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Original Article

Skeletal-related Events and Clinical Outcomes in Patients with Bone Metastases and Normal Levels of Osteolysis: Exploratory Analyses

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Abstract

Aims: High levels of bone resorption markers (e.g. N-telopeptide of type I collagen; NTX) have been correlated with increased risks of skeletal-related events and death in patients with bone metastases from solid tumours. However, the disease course has not been well characterised in patients with bone metastases but normal NTX levels. Therefore, the aim of this study was to evaluate the patterns of skeletal morbidity in patients with normal NTX levels.
Materials and methods: Exploratory analyses were carried out on patients with bone metastases from breast cancer, castration-resistant prostate cancer, non-small cell lung cancer or other solid tumours treated with zoledronic acid (ZOL) in phase III trials. The effects of covariates on the relative risk of death were estimated using the Cox proportional hazard model. The prognostic values of covariates were compared between patients with normal (<64 nmol/mmol creatinine) versus elevated (≥64 nmol/mmol creatinine) NTX levels.
Results: Among patients with normal baseline NTX ($n = 501$), less than 10% developed elevated NTX levels before a skeletal-related event or death during ZOL treatment over 12 months. The prognostic factors identified in these analyses were mostly similar across NTX groups. However, some indicators of aggressive disease (e.g. visceral/cerebral metastases from breast cancer) were associated with poor clinical outcomes only in the normal NTX group.
Conclusions: Skeletal-related events were generally not preceded or followed by transition to elevated NTX in patients treated with ZOL. Elevated baseline NTX and aggressive extraskeletal disease were independently associated with reduced survival.

Key words: Bone marker; bone metastases; bone resorption; skeletal-related events; survival; zoledronic acid

Introduction

With many solid tumours (e.g. breast and prostate cancer), the skeleton is the most common site for distant metastases [1]. One hypothesis on bone metastasis is that primary tumour cells in circulation interact with the bone microenvironment causing a positive feedback loop of tumour growth and bone destruction [1,2]. This weakens bone integrity and results in skeletal-related events (SREs), including pathological fracture, spinal cord compression, the need for palliative radiotherapy or surgery to bone, and hypercalcaemia of malignancy [1]. SREs may decrease patient quality of life, can reduce survival and are associated with increased healthcare costs [3–7].

Bone metastases have been associated with increases in biochemical markers of bone resorption, such as N-telopeptide of type I collagen (NTX), in up to 75% of patients [8,9]. Moreover, previous studies have established that elevated levels of NTX correlate with increased risks of SREs and death in patients with bone metastases [9,10]. Retrospective analyses of clinical trial data have shown that normalisation of elevated NTX levels with bisphosphonate treatment is associated with improved survival compared with persistently elevated NTX levels in this patient

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population [11]. Furthermore, reductions in elevated baseline NTX levels correlated with survival benefits regardless of whether a normal NTX level was achieved. However, it is unclear whether an SRE is preceded by an increase in bone marker levels.

The objective of this exploratory analysis was to examine the potential correlations between risk factors and NTX levels for clinical outcomes (e.g. SREs and death) in patients with normal baseline NTX levels.

Materials and Methods

Patient Inclusion/Exclusion Criteria

Analyses were carried out on patients with bone metastases from castration-resistant prostate cancer (CRPC), breast cancer and non-small cell lung cancer (NSCLC) or other solid tumours (OST) who received zoledronic acid (ZOL) in phase III trials [12–16]. Briefly, the CRPC trial enrolled only patients with confirmed bone metastases secondary to progressive CRPC (three consecutive increasing prostate-specific antigen levels) who received either ZOL (4 or 8 mg [later reduced to 4 mg]; $n = 435$) or placebo infusions ($n = 208$) every 3 weeks for up to 15 months with an optional 9 month extension (analyses were carried out at 15 and 24 months) [15,16]. The breast cancer trial enrolled patients with confirmed bone lesions secondary to breast cancer or multiple myeloma who received ZOL (4 or 8 mg [later reduced to 4 mg]; $n = 741$ for breast cancer) or pamidronate (90 mg; $n = 389$ for breast cancer) infusions every 3–4 weeks for up to 12 months (analyses were carried out at 13 months) [12]. The NSCLC or OST trial enrolled patients with confirmed bone metastases secondary to NSCLC or OST (excluding breast cancer and prostate cancer) who received ZOL (4 or 8 mg; $n = 519$) or placebo infusions ($n = 247$) every 3 weeks for up to 9 months with an optional 12 month extension (analyses were carried out at 9 and 21 months) [13,14]. Informed consent was obtained from all patients. Patients were randomised to 4 or 8 mg ZOL, 90 mg pamidronate (breast cancer patients) or placebo (CRPC or NSCLC and OST) for up to 24 months. After study initiation, the 8 mg ZOL dose was reduced to 4 mg to minimise the risk of renal toxicity, and this group was renamed the 8/4 mg group [12]. The current analyses excluded patients missing NTX assessments.

Assessments

The primary end point of each trial was the development of an SRE (pathological fracture, spinal cord compression and the need for palliative radiotherapy or surgery to bone). Secondary end points included hypercalcaemia of malignancy as an SRE and included the time to first SRE, bone disease progression and death, among other evaluations. Radionuclide bone scans and surveys were carried out quarterly throughout the studies. Bone disease progression was defined as the appearance of a new bone metastasis or progression of existing bone metastases. Urinary NTX levels were assessed at baseline and quarterly thereafter and were corrected for creatinine levels at international central laboratories [8,9]. The incidence of documented NTX elevation was assessed in patients with normal baseline NTX. Specifically, the proportions of patients whose first event was an SRE, death or documentation of elevated NTX were examined. However, because NTX was assessed only about every 3 months and SREs were observed continuously, it is possible that an NTX elevation occurred (but was not documented) before an SRE or death. To explore this further, times to NTX elevations, subsequent SREs and deaths were evaluated in patients with breast cancer after the occurrence of an on-study SRE ($n = 72$), using the time of this first SRE as the time of origin. Although radiation to bone was the most common SRE, this treatment could, itself, alter bone metabolism. Therefore, an analysis was carried out using the first pathological fracture (the second most common SRE) before NTX elevation as the time of origin.

Statistical Analysis

The bone resorption marker NTX has been associated with clinical outcomes in cancers typically associated with osteolytic lesions (e.g. breast cancer) as well as cancers associated with apparently osteoblastic bone lesions (e.g. prostate cancer) [8,9] and was, therefore, used for these exploratory analyses. Although different values have been described as 'normal' for NTX, in these analyses urinary NTX levels were categorised as normal ($<$64 nmol/mmol creatinine) or elevated ($\geq$64 nmol/mmol creatinine) based on the reported normal ranges and inferred upper limit of normal (ULN) in disease-free postmenopausal women and in prostate cancer patients with bone metastases versus no bone metastases [17,18]. Patients in the 4 and 8/4 mg ZOL treatment groups were retrospectively pooled to increase the sample size and to improve the statistical power. The effects of covariates on the risk of each event were examined using multivariate Cox proportional hazards models fitted separately for each tumour type and on overall risk using a Cox model stratified by tumour type. The final multivariate model was selected via backwards elimination with insignificant interactions removed first, followed by insignificant main effects that were not present in any interaction terms. Models were first fit with the baseline NTX status, the main effects of all potential risk factors and the interaction between the baseline NTX and the potential risk factors. The final models therefore report separate effects of risks factors by NTX status if they were represented in an interaction term; otherwise a common main effect was reported. All statistical tests were two-sided and at the 5% significance level. For analyses of non-fatal events (e.g. first SRE), a competing risk analysis was conducted through modelling of the cause-specific hazards; in this framework, individuals who were not observed to experience an SRE had their follow-up censored at either the regular censoring time or death. However, we examined the effect of an elevated baseline NTX in a simple, stratified, case-specific Cox model for the time to first SRE and in