-highest quartiles; ECOG PS$=0$ implies fully active; ECOG PS≥ 1 implies some impairment.

Conflict of Interest Statement

REC has served as a consultant/advisor to Novartis, and has previously given expert testimony on behalf of Novartis. AL has participated as a consultant for Amgen, Novartis, Acceleron Pharmaceuticals, Monogram Biosciences, and GlaxoSmithKline; received honoraria from Amgen, Pfizer, Acceleron Pharmaceuticals, GlaxoSmithKline, and Novartis; received research funding from Novartis, Monogram Biosciences, and Oncogene Science; and has given expert testimony for Novartis. LC has received honoraria from Novartis and Amgen, and speaker fees from Novartis. RJC has received honoraria and consulting fees from Abbott, Amgen, GlaxoSmithKline, and Novartis. FS has received research funding, attended advisory board meetings, and received honoraria for speaking on behalf of Novartis. JEB has received a travel grant and honoraria from Novartis; she has also received a travel grant, honoraria, research funding, and speaker fees from Amgen, and has participated in advisory boards for Bristol-Myers Squibb. ET has received honoraria and research funding from Novartis and Janssen-Cilag, and has participated in advisory boards and served on steering committees for Amgen. PPM has received consultancy fees from Novartis for participating in advisory boards and FDA meetings. NK has received honoraria from Pfizer and Novartis. JJB has received consultancy fees and speaker fees from Novartis and Amgen. MS reports no disclosures relevant to this manuscript. KAI reports no conflicts of interest.

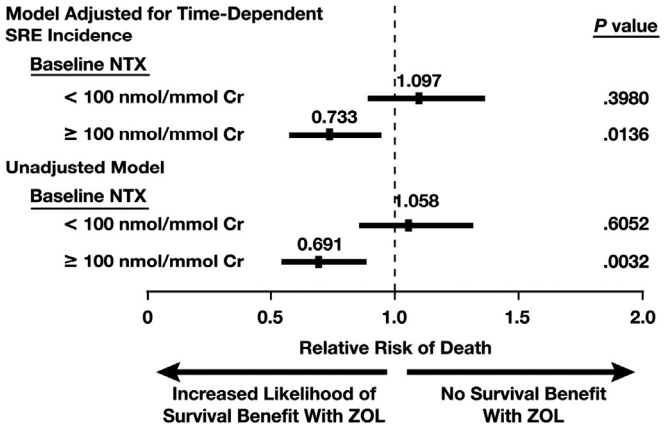

Fig. 3. Multivariate models for treatment-by-covariate effects on overall survival with zoledronic acid (ZOL) treatment adjusted for time-dependent skeletal-related event (SRE) incidence as a categoric variable. Model was stratified by tumour type and adjusted for prior chemotherapy status (yes vs. no) and baseline calcium levels (as a continuous variable); NTX level was dichotomized using 64 nmol/mmol creatinine as cut-point, baseline albumin and creatinine were categorized using study-specific quartiles, and lymphocytes were dichotomised around the median. Cr, creatinine; NTX, N-telopeptide of type I collagen.

Research support

This work, including medical editorial assistance, was supported by Novartis Pharmaceuticals Corporation.

Acknowledgments

We thank Shalini Murthy, PhD, ProEd Communications, Inc.®, for her editorial assistance with this manuscript. Medical editorial assistance was supported by Novartis Pharmaceuticals Corporation.

References

[1] Aapro M, Abrahamsson PA, Body JJ, et al. Guidance on the use of bisphosphonates in solid tumours: recommendations of an international expert panel. Annals of Oncology 2008;19:420–32.
[2] Major P, Lortholary A, Hon J, et al. Zoledronic acid is superior to pamidronate in the treatment of hypercalcemia of malignancy: a pooled analysis of two randomized, controlled clinical trials. Journal of Clinical Oncology 2001;19:558–67.
[3] Kohno N, Aogi K, Minami H, et al. Zoledronic acid significantly reduces skeletal complications compared with placebo in Japanese women with bone metastases from breast cancer: a randomized, placebo-controlled trial. Journal of Clinical Oncology 2005;23:3314–21.
[4] Saad F, Gleason DM, Murray R, et al. A randomized, placebo-controlled trial of zoledronic acid in patients with hormone-refractory metastatic prostate carcinoma. Journal of National Cancer Institute 2002;94:1458–68.
[5] Rosen LS, Gordon D, Tchekmedyian S, et al. Zoledronic acid versus placebo in the treatment of skeletal metastases in patients with lung cancer and other solid tumors: a phase III, double-blind, randomized trial—the Zoledronic Acid Lung Cancer and Other Solid Tumors Study Group. Journal of Clinical Oncology 2003;21:3150–7.
[6] Coleman RE, Winter MC, Cameron D, et al. The effects of adding zoledronic acid to neoadjuvant chemotherapy on tumour response: exploratory evidence for direct anti-tumour activity in breast cancer. British Journal of Cancer 2010;102:1099–105.
[7] Coleman R, de Boer R, Eidtmann H. et al. Zoledronic acid (zoledronate) for postmenopausal women with early breast cancer receiving adjuvant letrozole (ZO-FAST study): final 60-month results. Annal of Oncology 2012;.Oct 9th, E-pub ahead of print.
[8] Gnant M, Mlineritsch B, Stoeger H, et al. Adjuvant endocrine therapy plus zoledronic acid in premenopausal women with early-stage breast cancer: 62-month follow-up from the ABCSG-12 randomised trial. Lancet Oncology 2011;12:631–41.
[9] Guise TA. Antitumor effects of bisphosphonates: promising preclinical evidence. Cancer Treatment Reviews 2008;34(suppl 1):S19–24.
[10] Morgan G, Davies F, Gregory W, et al. Effects of induction and maintenance plus long-term bisphosphonates on bone disease in patients with multiple myeloma: the Medical Research Council Myeloma IX Trial. Blood 2012;119(23):5374–83.
[11] Mystakidou K, Katsouda E, Parpa E, et al. Randomized, open label, prospective study on the effect of zoledronic acid on the prevention of bone metastases in patients with recurrent solid tumors that did not present with bone metastases at baseline. Medical Oncology 2005;22:195–201.
[12] Zaghloul MS, Boutrus R, El-Hossieny H, et al. A prospective, randomized, placebo-controlled trial of zoledronic acid in bony metastatic bladder cancer. International Journal of Clinical Oncology 2010;15:382–9.
[13] Zarogoulidis K, Boutsikou E, Zarogoulidis P, et al. The impact of zoledronic acid therapy in survival of lung cancer patients with bone metastasis. International Journal of Cancer 2009;125:1705–9.
[14] Coleman RE, Marshall H, Cameron D, et al. Breast-cancer adjuvant therapy with zoledronic acid. New England Journal of Medicine 2011;365:1396–405.
[15] Saad F, Lipton A, Cook R, et al. Pathologic fractures correlate with reduced survival in patients with malignant bone disease. Cancer 2007;110:1860–7.
[16] Brown JE, Cook RJ, Major P, et al. Bone turnover markers as predictors of skeletal complications in prostate cancer, lung cancer, and other solid tumors. Journal of the National Cancer Institute 2005;97:59–69.
[17] Coleman RE, Major P, Lipton A, et al. Predictive value of bone resorption and formation markers in cancer patients with bone metastases receiving the bisphosphonate zoledronic acid. Journal of Clinical Oncology 2005;23:4925–35.
[18] Noguchi M, Kikuchi H, Ishibashi M, et al. Percentage of the positive area of bone metastasis is an independent predictor of disease death in advanced prostate cancer. British Journal of Cancer 2003;88:195–201.
[19] Lam PT, Leung MW, Tse CY. Identifying prognostic factors for survival in advanced cancer patients: a prospective study. Hong Kong Medical Journal 2007;13:453–9.
[20] Paralkar VR, Li T, Langer CJ. Population characteristics and prognostic factors in metastatic non-small-cell lung cancer: a Fox Chase Cancer Center retrospective. Clinical Lung Cancer 2008;9:116–21.
[21] Seve P, Ray-Coquard I, Trillet-Lenoir V, et al. Low serum albumin levels and liver metastasis are powerful prognostic markers for survival in patients with carcinomas of unknown primary site. Cancer 2006;107:2698–705.
[22] Vigano A, Bruera E, Jhangri GS, et al. Clinical survival predictors in patients with advanced cancer. Archives of Internal Medicine (Chicago, IL) 2000;160:861–8.
[23] Barbot AC, Mussault P, Ingrand P, et al. Assessing 2-month clinical prognosis in hospitalized patients with advanced solid tumors. Journal of Clinical Oncology 2008;26:2538–43.
[24] Lipton A, Cook R, Saad F, et al. Normalization of bone markers is associated with improved survival in patients with bone metastases from solid tumors and elevated bone resorption receiving zoledronic acid. Cancer 2008;113:193–201.
[25] Lipton A, Cook RJ, Major P, et al. Zoledronic acid and survival in breast cancer patients with bone metastases and elevated markers of osteoclast activity. The Oncologist 2007;12:1035–43.
[26] Cox DR. Regression models of life tables (with discussion). Journal of the Royal Statistical Society: Series B (Statistical Methodology) 1972;34:187–220.
[27] Kalbfleisch JD, Prentice RL. The statistical analysis of failure time data. Hoboken, NJ: John Wiley & Sons; 2002 462 p.
[28] Lawless JF. Statistical models and methods for lifetime data. Hoboken, NJ: John Wiley & Sons; 2003 630 p.
[29] Hirsh V, Major PP, Lipton A, et al. Zoledronic acid and survival in patients with metastatic bone disease from lung cancer and elevated markers of osteoclast activity. Journal of Thoracic Oncology 2008;3:228–36.
[30] Major PP, Cook RJ, Lipton A, et al. Natural history of malignant bone disease in breast cancer and the use of cumulative mean functions to measure skeletal morbidity. BMC Cancer 2009;9:272.
[31] Chua W, Charles KA, Baracos VE, et al. Neutrophil/lymphocyte ratio predicts chemotherapy outcomes in patients with advanced colorectal cancer. British Journal of Cancer 2011;104:1288–95.
[32] Fizazi K, Carducci M, Smith M, et al. Denosumab versus zoledronic acid for treatment of bone metastases in men with castration-resistant prostate cancer: a randomised, double-blind study. Lancet 2011;377:813–22.
[33] Henry DH, Costa L, Goldwasser F, et al. Randomized, double-blind study of denosumab versus zoledronic acid in the treatment of bone metastases in patients with advanced cancer (excluding breast and prostate cancer) or multiple myeloma. Journal of Clinical Oncology 2011;29:1125–32.
[34] Stopeck AT, Lipton A, Body JJ, et al. Denosumab compared with zoledronic acid for the treatment of bone metastases in patients with advanced breast cancer: a randomized, double-blind study. Journal of Clinical Oncology 2010;28:5132–9.
[35] Ibrahim A, Scher N, Williams G, et al. Approval summary for zoledronic acid for treatment of multiple myeloma and cancer bone metastases. Clinical Cancer Research 2003;9:2394–9.