New Research Findings on Clinical Benefits of Bisphosphonates in Patients With Advanced Prostate Cancer

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1. Introduction

Metastasis to bone occurs in the majority of patients with advanced prostate cancer and can lead to debilitating complications [1]. Patients with prostate cancer typically survive for several years after bone metastases are diagnosed [2], but this time is spent at high risk for skeletal complications, and if these occur, they are associated with substantial morbidity, reduced quality of life, and increased health care costs [3–5]. Bisphosphonates have become an integral component of treatment for malignant
bone disease and are now part of the guidelines of the European Association of Urology for the treatment of prostate cancer [6]. These agents inhibit the osteoclast-mediated bone resorption that occurs in association with both osteolytic and osteoblastic bone lesions. Although several bisphosphonates have been investigated, only zoledronic acid has demonstrated statistically significant long-term benefits in terms of a reduced incidence and delayed onset of skeletal-related events (SREs) and durable pain palliation in a randomised, placebo-controlled trial in men with bone metastases from hormone-refractory prostate cancer (HRPC; Fig. 1) [7–13].

Zoledronic acid is a nitrogen-containing bisphosphonate that binds avidly to bone and is subsequently ingested by active osteoclasts, whereby it inhibits osteoclast activity and induces osteoclast apoptosis [14]. Preventing or delaying the onset of SREs can provide meaningful benefits to patients and may allow for the preservation of functional independence throughout the continuum of care.

2. Results of clinical trials

In a multicenter, phase 3, randomised trial enrolling men with bone lesions secondary to HRPC, intravenous zoledronic acid (4 mg) every 3 wk for up to 24 mo provided significant benefits compared with placebo [7]. In the 24-mo analysis, zoledronic acid (4 mg) reduced all types of SREs, including fractures, spinal cord compression, requirement for change in antineoplastic therapy to treat bone pain, the requirement for surgery to bone, hypercalcaemia of malignancy, and the requirement for palliative radiotherapy to bone (Fig. 2) [7].

Zoledronic acid produced a 22% relative reduction in the proportion of patients who experienced an SRE compared with placebo (p = 0.028), and the difference between these groups remained statistically significant when asymptomatic fractures were excluded from the analysis [7]. As assessed by Andersen-Gill multiple event analysis, 4 mg zoledronic acid reduced the ongoing risk of SREs by 36% compared with placebo (p = 0.002) for the 24-mo trial duration [7]. The benefits of zoledronic acid were also evident in multiple exploratory analyses of the phase 3 trial data. This agent significantly reduced the risk of SREs compared with placebo in both of the prespecified trial periods, with a 36% risk reduction during months 1–15 (p = 0.004) and a 53% risk reduction during months 16–24 (p = 0.004) (Fig. 3) [7,11].
reduction during months 16–24 (p = 0.022; Fig. 3) [7,11,15]. These data suggest that patients continued to benefit from treatment after having received 15 mo of therapy previously.

In many patients, bone metastases might not be diagnosed until the onset of skeletal morbidity. However, a post-hoc analysis indicated that zoledronic acid provided significant benefits to patients regardless of whether they had experienced any SREs before study entry (Fig. 4) [7], suggesting that patients do not need to experience an SRE before they can benefit from treatment. Moreover, many urologists may discontinue treatment if patients experience an SRE while receiving zoledronic acid, considering this to be a treatment failure [16]. However, some events may not be preventable with current therapy options, and patients may still benefit from treatment. In a post-hoc analysis that examined SRE risks in patients who had experienced an on-study SRE, zoledronic acid significantly decreased the risk of developing a second SRE by 41% (hazard ratio = 0.601; p = 0.011) [7,16,17]. Therefore, these data support the continuation of zoledronic acid in patients who experience an SRE while on therapy.

Finally, an exploratory analysis of SREs in patients with or without pain at baseline showed that asymptomatic patients received greater benefit from treatment with zoledronic acid. In the subset of patients with no pain at study entry, zoledronic acid reduced the proportion of patients with an SRE by 39% relative to placebo versus 19% in patients with pain at study entry (Fig. 5) [18]. This analysis suggests that early treatment before the onset of pain may provide greater clinical benefit.

In addition to these objective benefits, zoledronic acid significantly decreased bone pain levels compared with placebo (p < 0.05 at months 3, 9, 21, and 24) [7]. Moreover, in a post-hoc analysis of pain reduction during the study, significantly more patients in the 4-mg zoledronic acid group than in the placebo group experienced clinically meaningful decreases in bone pain (defined as a decrease of ≥2 points of a 10-point scale; p = 0.036) [19].

Zoledronic acid was generally well tolerated with manageable side-effects. Adverse events (AEs; e.g., mild-to-moderate fatigue, myalgia, and fever) occurred more commonly in patients treated with zoledronic acid than with placebo during the core phase; the incidence of these AEs was similar between the zoledronic acid and placebo groups during the extension phase. Moreover, the rate of study discontinuation due to AEs did not differ substantially between treatment groups. The phase 3 trial excluded patients with renal impairment, and the mean time to first notable increase in serum creatinine was comparable between the zoledronic acid (4 mg by 15-min infusion) and placebo groups (p = 0.752) [20].

In addition to their effects on SREs, preclinical evidence suggests that bisphosphonates can inhibit cancer progression. Indeed, patients treated with 4 mg zoledronic acid showed a trend toward increased survival compared with the placebo group in a phase 3 trial in patients with bone metastases from HRPC [7]. Moreover, in preclinical studies zoledronic acid has demonstrated antitumour effects in human prostate cancer cells [21–23] and had synergistic antitumour activity when combined with docetaxel [24].
Zoledronic acid may provide benefits in addition to the prevention of SREs and preservation of patients’ functional independence. Ongoing and future studies are investigating the antitumour potential of bisphosphonates to determine whether bisphosphonate therapy can prevent or reduce the development of bone metastases.

Changes in bone metabolism in patients with early prostate cancer affect the growth factor milieu in the local bone environment, thereby facilitating metastasis to bone. This concept is supported by preclinical data from a mouse model system in which ADT increased metastasis to bone, but zoledronic acid (which inhibits osteoclast-mediated osteolysis) inhibited bone lesion development [25]. Further in vitro evidence in prostate cancer confirms the notion that bisphosphonates may act to prevent bone metastasis [23]. Supporting data in humans indicate that adjuvant clodronate delayed metastasis to bone compared with placebo in patients with high-risk breast cancer [26,27]. In a recent pilot study in 40 patients with advanced solid tumours, administration of 4 mg zoledronic acid every 3–4 wk resulted in a 12-mo bone metastasis-free survival rate of 60% compared with only 10% for the control group (Fig. 6) [28]. This was a small study, and patients with a variety of tumour types were enrolled. The preliminary results are intriguing.

### 3. Conclusions

Larger prospective, randomised trials in patients with early prostate cancer are ongoing. These include the Zoledronic Acid European Study (ZEUS; high-risk prostate cancer patients in Europe), Central European Cooperative Oncology Group (CECOG; high-risk prostate cancer patients in Austria), Systemic Therapy in Advancing or Metastatic Prostate Cancer: Evaluation of Drug Efficacy (STAMPEDE; high-risk prostate cancer patients initiating

### Table 1 – Adjuvant/prevention studies of zoledronic acid in patients with prostate cancer

<table>
<thead>
<tr>
<th>Study/primary country</th>
<th>End points</th>
<th>Target accrual</th>
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<tbody>
<tr>
<td>ZEUS Europe (high-risk patients)</td>
<td>Rate of bone metastases, time to bone metastases, overall survival, PSA doubling time, substudies on bone markers and bone mineral density</td>
<td>1300</td>
</tr>
<tr>
<td>CECOG Austria</td>
<td>Time to occurrence of first bone metastasis, composite pain score, analgesic score, time to first event of bone pain, time to first SRE, proportion of patients having SRE, serum PSA</td>
<td>654</td>
</tr>
<tr>
<td>STAMPEDE United Kingdom</td>
<td>Failure-free survival (PSA failure, new lesions, or increase of baseline lesions, death), QOL, cost effectiveness, toxicity, SREs, overall survival (AD + zoledronic acid, AD + docetaxel, AD + celecoxib, AD + zoledronic acid + docetaxel, AD + zoledronic acid + celecoxib vs. AD)</td>
<td>3300</td>
</tr>
<tr>
<td>RADAR Australia</td>
<td>PSA relapse-free survival, prevention of CTIBL and bone metastases, QOL, overall survival, local failure (6 mo vs. 18 mo ADT ± zoledronic acid for 18 mo)</td>
<td>1000</td>
</tr>
<tr>
<td>AD-ZAP Australia</td>
<td>Biochemical (PSA) relapse-free survival and safety at 2 yr, locoregional relapse, distant/bone metastases, overall survival, QOL, and health resource use</td>
<td>116</td>
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ZEUS = Zoledronic Acid European Study; CECOG = Central European Cooperative Oncology Group; STAMPEDE = Systemic Therapy in Advancing or Metastatic Prostate Cancer: Evaluation of Drug Efficacy; RADAR = Randomised Androgen Deprivation and Radiotherapy; AD-ZAP = Adjuvant Docetaxel-Zoledronic Acid in High-Risk Early Prostate Cancer Following Prostatectomy; PSA = prostate-specific antigen; SRE = skeletal-related event; QOL = quality of life; AD = androgen suppression/deprivation; CTIBL = cancer treatment-induced bone loss.
ADT in the United Kingdom), Randomised Androgen Deprivation and Radiotherapy (RADAR; patients undergoing short- and intermediate-term ADT in Australia), and Adjuvant Docetaxel-Zoledronic Acid in High-Risk Early Prostate Cancer Following Prostatectomy (AD-ZAP; high-risk prostate cancer patients in Australia; Table 1).

References
