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European Association of Urology

Treatment Strategies in Advanced Prostate Cancer/Genitourinary Malignancies: The Use of Bisphosphonates Across the Continuum

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Article info

Keywords:
Bisphosphonates
Bladder cancer
Bone disease
Bone markers
Bone metastases
Osteoclasts
Prostate cancer
Renal cell carcinoma

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Abstract

Context: Patients with metastatic bone disease often have severe bone pain and debilitating skeletal complications. Bisphosphonates, including zoledronic acid, are widely used in the management of metastatic bone disease.

Objective: To summarise current insights into the use of zoledronic acid in patients with bone metastases secondary to genitourinary malignancies, including prostate cancer (PCa), renal cell carcinoma (RCC), and bladder cancer (BCa). In addition, the potential of bone marker measurements to guide treatment decisions in PCa will be discussed.

Evidence acquisition: This manuscript is based on presentations given at an educational session held during the 2nd World Congress on Controversies in Urology (CURy) in Lisbon, Portugal. Data were retrieved from original manuscripts, recent review papers, and abstracts on the use of zoledronic acid for treatment of bone metastases from PCa, RCC, or BCa and the potential of bone markers to facilitate treatment decisions in PCa.

Evidence synthesis: In patients with bone metastases secondary to PCa, RCC, and BCa enrolled in randomised, placebo-controlled trials, monthly zoledronic acid at 4 mg significantly reduced the proportion of patients with at least one skeletal-related event (SRE) and delayed the onset of SREs compared with placebo. Although more research is warranted, zoledronic acid seems to improve overall survival in these patients. In addition, ongoing trials are evaluating the antitumour effect of zoledronic acid. Based on retrospective trials, biochemical markers of bone remodelling, including N-telopeptide of type I collagen, seem to identify metastatic PCa patients at high risk for SREs or death.

Conclusions: The use of zoledronic acid has been shown to be effective in reducing SREs in patients with bone metastases from genitourinary malignancies. Clinical trials are currently ongoing to evaluate whether zoledronic acid also has a direct antitumour activity in addition to its bone-preserving activity. Although well-designed, prospective, randomised trials are needed, bone marker measurements may be used as a tool to guide treatment decisions.

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1569-9056/$ – see front matter doi:10.1016/j.eursup.2009.06.012

1. Introduction

Solid tumours, such as prostate cancer (PCa), renal cell carcinoma (RCC), and bladder cancer (BCa) often metastasise to other parts of the body. Bone metastases can result in severe bone pain, significant skeletal morbidity, and skeletal-related events (SREs), including spinal cord compression, pathologic fractures, and the need for surgery or radiation therapy (RT) to bone [1–3]. Skeletal complications can significantly impair a patient's quality of life (QoL) and are associated with an increased risk of death and significant costs [3,4]. Therefore, delaying or preventing skeletal complications is an important clinical asset for patients with genitourinary malignancies and bone metastases [3,5].

In normal, healthy bone, there is a balanced bone remodelling sequence through the coordinated activity of osteoclasts and osteoblasts, which are responsible for bone resorption and bone formation, respectively. Tumour cells can alter this physiologic balance, resulting in an increased osteoclast activity in most tumour types. The osteoclast-induced bone destruction provides a rationale for treatment. Bisphosphonates are potent inhibitors of osteoclast-mediated bone resorption and are widely used in the management of metastatic bone disease. Bisphosphonate therapy with pamidronate has been shown to reduce and prevent skeletal complications in multiple myeloma and breast cancer patients with bone metastases [6–8] but not in patients with metastatic PCa [9]. This paper summarises current insights into the use of the bisphosphonate zoledronic acid in patients with bone metastases secondary to genitourinary malignancies, including PCa, RCC, and BCa. In addition, the potential value of bone marker assessments as routine diagnostic tools to guide treatment decisions in advanced PCa will be discussed.

2. Evidence acquisition

This paper is based on presentations given at an educational session on the use of bisphosphonates for the treatment of bone metastases secondary to genitourinary malignancies that took place during the 2nd World Congress on Controversies in Urology (CURy) on 7 February 2009 in Lisbon, Portugal. Data were retrieved from original manuscripts, recent review articles, and abstracts on the use of zoledronic acid in the treatment of bone metastases from PCa, RCC, or BCa and the potential of bone markers in guiding treatment decisions.

3. Evidence synthesis

3.1. *Balancing the efficacy and safety of bisphosphonate therapy throughout long-term treatment*

3.1.1. *Prostate cancer*

Bone metastases are a common cause of morbidity in patients with PCa. According to the largest multicentre, randomised, placebo-controlled phase 3 trial in men with hormone-refractory PCa (HRPC) and bone metastases, zoledronic acid significantly reduced skeletal complications at 15 mo [1]. Patients were randomised to receive, via a 15-min infusion, 4 mg of zoledronic acid ($n = 214$), 8 mg zoledronic acid (subsequently reduced to 4 mg because of renal toxicity; $n = 221$), or placebo ($n = 208$) every 3 wk for 15 mo. Treatment with 4 mg of zoledronic acid significantly reduced the proportion of patients with at least one SRE compared with placebo (33% vs. 44%; $p = 0.021$) [1]. Patients who were treated with zoledronic acid reported less bone pain than those who received placebo and had an increased overall survival (OS), although the results were not statistically significant. The severity and interference of pain were evaluated via Brief Pain Inventory (BPI) scores (a lower score indicates less pain). The mean score increased from baseline in all treatment groups. However, the mean increase from baseline in pain score at 15 mo was 0.88 for patients who received placebo compared with 0.58 for patients who received 4 mg of zoledronic acid ($p = 0.134$). The median time of survival was 546 d for the 4 mg of zoledronic acid group and 464 d for the placebo group ($p = 0.091$). At a follow-up period of 24 mo, comparable results were found in terms of the proportion of patients developing a SRE (Fig. 1) and OS. However, at 24 mo of therapy, a significant difference in mean reduction in BPI composite pain scores was found between 4 mg of zoledronic acid and placebo ($p = 0.024$) [2,3].

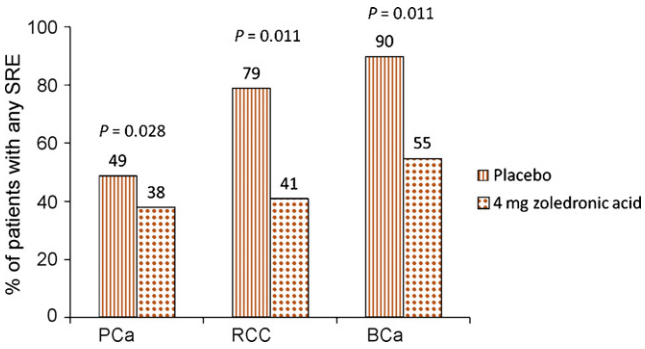

Fig. 1 – Proportion of patients with bone metastases secondary to prostate cancer, renal cell carcinoma, and bladder cancer with at least one skeletal-related event [2,3,20].
SRE = skeletal-related event; PCa = prostate cancer; RCC = renal cell carcinoma; BCa = bladder cancer.

The optimal scheduling of zoledronic acid in PCa is still unclear. However, determination of the optimal regimen is very important because of the impact SREs have on QoL. According to a retrospective analysis of a US medical claims database in patients with solid tumours of the breast, prostate, or lung and bone metastases, the recommended dosing schedule of 4 mg of zoledronic acid every 3 to 4 wk resulted in a 48% reduced monthly rate of skeletal complications when compared with nonrecommended dosing schedules (0.16 vs 0.31; $p < 0.05$) [10]. With regard to the optimal timing, Saad et al [2] demonstrated that 4 mg of zoledronic acid continued to reduce the risk of developing SREs in patients treated for 24 mo compared with 15 mo,

regardless of prior SRE history. In addition, the risk of renal function deterioration did not differ between patients receiving zoledronic acid and patients receiving placebo.

Furthermore, zoledronic acid has demonstrated intriguing antitumour activity on human PCa in in vitro and animal models. The effect of zoledronic acid was associated with reduced cell viability of human PCa cell lines [11,12], decreased PCa tumour growth and prostate-specific antigen (PSA) levels in mice [13], increased efficacy of other anticancer therapies (eg, chemotherapy) [14], inhibited cell adhesion and matrix invasion [15,16], and reduced prostate vascularisation in response to testosterone [17]. These findings suggest that zoledronic acid may have a direct effect on PCa cells in PCa patients with bone metastases. Clinical trials are currently ongoing to determine the antitumour efficacy of zoledronic acid in PCa.

3.1.2. Renal cancer

Approximately 20% of patients with RCC have metastatic disease, and up to 35% of patients with RCC will develop bone metastases, which are associated with a high frequency of bone complications [5]. A retrospective subset analysis of patients with RCC enrolled in a multicentre, randomised, placebo-controlled trial was performed to determine the efficacy of zoledronic acid. Patients with bone metastases from solid tumours other than breast cancer or PCa were randomised to receive zoledronic acid (4 mg [$n = 27$] or 8 mg [$n = 28$] as a 15-min infusion) or placebo ($n = 19$) with concomitant antineoplastic therapy every 3 wk for 9 mo [3,5,18]. Subsequently, the 8 mg of zoledronic acid dose was reduced to 4 mg. Among the subset of 46 patients with RCC, 4 mg of zoledronic acid was found to reduce the proportion of patients with any SRE. Significantly fewer patients had at least one SRE when treated with zoledronic acid compared with placebo (Fig. 1) [3]. Zoledronic acid also significantly delayed the time to first SRE by almost 1 yr compared with placebo ($p = 0.007$). The overall risk of developing an SRE was significantly decreased by 58% in patients treated with zoledronic acid compared with placebo ($p = 0.01$). Secondary efficacy end points showed that zoledronic acid significantly delayed bone lesion progression by > 5.5 mo compared with placebo ($p = 0.014$). Kaplan-Meier analysis showed an improved OS, though the difference was not significant. Zoledronic acid increased the median survival by 131 d compared with placebo (347 d vs 216 d; $p = 0.104$) [3].

3.1.3. Bladder cancer

With regard to BCa, the cumulative 3-yr incidence of bone metastasis in patients with transitional cell carcinoma increases with clinical stage: 8.4% for stage 2 and 49.1% for stage 4. It is estimated that 70% of distant metastases are found in the bone, primarily in the pelvis and spine, but they can also be found in the extremities [19]. According to a recent prospective, randomised, placebo-controlled trial presented at the American Society of Clinical Oncology 2008 annual meeting, zoledronic acid seems to be effective in reducing SREs in patients with metastatic BCa. Patients were treated with palliative RT and, 1 wk later, were randomly assigned to receive 4 mg of zoledronic acid ($n = 20$) or placebo ($n = 20$) [20]. Patients were followed for a median period of 183 d. As observed in PCa and RCC patients, zoledronic acid versus placebo significantly reduced the incidence of SREs in patients with metastatic BCa (Fig. 1) [20]. Furthermore, compared with placebo, zoledronic acid significantly prolonged the time to first SRE ($p = 0.0004$) and reduced the mean pain score ($p = 0.015$). In addition, a significant OS benefit ($p = 0.02$) for zoledronic acid over placebo-treated patients was demonstrated.

3.2. The use of bone marker measurements in treatment decisions in prostate cancer

Biochemical markers of bone remodelling, including N-telopeptide of type I collagen (NTX), are potentially useful tools in the diagnosis and follow-up of PCa patients with bone disease and may allow the identification of patients at high risk for SREs or death who may respond to treatment [1,21]. During the symposium, some arguments in favour of or against introducing bone marker measurements as an additional tool for making treatment decisions in PCa patients with bone metastases were debated.

Bone markers can be assessed through noninvasive, convenient measurements in serum or urine. Sample collection can be combined with routine laboratory tests without the need for sophisticated equipment, which is a first argument in favour of introducing bone marker measurements. In addition, Noguchi et al [22] demonstrated that serum levels of bone markers parallel the results of bone scintigraphy in monitoring bone activity of PCa. Serial measurements of bone markers, PSA, and bone scans were prospectively performed before and after hormone therapy in 84 patients with bone metastases from PCa. In 48 patients without progression of bone metastases, bone marker levels decreased over time to nearly normal levels. The remaining 36 patients who had PSA failure with progression of bone metastases showed an increase in bone marker levels over time. The use of bone markers for detecting progression of bone metastases was even more reliable than using PSA levels. Furthermore, Cook et al [23] reported on the prognostic value of baseline NTX levels in terms of SRE and OS among men with metastatic HRPC. Saad et al [1] showed that urinary NTX levels significantly ($p = 0.001$) decreased in patients with HRPC who received zoledronic acid compared with placebo. Correlations between NTX normalisation during bisphosphonate treatment and clinical outcomes were retrospectively analysed in three large phase 3 trials [24]. Urinary NTX levels were measured at baseline and at month 3 in patients with bone metastases from breast cancer ($n = 578$), HRPC ($n = 472$), or non–small-cell lung cancer (NSCLC) and other solid tumours (OST; $n = 291$) who received zoledronic acid or control for up to 24 mo. In most patients with elevated NTX levels at baseline, their NTX levels normalised after 3 mo of bisphosphonate

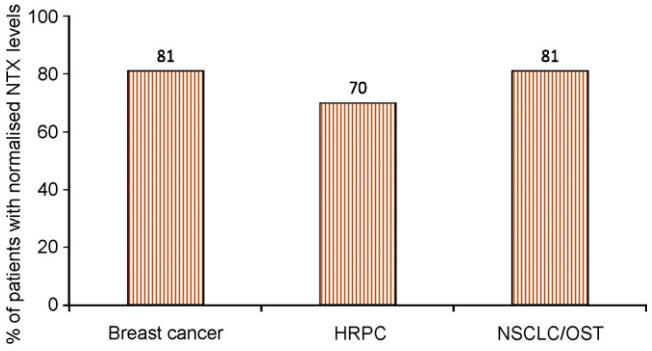

Fig. 2 – Proportion of patients with bone metastases from breast cancer, hormone-refractory prostate cancer, or non–small-cell lung cancer and other solid tumours with normalised N-telopeptide of type I collagen levels after 3 mo of zoledronic acid treatment and elevated N-telopeptide of type I collagen levels at baseline [24].
NTX = N-telopeptide of type I collagen; HRPC = hormone-refractory prostate cancer; NSCLC = non–small-cell lung cancer; OST = other solid tumours.

therapy (Fig. 2) [24]. In addition, normalisation of NTX levels was associated with a reduced risk of death (59% risk reduction for PCa; $p < 0.0001$) and a reduced risk in first SRE (38% risk reduction for PCa; $p = 0.0411$).

However, there is a lack of well-established prospective, randomised, clinical trials to support the use of bone marker measurements in PCa patients with bone metastases. Existing studies are rather small, and data are mostly derived from retrospective analyses of patient subsets in completed trials. In addition, there seems to be no consensus on the definition of "normal" and "elevated" levels of bone markers in the different studies. Furthermore, there are a number of potential bone markers, but general agreement on which markers are most reflective of disease progression is needed. Some studies suggest using a combination rather than any single marker to monitor disease progression or response to therapy [25,26]. Data from prospectively designed clinical trials (eg, the Zometa European Study [ZEUS]) are highly warranted to establish the value of bone markers as a tool to guide treatment decisions.

4. Conclusions

Bone metastases are common and can result in severe morbidity in patients with solid tumours, including PCa, RCC, and BCa. Zoledronic acid in a 4-mg monthly regimen has been shown to significantly reduce the incidence and delay the onset of SREs compared with placebo in patients with bone metastases secondary to PCa, RCC, and BCa. Additional survival benefits have been reported with zoledronic acid treatment, but further investigations are needed. Ongoing clinical trials are evaluating the anti-tumour effect of zoledronic acid in the PCa setting. Although changes in bone marker levels during treatment with zoledronic acid are correlated with clinical outcomes, well-designed prospective, randomised trials are needed to assess the potential value of bone markers as a tool in guiding treatment decisions in PCa.

Conflicts of interest

John M. Fitzpatrick is a consultant and received honoraria from sanofi aventis, Pfizer, GSK, Ipsen, Orion, and Astra Zeneca. Marc Colombel has no conflicts of interest. Fred Saad received honoraria and serves on advisory boards from Novartis, sanofi aventis, and Pfizer. Cora N. Sternberg received honoraria from Novartis, sanofi aventis, and Pfizer. Andrea Tubaro is consultant for Allergan, Astellas, GSK, Orion, Novartis, Pfizer, Specialty European Pharma, and Takeda-Millennium.

Funding support

None.

Acknowledgements

The authors are grateful to Ismar Healthcare NV for assistance in the writing of this manuscript.

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