



Zoledronic acid for the treatment of prostate cancer

Antoine Finianos & Jeanny B. Aragon-Ching

To cite this article: Antoine Finianos & Jeanny B. Aragon-Ching (2019) Zoledronic acid for the treatment of prostate cancer, *Expert Opinion on Pharmacotherapy*, 20:6, 657-666, DOI: [10.1080/14656566.2019.1574754](https://doi.org/10.1080/14656566.2019.1574754)

To link to this article: <https://doi.org/10.1080/14656566.2019.1574754>



Published online: 07 Feb 2019.



Submit your article to this journal [↗](#)



Article views: 560



View related articles [↗](#)



View Crossmark data [↗](#)




Citing articles: 13 View citing articles [↗](#)

DRUG EVALUATION



Zoledronic acid for the treatment of prostate cancer

Antoine Finianos^a and Jeanny B. Aragon-Ching ^b

^aDepartment of Internal Medicine, American University of Beirut Medical Center, Beirut, Lebanon; ^bGenitourinary Oncology, Inova Schar Cancer Institute, Fairfax, VA, USA

ABSTRACT

Introduction: Prostate cancer remains the most common solid tumor afflicting men in the developed world. Metastatic prostate cancer is a source of great morbidity and mortality especially due to osseous involvement that gives rise to significant symptoms of pain or pathologic fractures or cord compression. Bisphosphonates had been widely used in the treatment of metastatic prostate bone metastases given their demonstrated benefit with a delay of skeletal-related events (SREs) but without prostate-specific antigen (PSA) response or overall survival benefit.

Areas covered: In this review, the authors summarize the available literature on the clinical studies that led to the development and regulatory approval of zoledronic acid in men with metastatic prostate cancer. The authors also provide their expert opinion and future perspectives on this therapeutic.

Expert opinion: Zoledronic acid is an established adjunctive treatment and bone-targeted therapy for the supportive care of men with metastatic castration-resistant prostate cancer. Efforts to study its utility in earlier phases of metastatic hormone-sensitive prostate cancer has not shown superior outcomes compared with standard androgen deprivation therapy (ADT) or docetaxel alone.

ARTICLE HISTORY

Received 8 October 2018
Accepted 22 January 2019

KEYWORDS

Metastatic castration-resistant prostate cancer; zoledronic acid; prostate cancer; bone-targeted agents

1. Introduction

The estimated incidence of new prostate cancer patients is around 164,690 with estimated deaths from prostate cancer around 29,430 cases. Prostate cancer accounts for around one in five new cases [1]. Around 80% of bone metastasis occur in patients with advanced breast and prostate cancer [2]. 70–80% of prostate cancer patients will eventually develop symptomatic skeletal involvement putting them at risk for pathologic fractures, pain, vertebral deformity, and spinal cord compression [3,4]. Although prostate cancer cells produce a variety of growth factors that can stimulate osteoblasts, there is evidence to suggest that bone metastasis lesions associated with prostate cancer are actually mixed with stimulation of osteolysis [5–9].

Bisphosphonates have an established role in various solid tumors in reducing skeletal-related events [10–13]. Various bisphosphonates like clodronate, pamidronate, etidronate, and alendronate have been studied in prostate cancer with bone metastasis [14–21]. Zoledronic acid, the most potent of current bisphosphonates due to its high bioavailability in bone, is currently the recommended bisphosphonate to manage bone metastasis in various solid tumors. In *in vitro* and *in vivo* models, Zoledronic acid has shown antitumor activity affecting apoptosis, tumor cell growth, adhesion, invasion, and angiogenesis moving beyond its anti-osteoclastic activity (see [Box 1](#)). Phase I trials have looked into this activity which could be synergistic when added to chemotherapy regimens in various tumors especially prostate cancer, some even showing possible better activity when given in a metronomic fashion after docetaxel in metastatic castrate-resistant prostate cancer patients, as

reported in the phase I ZANTE trial [22]. This has led to increased interest in incorporating zoledronic acid with various therapeutic agents in prostate cancer in larger trials. In this review, we will discuss the various characteristics and different trials evaluating zoledronic acid in prostate cancer patients.

2. Overview of the market

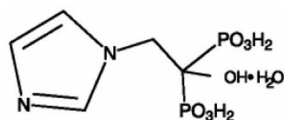
Zoledronic acid (za) has been available in the market since the United States Food and Drug Administration (FDA) approval in 2002 for solid tumors. Prostate cancer is one of the established tumor types for which treatment with at least one hormonal therapy had to be met [23]. The competitor drug in this market has been the RANK-ligand inhibitor denosumab. Denosumab, a monoclonal antibody that binds RANKL was found in a double-blind randomized phase 3 trial to be non-inferior, and with further statistical analyses, more effective than zoledronic acid in reducing the incidence of skeletal-related events (SREs) in patients with metastatic castrate-resistant prostate cancer (mCRPC) [24].

A total of 1904 patients were randomized to zoledronic acid 4 mg IV every 4 weeks versus denosumab 120 mg SQ every 4 weeks. Denosumab was significantly better than zoledronic acid in reducing the time to first SRE, which was the primary endpoint of the study, by 18% (20.7 months vs 17.1 months, $p = 0.0002$). Denosumab also maintained this differential effect for subsequent SREs; however, there was no difference between both in terms of survival and time to disease progression.

Box 1. Drug summary box.

Drug name	Zoledronic Acid
Phase	III
Indication	Prostate Cancer
Pharmacology description	Osteoclast inhibitor. Also inhibits skeletal calcium release induced by tumours.
Route of administration	Intravenous

Chemical structure



Pivotal trial(s) [57,58]

Pharmaprojects – copyright to Citeline Drug Intelligence (an Informa business). Readers are referred to Informa-Pipeline (<http://informa-pipeline.citeline.com>) and Citeline (<http://informa.citeline.com>).

3. Introduction to the compound

Bisphosphonates are synthetic analogs of pyrophosphate. After being used initially for bone scanning, bisphosphonates were found to be effective in disorders of bone resorption like Paget's disease and skeletal manifestations of malignancies [25]. It was later found to be effective for the treatment of osteoporosis in addition to preventing and treating skeletal-related events (SREs) in malignant settings, like fractures and malignant hypercalcemia [10,12,26–29]. Zoledronic acid is a heterocyclic imidazole third-generation bisphosphonate that was shown to be more potent than other medications in its class and given as a short intravenous infusion [30]. Zoledronic acid, like other nitrogen-containing bisphosphonates, was found to inhibit farnesyl diphosphate synthase in the mevalonate pathway in rabbit osteoclasts [31,32]. This inhibition results in the loss of geranylgeranylated small GTP-binding proteins that results in inhibition of osteoclast formation, loss of osteoclast function, and osteoclast apoptosis.

4. Chemistry

Zoledronic acid is designated chemically as 1-Hydroxy-2-imidazole-1-yl-phosphonoethyl phosphonic acid monohydrate (C₅H₁₀N₂O₇P₂·H₂O) and it comes as a white crystalline powder. It is available in 100 ml bottles with inactive ingredients comprised of: mannitol, USP, as a bulking agent, water, and sodium citrate, USP, as a buffering agent [33].

The presence of the highly charged P-C-P motif in various bisphosphonates is responsible for the high affinity for the bone mineral hydroxyapatite [34]. With the addition of one nitrogen molecule to the side chains attached to the P-C-P motif, the molecule becomes significantly more potent than the original compounds (Etidronate, Clodronate, Tiludronate) [35,36]. Further compound manipulation with the formation of nitrogen containing heterocyclic rings attached to the P-C-P moiety resulted in the more potent medication risedronate [37,38]. The further addition of another nitrogen molecule to the ring resulted in the most potent of all, zoledronic acid [39].

5. Pharmacodynamics

Zoledronic acid was found to be at least 8 times more potent than various bisphosphonates at reducing calcium levels in 1,25-dihydroxyvitamin D₃-induced hypercalcemia thyroparathyroidectomized rats [39]. In addition, zoledronic acid (0.028–2.8 µg/Kg) given subcutaneously over 10 days resulted in dose-dependent reduction of bone resorption [40].

In an *in vitro* study of fetal rat calvariae, zoledronic acid was shown to decrease the number of osteoclasts but also shown to inhibit the fusion of more mature osteoclast precursor cells on bone surface while little effect on osteoblasts was seen except at high doses (50 µmol/L) [41].

In an 8-week dose-finding trial involving 44 patients with metastatic bone disease, zoledronic acid at a dose ≥2 mg [2,4,8,16], given as a single intravenous (IV) bolus injection over 30–60 s, was found to suppress various markers of bone resorption in the study period. At 8 weeks, there was reduction from baseline of urinary calcium/creatinine ratio, N-telopeptide/creatinine ratio, hydroxyproline/creatinine ratio, pyridinoline/creatinine ratio, and deoxypyridinoline/creatinine ratio, while the value of these markers remained above baseline with the 1 mg dose [42–44].

In an open-label study evaluating the pharmacokinetics and pharmacodynamics of zoledronic acid in patients with bone metastasis, Chen et al. evaluated 36 patients divided into three dose groups: zoledronic acid 4 mg IV over 5 min or 15 min, zoledronic acid 8 mg IV over 15 min, and zoledronic acid 16 mg IV infusion over 15 min; all repeated every 28 days as tolerated [45]. The 16 mg arm was later dropped because the lower doses were proven in parallel studies to be more renally acceptable. When looking at pharmacodynamic effects of zoledronic acid, bone-specific alkaline phosphatase was elevated 12% above baseline while the remaining markers of bone turnover were all statistically significant in terms of decline at all evaluation times post-dose with maximal declines as follows: C-telopeptide at 24-h post-dose and the rest (N-telopeptide, hydroxyproline, pyridinoline, deoxypyridinoline) at 8 days post infusion. Further analysis revealed no significant differences between bone marker values on days 8, 15, and 29 thus showing the long-term inhibition effect of zoledronic acid. Moreover, when looking at various dose effects of zoledronic acid on bone turnover markers, there was no difference between all doses revealing that maximum declines are already achieved with the 4 mg dose.

6. Pharmacokinetics and metabolism

The kidney is the primary route of excretion of bisphosphonates. However, in the first 24-h post administration, there is a rapid decline in the bisphosphonate concentration as one-third to two-thirds of the dose is excreted by the kidney but a major amount of the dose is taken up in plasma by bone [46]. Ongoing bone remodeling results in small amounts of the drug released in the circulation with long-term small traces detected in the urine thereafter [47]. Zoledronic acid excretion in urine at post-dose duration of 24 h, 6 months, and 12 months, were 40%, 50%, and 60%, respectively.

A study was done to investigate the biodistribution and elimination of zoledronic acid (^{14}C -zoledronic acid) in rats and dogs. Concentrations of radioactivity showed a rapid decline in plasma and non-calcified tissue but only a slow decline in bone, to ~50% of peak at 240 days post-dose, whereas the terminal half-lives (50–200 days) were similar in bone and non-calcified tissues, suggesting redistribution of drug from the former rather than prolonged retention in the latter. This evidently shows that there is a high concentration of the drug in bone shortly after infusion and declines slowly thereafter for the next 8 months [48,49].

In the open-label study by Chen et al. mentioned earlier, the urinary excretion of zoledronic acid was independent of the number of zoledronic acid doses ($p = 0.98$) with $41\% \pm 10\%$, $42\% \pm 11\%$, and $41\% \pm 11\%$ following the first, second, and third doses, respectively [45]. Peak systemic zoledronic acid concentrations declined rapidly after the infusion to $<1\%$ C_{max} at 24 h. The average post-infusion concentration C_{max} for a 15-min infusion was lower by 34.5% ($p = 0.007$) compared to the 5-min infusion. However, there was no statistically significant difference in AUC after 24 h from infusion (AUC_{0-24 h}) and in the cumulative amount of drug excreted into the urine from time 0 to 24-h post-dose (Ae_{0-24 h}). These findings suggest a multiphasic process in zoledronic acid plasma concentrations, whereby there is a rapid decline 24-h post-infusion followed by slow decline of concentration from the bone compartment.

7. Phase 1 trials

A phase I multi-center, dose-finding study of zoledronic acid in patients with hypercalcemia of malignancy (HCM) revealed that zoledronic acid given via 30-min infusion at doses of 0.02 and 0.04 mg/kg was safe and effective in normalizing corrected serum calcium [50]. Initial phase 1 trials looking at zoledronic acid in patients with bone metastases were performed with doses ranging from 0.1 to 16 mg. These studies evaluated bone resorption markers as indicators of clinical efficacy along with safety of increasing doses [42,43]. In the first trial, 59 patients were treated with one of eight zoledronic acid doses (0.1, 0.2, 0.4, 0.8, 1.5, 2, 4, and 8 mg), all as a 5-min IV infusion monthly. In terms of efficacy, bone resorption markers (pyridinoline, deoxypyridinoline-DPD, and N-telopeptide-NTX) were assessed weekly. In summary, greater decreases for urinary NTX were observed in the 0.8 mg and higher doses (70–80%) than with lower doses (40–60%), whereas the suppression of the rest of the markers was most rapid with the doses 1.5 mg and higher.

In the second trial, zoledronic acid was given as 30–60 s injections of 1, 2, 4, 8, or 16 mg doses monthly. Regardless of the dose, there was significant decline in bone resorption markers in the first week of administration. However, these markers remained suppressed until the end of the study in patients receiving doses of 2 mg and above.

8. Phase 2 trial

Based on phase I trial results which showed reasonable safety and efficacy of zoledronic acid, a randomized, double-blind, phase II study was conducted in patients with bone metastases

[44]. A total of 280 patients were randomized to zoledronic acid at doses of 0.4, 2, 4, and pamidronate 90 mg. The 0.4 mg zoledronic acid dose did not meet the study criterion for efficacy as 24% of patients in this group had eventually radiation to bone, while in the remaining zoledronic acid doses 19% in the 2 mg group, and 21% in the 4 mg group had radiation to bone, while in the pamidronate group, 18% had bone radiation. At least one SRE occurred in 35%, 33%, and 30% of patients in the 2.0 or 4.0 mg zoledronic acid groups and 90-mg pamidronate group, respectively, as compared to 46% of patients in the 0.4 mg zoledronic acid group ($p < 0.05$ vs. pamidronate). Mean percentage change in anteroposterior lumbar spine bone mineral density from baseline to end of study was 6.2%, 9.0%, 9.6%, for the 0.4, 2.0, and 4.0 mg zoledronic acid groups, respectively, versus 9.2% for the pamidronate group with $p < 0.05$ for the 4.0 mg zoledronic acid vs. 0.4 mg zoledronic acid.

9. Phase 3 trials in prostate cancer

9.1. Zoledronic acid in metastatic castrate-resistant prostate cancer (mCRPC)

Androgen deprivation therapy (ADT), either through surgical orchiectomy or chemical castration through hormonal treatment, results in increased risks of bone fractures, pain, and other skeletal-related events [51–54]. Bone metastasis from prostate cancer is very common in those with mCRPC or advanced prostate cancer, and results in skeletal-related complications including fractures, pain, hypercalcemia, and spinal cord compression. Bony lesions in prostate cancer are typically mixed between excessive bone formation by osteoblasts (osteoblastic) and increased osteoclastic activities [4,9,55,56]. Zoledronic acid was approved by the US FDA in 2002 to prevent SREs in men with castrate-resistant metastatic prostate cancer based on a phase 3, double-blind, placebo-controlled study that evaluated the efficacy of zoledronic acid vs placebo in mCRPC [57].

This trial evaluated 643 patients with bone metastases who were randomized to receive either zoledronic acid at 4 or 8 mg (protocol later amended to make infusion time 15 min instead of 5 min and dose 4 mg instead of 8 mg due to renal side effects) versus placebo every 3 weeks for 20 cycles or 15 months. The primary endpoint was the proportion of patients with at least one SRE (defined as pathologic fractures, spinal cord compression, surgery to bone, radiation to bone, or a change of antineoplastic therapy to treat bone pain). The study evidently met its primary endpoint with zoledronic acid arm developing less SREs compared to placebo (44.2% vs. 33.2%, $p = 0.021$). Zoledronic acid was more favorable in terms of fractures (13.1% vs. 22.1%, $p = 0.015$) and nonfracture SREs, median time to first occurrence of any SRE (NR vs. 321 days, $p = 0.011$), and mean skeletal morbidity rates for all SREs combined or individually. In terms of bony lesion response, there was no difference in terms of median time to radiographic progression nor response rates.

An extension phase of the above study evaluated efficacy at 24 months in 122 patients who completed the period [58]. Thirty-eight percent in the zoledronic acid group vs. 49% in the placebo group ($p = 0.028$) had at least one SRE. Compared

to placebo, zoledronic acid was significantly better in terms of the annual incidence of SREs (0.77 for the ZA group vs. 1.47 for the placebo, $p = 0.005$), and the median time to the first SRE (488 days for the ZA group versus 321 days for the placebo group, $p = 0.009$). Furthermore, zoledronic acid reduced the ongoing risk of SREs by 36% (risk ratio = 0.64, $p = 0.002$).

The TRAPEZE trial [59] is a randomized phase 3 open-label trial with a 2×2 factorial design, 4 arms comparing docetaxel (the standard of care then as enzalutamide and abiraterone were not approved yet) alone or with zoledronic acid, strontium 89, or both in men with mCRPC. Primary outcome included clinical progression-free survival (CPFS) defined as pain progression, SREs or death. A total of 757 patients were eligible for the study. The overall findings revealed that zoledronic acid did not improve CPFS (HR 0.98, $p = 0.81$) nor overall survival (HR 0.99, $p = 0.91$). However, zoledronic acid had a favorable effect on SRE-free interval, found in Table 1.

10. Zoledronic acid in hormone-naive prostate cancer

10.1. Effect of zoledronic acid on BMD and bone loss

Bone mineral density (BMD) loss associated with ADT occurs early in the course of treatment ranging from 2% to 4% per year but loss continues over the course of treatment [60–62]. A multicenter double-blind randomized placebo-controlled clinical trial enrolled 106 men on ADT for non-metastatic prostate cancer and randomized these patients to receive 4 mg zoledronic acid or placebo IV every 3 months for 1 year [63]. Mean BMD in the lumbar spine increased by 5.6% in men receiving zoledronic acid while it decreased by 2.2% in patients given placebo ($p < 0.001$). Moreover, men in the zoledronic acid group experienced significant improvement in BMD from baseline in the femoral neck, trochanter and total hip ($p < 0.001$) but not in the non-dominant forearm. However, this study did not assess the effect of zoledronic acid on fractures.

At the time of the study conduct, RTOG 0518 was the first randomized phase 3 trial that evaluated the benefit of zoledronic acid in preventing bone fractures for patients with non-metastatic locally advanced and/or high-grade prostate adenocarcinoma receiving luteinizing hormone-releasing hormone (LHRH) agonist and radiotherapy [64]. While this study failed to accrue adequately, results reveal that among the 96 patients evaluated, zoledronic acid was shown to improve BMD although it did not decrease the incidence of bone fractures. In a meta-analysis of 10 placebo-controlled trials of various bisphosphonates in men with non-metastatic prostate cancer receiving ADT, bisphosphonates were as effective as placebo in decreasing the incidence of fractures but were better in increasing BMD of the lumbar spine, femoral neck, and total hip [65].

A single institution 3-arm phase 2 randomized trial assessed the ability of zoledronic acid to prevent or ameliorate ADT-associated BMD loss in patients with recurrent and/or metastatic prostate cancer who were beginning ADT. Arm 1 included patients on gonadotropin-releasing hormone (GnRH) for 1 year plus zoledronic acid 4 mg IV given once 7 days before the start of ADT; Arm 2 was GnRH for 1 year plus zoledronic acid 4 mg IV

Table 1. Phase III RCTs of zoledronic acid in prostate cancer.

Study	Study Characteristics	N	Endpoints	Results
Saad et al [57].	ZA (4 mg every 3 weeks) vs placebo mCRPC	643	Primary Endpoint: Proportion of patients with at least one SRE	ZA 4 mg 33.2% vs placebo 44.2% $p = 0.021$
RADAR [73]	Locally advanced prostate cancer first line hormone-naive STAS: ADT (6mo) +RT ± ZA ITAS: ADT (18 mo) +RT ± ZA	1071	Primary endpoint: Prostate cancer specific mortality Other endpoint: Incidence of all-cause mortality	Prostate Cancer specific mortality: STAS 4.1%, STAS +ZA 7.8%, ITAS 7.4%, ITAS +ZA 4.3% All-cause mortality: STAS 17%, STAS +ZA 18.9%, ITAS 19.4%, ITAS +ZA 13.9%
STAMPEDE [84]	Metastatic hormone naive prostate cancer High risk locally advanced prostate cancer Standard of Care (SOC), SOC +ZA, SOC + Docetaxel SOC +ZA+Docetaxel	2797	Overall survival PFS Prostate Cancer specific survival	5-yr OS rate SOC 55%, SOC +ZA 57%; $p = 0.45$ SOC + Docetaxel 63%; $p = 0.006$ (vs SOC) SOC + Docetaxel ± ZA: $p = 0.592$ SOC + Docetaxel + ZA 60%; $p = 0.0022$ (vs SOC) Proportion of bone mets: 17.1% versus 17% OS: nonsignificant $p = 0.76$
ZEUS [72]	Hormone-naive prostate cancer with bone mets High risk nonmetastatic prostate cancer ZA 4 mg every 3 weeks ± ADT vs Placebo	1433	Primary endpoint: proportion of bone metastases at 4 years Secondary endpoint: OS	Time to first SRE: 31.9 mo vs 28.8 mo, $p = 0.385$ Time to SRE if SRE present prior to randomization: 31.9 mo vs 17.6 mo HR 0.56 PFS: 10.6 mo vs 9.2 mo HR 0.89, $p = 0.22$ OS: 37.9 mo vs 36 mo HR 0.88, $p = 0.29$
CALGB 90202 (ALLIANCE) [71]	Metastatic hormone naive prostate cancer ZA every 4 weeks vs placebo	645	Primary endpoint: time to first SRE Secondary endpoints: OS, PFS	No significant effect of adding ZA on clinical PFS HR 0.98, $p = 0.81$ No significant effect in pain PFS for ZA HR 0.91, $p = 0.31$ ZA increased SRE-free interval from 11.2 mo to 13.6 mo HR 0.78, $p = 0.01$ Total SREs decreased by 30% with ZA with fewer severe SREs with ZA (54% fewer)
TRAPEZE [59]	Docetaxel vs Docetaxel +ZA vs Docetaxel + Strontium89 vs Docetaxel + ZA + Strontium89 mCRPC	757	Primary endpoint: Clinical PFS (Pain progression SREs, Death) Secondary endpoint: pain PFS, Total SRE, SRE free interval	

once given at 6 months, while arm 3 constituted GnRH given for 1 year plus zoledronic acid 4 mg IV given monthly for 6 total doses beginning at 6 months. This study has shown that ADT-associated bone loss could be halted after a single dose of zoledronic acid, but it was the repeated dosing of zoledronic acid that actually improved lumbar spine BMD above baseline. Arms 2 and 3 showed improved BMD in the lumbar spine at the 12-month assessment, though only arm 3 was statistically significant ($2.9\% \pm 3.4\%$, $p = 0.009$). This study suggested that more frequent dosing was needed to increase BMD in patients with prostate cancer on ADT.

In another randomized, placebo-controlled study, yearly zoledronic acid 4 mg was evaluated in men with non-metastatic hormone-sensitive prostate cancer in terms of effect on BMD [66]. The number of patients in the study was rather small ($N = 44$). Mean percent changes in BMD were significantly better in favor of zoledronic acid in the lumbosacral spine, total hip, and trochanter. For example, the mean BMD of lumbosacral spine decreased by $3.1\% \pm 1.0\%$ in the placebo group from baseline to 12 months versus an increase by $4.0\% \pm 1.0\%$ in the zoledronic acid group ($p < 0.001$).

10.2. Effect of zoledronic acid on SREs and survival

Zoledronic acid in preclinical studies have been shown to exert direct anti-tumor effects, activate cytotoxic T-cells, and inhibit tumor-related angiogenesis thus decreasing metastatic potential of prostate cancer cells [67–69]. Prostate cancer is known for its propensity for bone metastases in its advanced stages [70] with subsequent significant skeletal-related complications affecting significantly prognosis and patients' quality of life. Therefore, investigating the role of bisphosphonates in this setting as treatment and/or prevention of bone metastasis may significantly affect patients' outcome.

CALGB 90,202 (Alliance) is a phase 3 randomized controlled trial evaluating the early use of zoledronic acid in men with hormone-naïve prostate cancer with bone metastasis [71]. Patients were randomized to early zoledronic acid 4 mg IV every 4 weeks versus placebo. All patients who progress to castrate-resistance were allowed to receive zoledronic acid (4 mg over 15 min every 3 weeks) in an open-label fashion. The primary endpoint was time to first SRE. A total of 645 patients were randomized to both groups. There was no statistically significant difference between both groups in terms of the median time to first SRE (31.9 months for zoledronic acid versus 28.8 months for placebo, HR 0.97, $p = 0.385$). Zoledronic acid was significantly better than placebo in prolonging time to first SRE (31.9 months versus 17.6 months, HR = 0.56). However, there was no significant difference between both groups in terms of median PFS (10.6 months for zoledronic acid versus 9.2 months for placebo, HR 0.89, $p = 0.22$). Median overall survival was 37.9 months for zoledronic acid versus 36 months for placebo (HR = 0.88, $p = 0.29$). In contrast to the Medical Research Council Pr05 trial with clodronate, zoledronic acid failed to show improved survival in patients with hormone-naïve metastatic prostate cancer but also failed to show significant delay in the first SRE when compared to patients who received it when the disease became castrate-resistant. It was

only the subset of patients with an SRE prior to the use of zoledronic acid that had significant benefit.

The ZEUS trial assessed the efficacy of zoledronic acid (4 mg IV over 15-min \pm ADT) every 3 months in preventing bone metastasis versus placebo (\pm ADT) in men with high-risk non-metastatic hormone-naïve prostate cancer [72]. A total of 1433 patients were randomized, and high-risk prostate cancer was defined as at least one of the following: Gleason score 8–10, node-positive disease, or PSA at diagnosis ≥ 20 ng/ml. There was no difference in the incidence of bone metastasis between both arms (around 17%) irrespective of ADT use. Similarly, there was no difference in terms of survival. Therefore, zoledronic acid in this study failed to show any efficacy in preventing bone metastasis with prolonged use nor in improving survival.

The Randomized Androgen Deprivation and Radiotherapy (RADAR) trial [73] assessed men with locally advanced prostate cancer in a 2×2 factorial design assessing short-term androgen deprivation (6 months) versus intermediate-term (18 months), with or without zoledronic acid (18 months). There was no significant difference in terms of incidence of all-cause or prostate cancer-specific mortality, and cumulative incidence of bone progression between the four arms. Intermediate-term ADT plus zoledronic acid was found to have more favorable effects than the rest in terms of cumulative incidence of PSA progression (HR 0.71, $p = 0.021$) and cumulative incidence of secondary therapeutic interventions (HR 0.67, $p = 0.024$). Interestingly, these differences were only seen in patients with tumors having Gleason score 8–10.

Prognosis of patients with mCRPC have improved significantly over the years beyond androgen deprivation, with the finding of improved survival of these patients with various agents like docetaxel, abiraterone, enzalutamide, cabazitaxel, radium-223, and sipuleucel-T [74–81]. Adding docetaxel to ADT in hormone-naïve metastatic prostate patients have been shown to improve overall survival as shown in the CHAARTED and to improve failure-free survival as evident also in the CHAARTED trial and the GETUG-15 trial [82,83]. The STAMPEDE trial was a large randomized controlled trial using a multi-arm, multi-stage design to test the effects on survival of adding various treatments (docetaxel-Doc, zoledronic acid-ZA, celecoxib, abiraterone, enzalutamide in combination with abiraterone) on ADT in patients not only with metastatic hormone-naïve prostate cancer but also with high-risk locally advanced disease defined by at least two of the following: T3/T4, Gleason score 8–10, and PSA ≥ 40 ng/ml, and node-positive cancer who were newly diagnosed or had high-risk recurrent disease following previous radiation, surgery, or both [84]. Zoledronic acid was given as 4 mg infusion every 3 weeks for 6 cycles then every 4 weeks until 2 years. Standard of care (SOC) comprised of hormone therapy for at least 2 years with GnRH agonists or antagonists, orchidectomy, or anti-androgens alone. The allocation of patients was in a 2:1:1:1 ratio to SOC only, SOC + ZA, SOC + Doc, or SOC + ZA + Doc. The arms with docetaxel were the only ones that showed survival advantage when compared to SOC. When comparing median survivals between different arms, adding zoledronic acid to SOC did not achieve any significant improvement. Moreover, the addition of zoledronic acid to docetaxel did not achieve statistical significance with HR 1.06 and

$p = 0.592$. Median survival and 5-year survival rate for SOC + Doc were 60 months and 50% respectively; while the same parameters for SOC + Doc + ZA were 55 months and 46%, respectively. The same conclusions were found when looking at prostate cancer-specific survival and failure-free survival in metastatic and non-metastatic patients with survival advantage found in the arms containing docetaxel versus SOC with no significant contribution from zoledronic acid. Interestingly, when looking at time to first SRE, still the docetaxel arms showed significant improvement (SOC + Doc HR 0.6 $p = 0.127 \times 10^{-5}$, SOC + Doc + ZA HR 0.55 $p = 0.277 \times 10^{-7}$) which was not the case when comparing SOC to SOC + ZA (HR 0.89, $p = 0.221$).

A systematic review of trials involving the addition of bisphosphonates or docetaxel to standard of care in men with localized or metastatic, hormone-naïve prostate cancer failed to show any benefit in terms of overall survival with the addition of zoledronic acid to standard of care in metastatic (HR 0.94, $p = 0.323$) and non-metastatic patients (HR 0.98, $p = 0.782$) [85].

11. Safety and post-marketing experience

The most common adverse events described with zoledronic acid in various trials include fever, myalgias, influenza-like symptoms, and gastrointestinal (nausea, vomiting, constipation, and diarrhea). In the phase I dose ranging trial of IV zoledronic acid in cancer patients with bone metastases, Berenson et al. evaluated zoledronic acid at doses of 1, 2, 4, 8, and 16 mg [43]. The most frequently reported adverse events were skeletal pain (34%) and fever (18%), reported equally across patients in each treatment group. The most common grade 3 or 4 electrolyte abnormality was hypophosphatemia in four patients (one in the 2 mg and 8 mg groups and two in the 16 mg group). No serious (grade 3 or 4) events were seen in the 4 mg group while the majority were in the 8 mg (disease progression, anorexia, diarrhea, nausea, vomiting, sepsis, skeletal pain, and pneumonia) and the 16 mg group (disease progression, anorexia, constipation, nausea, dehydration, bronchitis, hypoxia, tinnitus, vertigo, and acute renal failure). Of note, the only occurrence of acute renal failure occurred in the 16 mg group in one patient (10%). In their placebo-controlled trial evaluating zoledronic acid 4 mg, or zoledronic acid 8/4 mg versus placebo in mCRPC, Saad et al. [57] reported fatigue, fever, myalgia, and lower limb edema to occur more in both zoledronic acid groups as compared to placebo. As for renal adverse events, incidences were: 20.7% in the 8/4 mg arm, 15.2% in the 4 mg arm, and 11.5% in the placebo arm. In their analysis of zoledronic acid versus pamidronate in patients with hypercalcemia of malignancy, Major et al. report more frequent renal side effects in the 8 mg zoledronic acid arm when compared to the 4 mg arm or pamidronate [86]. Grade 3 serum creatinine values were 2.3% in the 4 mg arm, 3.1% in the 8 mg arm, and 3% in the pamidronate arm. Grade 4 serum creatinine values were 0% in the 4 mg arm, 2.1% in the 8 mg arm, and 1% in the Pamidronate arm. The reported risk of adverse renal events is higher in cancer patients due to the disease itself along with associated comorbidities and possible nephrotoxic agents [87]. The Food and Drug Administration (FDA) Adverse Event Reporting System identified 72 cases of physician reported

renal failure between August 2001 and March 2003. Renal failure developed after an average of 56 days of zoledronic acid use with 25% receiving only one dose with renal failure occurring after 11 days of use [88]. Aside from similar efficacy of both 4 and 8 mg doses of zoledronic acid in hypercalcemia of malignancy and SREs, safety profile, especially renal, favors the 4 mg dose and thus is the standard dose used.

Osteonecrosis of the jaw (ONJ) has been consistently described as a rare but significant side effect associated with various bisphosphonates. This risk is present no matter what the bisphosphonate used or its mode of delivery.

Oral bisphosphonates tend to have a lower risk of ONJ likely because of their low potency compared to IV bisphosphonates plus the lower drug concentrations in the bones when compared to the IV forms. The major risk of ONJ remains in patients with malignancy treated with IV bisphosphonates ranging from 0.8% to 12% depending on the study reporting it. For example, in the AZURE trial, involving 3360 women with stage II and III breast cancer randomized to adjuvant treatment with or without zoledronic acid 4 mg IV for 19 doses over 5 years, the cumulative incidence of ONJ in the zoledronic group was 2.1% after a median follow-up of 73.9 months [89]. In a retrospective trial at MD Anderson Cancer Center, 29 ONJ cases out of 3965 charts reviewed of cancer patients on IV bisphosphonates were identified. There were 7 cases on pamidronate, 9 on zoledronic acid, and 13 on pamidronate followed by zoledronic acid. What was noted in this study is that ONJ tend to occur more in patients with longer median duration of malignant disease (5.75 yrs vs 3.11 yrs, $p = 0.0001$), longer median duration of bone metastasis (5.22 yrs vs 1.53 yrs, $p < 0.001$), higher median doses of bisphosphonates when compared to those without ONJ. Moreover, zoledronic acid treatment was more frequently observed in pts with ONJ compared to those without (42%:22 out of 29 patients versus 1684 of 3965, $p = 0.0004$) [90]. In a retrospective study looking at ONJ in prostate cancer patients with bone metastasis, ONJ occurred in around 12% of patients studied with higher risk in those with higher median number of zoledronic acid administration [17] as compared to those without ONJ (8, $p = 0.02$). In this trial, docetaxel was associated with a non-significant trend towards increased risk of ONJ with OR 3.8, $p = 0.24$ [91]. In the STAMPEDE trial, the incidence of ONJ was 2% in the standard of care plus zoledronic acid versus 4% when docetaxel was added to the same combination. This alludes to the possibility of an additive effect of chemotherapy on the risk of ONJ. Other risk factors for ONJ in cancer patients using bisphosphonates are poor dental hygiene, history of tooth extraction or use of dental appliance. In the denosumab versus zoledronic acid trial, 77% of ONJ patients on Denosumab and 83% of ONJ patients on zoledronic acid had any of the above-mentioned factors.

Several small post-marketing reports were describing possible cardiac side effects associated with zoledronic acid use, namely atrial fibrillation or other arrhythmias. However, prospective studies and reviews negated that [92–94]. Other reported side effects in small reports include acute tubular necrosis, severe polyarthritis, severe debilitating myalgias, ocular disease like uveitis, atypical subtrochanteric and diaphyseal

femoral fractures [95–100] and severe systemic inflammatory response syndrome [101].

12. Expert opinion

The use of zoledronic acid in prostate cancer has marked the cornerstone of treatment for delaying skeletal-related events. The advent of use of other bone-targeted agents such as denosumab, a RANK-ligand inhibitor, has also changed the treatment landscape and while denosumab has been shown to be non-inferior, and additionally superior in a phase III trial [24] compared to zoledronic acid, use of the two agents has been considered interchangeably in a lot of different guidelines. In addition, given lack of overall survival data or radiographic progression-free survival information, recommendations beyond offering bone protective agents with one or another agent cannot be unanimously made. While data for zoledronic acid is the strongest in the supportive treatment of metastatic prostate cancer, since the biggest morbidity from metastatic prostate cancer does arise from the bone involvement with effects such as pain and skeletal-related events, the major limitation remains to be the lack of overwhelming survival or PSA or radiographic benefits. Several, if not all, other androgen signaling targeted therapies do show some benefit in terms of skeletal-related events upon secondary analyses. Therefore, the benefit seen from the use of zoledronic acid may not be unique. The greatest potential and one of the most important goals in the field is therefore exploration of the use of zoledronic acid in the earlier phases of the disease, in the early metastatic castration-sensitive phase. Given early findings of possible inherent anti-tumor effects of zoledronic in the tumor microenvironment, the research question of whether combining it with docetaxel or just using it early in the phase of prostate cancer disease, would yield beneficial results. However, attempts to extend the potential benefits in combination with docetaxel in the early metastatic castration-sensitive setting in the STAMPEDE trial as well as the ALLIANCE trial did not yield the anticipated benefits, hence defining the use of bone-targeted agents still in the mCRPC setting solely for the prevention of skeletal-related events remains the standard of care. Perhaps capitalizing on zoledronic acid's known effects on the tumor-associated macrophages and the microenvironment, may pave the way for future investigation to overcome mechanisms of resistance. Given the concerns regarding the emergence of toxicity over long-term use, and the potential for long skeletal half-lives with the use of zoledronic acid, the possibility of administering the drug in a more protracted manner, without losing the benefits, have been underway. These constitute the potential limitations regarding the use of bone-targeted agents. The risk for osteonecrosis of the jaw is not miniscule. In addition, hypocalcemia and other metabolic effects, renal dysfunction and infusion side-effects are all potential concerns. On the other hand, since zoledronic acid is already available generically, cost containment makes it an equivalent and attractive option compared to denosumab. It is, however, uncertain whether zoledronic acid will further expand the field of prostate cancer therapy beyond what it is already being studied now due to the lack of convincing evidence of survival which remains the gold standard in evaluating the benefit of key drugs that are out in the market. Similarly, given the seminal results of STAMPEDE that has treatment arms that

combined docetaxel and zoledronic acid, no additional benefit was seemingly gained with zoledronic acid in this setting beyond which is seen with docetaxel alone. These results are likely to dampen any further enthusiasm about further combination therapies with the use of zoledronic acid. In summary, zoledronic acid has maintained its integral role in the management of mCRPC patients but mainly with the goal of delaying skeletal-related events but not overall survival or other disease-oriented parameters like PSA progression or radiographic progression improvements. It remains an important adjunctive treatment strategy in the care of metastatic CRPC patients.

Funding

This manuscript has not been funded.

Declaration of interest

JB Aragon-Ching has served on the advisory boards of Janssen Pharmaceuticals, Astellas, Dendreon and Bayer Healthcare and has served on the speaker's bureau of Bristol-Myers Squibb. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Referee disclosures

Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

ORCID

Jeanny B. Aragon-Ching  <http://orcid.org/0000-0002-6714-141X>

References

Papers of special note have been highlighted as either of interest (*) or of considerable interest (***) to readers.

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. *CA Cancer J Clin.* 2018;68(1):7–30.
2. Coleman RE. Skeletal complications of malignancy. *Cancer.* 1997;80(8 Suppl):1588–1594.
3. Jacobs SC. Spread of prostatic cancer to bone. *Urology.* 1983;21(4):337–344.
4. Berruti A, Dogliotti L, Bitossi R, et al. Incidence of skeletal complications in patients with bone metastatic prostate cancer and hormone refractory disease: predictive role of bone resorption and formation markers evaluated at baseline. *J Urol.* 2000;164(4):1248–1253.
5. Berruti A, Dogliotti L, Tucci M, et al. Metabolic bone disease induced by prostate cancer: rationale for the use of bisphosphonates. *J Urol.* 2001;166(6):2023–2031.
6. Dunstan CR, Boyce R, Boyce BF, et al. Systemic administration of acidic fibroblast growth factor (FGF-1) prevents bone loss and increases new bone formation in ovariectomized rats. *J Bone Miner Res.* 1999;14(6):953–959.
7. Izbicka E, Dunstan C, Esparza J, et al. Human amniotic tumor that induces new bone formation in vivo produces growth-regulatory activity in vitro for osteoblasts identified as an extended form of basic fibroblast growth factor. *Cancer Res.* 1996;56(3):633–636.
8. Nelson JB, Hedican SP, George DJ, et al. Identification of endothelin-1 in the pathophysiology of metastatic adenocarcinoma of the prostate. *Nat Med.* 1995;1(9):944–949.

9. Clarke NW, McClure J, George NJ. Morphometric evidence for bone resorption and replacement in prostate cancer. *Br J Urol.* 1991;68(1):74–80.
10. Hortobagyi GN, Theriault RL, Porter L, et al. Efficacy of pamidronate in reducing skeletal complications in patients with breast cancer and lytic bone metastases. Protocol 19 aredia breast cancer study group. *N Engl J Med.* 1996;335(24):1785–1791.
 - **One of the earlier studies that showed use of bisphosphonate is an important treatment for cancer patients**
11. Hortobagyi GN, Theriault RL, Lipton A, et al. Long-term prevention of skeletal complications of metastatic breast cancer with pamidronate. Protocol 19 aredia breast cancer study group. *J Clin Oncol.* 1998;16(6):2038–2044.
12. Theriault RL, Lipton A, Hortobagyi GN, et al. Pamidronate reduces skeletal morbidity in women with advanced breast cancer and lytic bone lesions: a randomized, placebo-controlled trial. Protocol 18 Aredia Breast Cancer Study Group. *J Clin Oncol.* 1999;17(3):846–854.
13. Lipton A, Theriault RL, Hortobagyi GN, et al. Pamidronate prevents skeletal complications and is effective palliative treatment in women with breast carcinoma and osteolytic bone metastases: long term follow-up of two randomized, placebo-controlled trials. *Cancer.* 2000;88(5):1082–1090.
14. Clarke NW, Holbrook IB, McClure J, et al. Osteoclast inhibition by pamidronate in metastatic prostate cancer: a preliminary study. *Br J Cancer.* 1991;63(3):420–423.
15. Carey PO, Lippert MC. Treatment of painful prostatic bone metastases with oral etidronate disodium. *Urology.* 1988;32(5):403–407.
16. Kylmala T, Tammela TL, Lindholm TS, et al. The effect of combined intravenous and oral clodronate treatment on bone pain in patients with metastatic prostate cancer. *Ann Chir Gynaecol.* 1994;83(4):316–319.
17. Adami S. Bisphosphonates in prostate carcinoma. *Cancer.* 1997;80(8 Suppl):1674–1679.
18. Pelger RC, Hamdy NA, Zwinderman AH, Lycklama a Nijeholt AA, Papapoulos SE. Effects of the bisphosphonate olpadronate in patients with carcinoma of the prostate metastatic to the skeleton. *Bone.* 1998;22(4):403–408.
19. Smith JA Jr. Palliation of painful bone metastases from prostate cancer using sodium etidronate: results of a randomized, prospective, double-blind, placebo-controlled study. *J Urol.* 1989;141(1):85–87.
20. Strang P, Nilsson S, Brandstedt S, et al. The analgesic efficacy of clodronate compared with placebo in patients with painful bone metastases from prostatic cancer. *Anticancer Res.* 1997;17(6D):4717–4721.
21. Adami S, Salvagno G, Guarrera G, et al. Dichloromethylene-diphosphonate in patients with prostatic carcinoma metastatic to the skeleton. *J Urol.* 1985;134(6):1152–1154.
22. Facchini G, Caraglia M, Morabito A, et al. Metronomic administration of zoledronic acid and taxotere combination in castration resistant prostate cancer patients: phase I ZANTE trial. *Cancer Biol Ther.* 2010;10(6):543–548.
23. Ibrahim A, Scher N, Williams G, et al. Approval summary for zoledronic acid for treatment of multiple myeloma and cancer bone metastases. *Clin Cancer Res.* 2003;9(7):2394–2399.
 - **Seminal review on the use of zoledronic acid for cancers**
24. 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(9768):813–822.
 - **Key trial that compared denosumab to zoledronic acid in men with metastatic castration-resistant prostate cancer**
25. Green JR, Rogers MJ. Pharmacologic profile of zoledronic acid: a highly potent inhibitor of bone resorption. *Drug Dev Res.* 2002;55(4):210–224.
 - **Key review on pharmacology of zoledronic acid.**
26. Liberman UA, Weiss SR, Broll J, et al. Effect of oral alendronate on bone mineral density and the incidence of fractures in postmenopausal osteoporosis. The alendronate phase III osteoporosis treatment study group. *N Engl J Med.* 1995;333(22):1437–1443.
27. Berenson JR, Lichtenstein A, Porter L, et al. Efficacy of pamidronate in reducing skeletal events in patients with advanced multiple myeloma. Myeloma Aredia Study Group. *N Engl J Med.* 1996;334(8):488–493.
28. Berenson JR, Lichtenstein A, Porter L, et al. Long-term pamidronate treatment of advanced multiple myeloma patients reduces skeletal events. Myeloma Aredia Study Group. *J Clin Oncol.* 1998;16(2):593–602.
29. Conte PF, Latreille J, Mauriac L, et al. Delay in progression of bone metastases in breast cancer patients treated with intravenous pamidronate: results from a multinational randomized controlled trial. The aredia multinational cooperative group. *J Clin Oncol.* 1996;14(9):2552–2559.
30. Body JJ. Clinical research update: zoledronate. *Cancer.* 1997;80(8 Suppl):1699–1701.
31. Bergstrom JD, Bostedor RG, Masarachia PJ, et al. Alendronate is a specific, nanomolar inhibitor of farnesyl diphosphate synthase. *Arch Biochem Biophys.* 2000;373(1):231–241.
32. Coxon FP, Helfrich MH, Van't Hof R, et al. Protein geranylgeranylation is required for osteoclast formation, function, and survival: inhibition by bisphosphonates and GGTI-298. *J Bone Miner Res.* 2000;15(8):1467–1476.
33. Novartis. Zometa. FDA. 2014. Available from: <https://www.pharma.us.novartis.com/sites/www.pharma.us.novartis.com/files/Zometa.pdf>
34. Jung A, Bisaz S, Fleisch H. The binding of pyrophosphate and two diphosphonates by hydroxyapatite crystals. *Calcif Tissue Int.* 1973;11(4):269–280.
35. Schenk R, Egli P, Fleisch H, et al. Quantitative morphometric evaluation of the inhibitory activity of new aminobisphosphonates on bone resorption in the rat. *Calcif Tissue Int.* 1986;38(6):342–349.
36. Shinoda H, Adamek G, Felix R, et al. Structure-activity relationships of various bisphosphonates. *Calcif Tissue Int.* 1983;35(1):87–99.
37. Sietsema WK, Ebetino FH, Salvagno AM, et al. Antiresorptive dose-response relationships across three generations of bisphosphonates. *Drugs Exp Clin Res.* 1989;15(9):389–396.
38. van Beek ER, Lowik CW, Ebetino FH, et al. Binding and antiresorptive properties of heterocycle-containing bisphosphonate analogs: structure-activity relationships. *Bone.* 1998;23(5):437–442.
39. Green JR, Muller K, Jaeggi KA. Preclinical pharmacology of CGP 42'446, a new, potent, heterocyclic bisphosphonate compound. *J Bone Miner Res.* 1994;9(5):745–751.
40. Pataki A, Muller K, Green JR, et al. Effects of short-term treatment with the bisphosphonates zoledronate and pamidronate on rat bone: a comparative histomorphometric study on the cancellous bone formed before, during, and after treatment. *Anat Rec.* 1997;249(4):458–468.
41. Evans CE, Braidman IP. Effects of two novel bisphosphonates on bone cells in vitro. *Bone Miner.* 1994;26(2):95–107.
42. Berenson JR, Vescio RA, Rosen LS, et al. A phase I dose-ranging trial of monthly infusions of zoledronic acid for the treatment of osteolytic bone metastases. *Clin Cancer Res.* 2001;7(3):478–485.
 - **Phase I trial of zoledronic acid in the treatment of bone metastases**
43. Berenson JR, Vescio R, Henick K, et al. A Phase I, open label, dose ranging trial of intravenous bolus zoledronic acid, a novel bisphosphonate, in cancer patients with metastatic bone disease. *Cancer.* 2001;91(1):144–154.
44. Berenson JR, Rosen LS, Howell A, et al. Zoledronic acid reduces skeletal-related events in patients with osteolytic metastases. *Cancer.* 2001;91(7):1191–1200.
45. Chen T, Berenson J, Vescio R, et al. Pharmacokinetics and pharmacodynamics of zoledronic acid in cancer patients with bone metastases. *J Clin Pharmacol.* 2002;42(11):1228–1236.
46. Lin JH. Bisphosphonates: a review of their pharmacokinetic properties. *Bone.* 1996;18(2):75–85.
47. Green JR, Seltenmeyer Y, Jaeggi KA, et al. Renal tolerability profile of novel, potent bisphosphonates in two short-term rat models. *Toxicol Pharmacol.* 1997;80(5):225–230.
48. Weiss HM, Pfaar U, Schweitzer A, et al. Biodistribution and plasma protein binding of zoledronic acid. *Drug Metab Dispos.* 2008;36(10):2043–2049.

49. Ruza I, Mirfakhraee S, Orwoll E, et al. Clinical experience with intravenous zoledronic acid in the treatment of male osteoporosis: evidence and opinions. *Ther Adv Musculoskelet Dis*. 2013;5(4):182–198.
50. Body JJ, Lortholary A, Romieu G, et al. A dose-finding study of zoledronate in hypercalcemic cancer patients. *J Bone Miner Res*. 1999;14(9):1557–1561.
51. Townsend MF, Sanders WH, Northway RO, et al. Bone fractures associated with luteinizing hormone-releasing hormone agonists used in the treatment of prostate carcinoma. *Cancer*. 1997;79(3):545–550.
52. Collinson MP, Tyrrel CJ, Hutton C. Osteoporosis occurring in two patients receiving LHRH analogs for carcinoma of the prostate. *Calcif Tissue Int*. 1994;54(4):327–328.
53. Daniell HW. Osteoporosis after orchiectomy for prostate cancer. *J Urol*. 1997;157(2):439–444.
54. Clarke NW, McClure J, George NJ. The effects of orchidectomy on skeletal metabolism in metastatic prostate cancer. *Scand J Urol Nephrol*. 1993;27(4):475–483.
55. Scher HI, Chung LW. Bone metastases: improving the therapeutic index. *Semin Oncol*. 1994;21(5):630–656.
56. Garnero P, Buchs N, Zekri J, et al. Markers of bone turnover for the management of patients with bone metastases from prostate cancer. *Br J Cancer*. 2000;82(4):858–864.
57. Saad F, Gleason DM, Murray R, et al. A randomized, placebo-controlled trial of zoledronic acid in patients with hormone-refractory metastatic prostate carcinoma. *J Natl Cancer Inst*. 2002;94(19):1458–1468.
- **Seminal trial on use of zoledronic acid in men with metastatic castration-resistant prostate cancer that formed the basis of the initial FDA approval for its use**
58. Saad F, Gleason DM, Murray R, et al. Long-term efficacy of zoledronic acid for the prevention of skeletal complications in patients with metastatic hormone-refractory prostate cancer. *J Natl Cancer Inst*. 2004;96(11):879–882.
- **Long term data on the comparison trial of zoledronic acid versus placebo**
59. James ND, Pirrie SJ, Pope AM, et al. Clinical outcomes and survival following treatment of metastatic castrate-refractory prostate cancer with docetaxel alone or with strontium-89, zoledronic acid, or both: the TRAPEZE randomized clinical trial. *JAMA Oncol*. 2016;2(4):493–499.
- **Key trial examining the utility of zoledronic in combination with other agents**
60. Eriksson S, Eriksson A, Stege R, et al. Bone mineral density in patients with prostatic cancer treated with orchidectomy and with estrogens. *Calcif Tissue Int*. 1995;57(2):97–99.
61. Maillefert JF, Sibilia J, Michel F, et al. Bone mineral density in men treated with synthetic gonadotropin-releasing hormone agonists for prostatic carcinoma. *J Urol*. 1999;161(4):1219–1222.
62. Morote J, Morin JP, Orsola A, et al. Prevalence of osteoporosis during long-term androgen deprivation therapy in patients with prostate cancer. *Urology*. 2007;69(3):500–504.
63. Smith MR, Eastham J, Gleason DM, et al. Randomized controlled trial of zoledronic acid to prevent bone loss in men receiving androgen deprivation therapy for nonmetastatic prostate cancer. *J Urol*. 2003;169(6):2008–2012.
- **Important trial analyzing the utility of zoledronic acid to preserve bone mineral density.**
64. Kachnic LA, Pugh SL, Tai P, et al. RTOG 0518: randomized phase III trial to evaluate zoledronic acid for prevention of osteoporosis and associated fractures in prostate cancer patients. *Prostate Cancer Prostatic Dis*. 2013;16(4):382–386.
65. Ding H, Yang L, Du W, et al. Bisphosphonates for osteoporosis in nonmetastatic prostate cancer patients receiving androgen-deprivation therapy: a systematic review and meta-analysis. *Asian Pac J Cancer Prev*. 2013;14(5):3337–3343.
66. Michaelson MD, Kaufman DS, Lee H, et al. Randomized controlled trial of annual zoledronic acid to prevent gonadotropin-releasing hormone agonist-induced bone loss in men with prostate cancer. *J Clin Oncol*. 2007;25(9):1038–1042.
67. Nada MH, Wang H, Workalemahu G, et al. Enhancing adoptive cancer immunotherapy with Vgamma2Vdelta2 T cells through pulse zoledronate stimulation. *J Immunother Cancer*. 2017;5:9.
68. Wood J, Bonjean K, Ruetz S, et al. Novel antiangiogenic effects of the bisphosphonate compound zoledronic acid. *J Pharmacol Exp Ther*. 2002;302(3):1055–1061.
69. Fragni M, Bonini SA, Stabile A, et al. Inhibition of survivin is associated with zoledronic acid-induced apoptosis of prostate cancer cells. *Anticancer Res*. 2016;36(3):913–920.
70. Carlin BI, Andriole GL. The natural history, skeletal complications, and management of bone metastases in patients with prostate carcinoma. *Cancer*. 2000;88(12 Suppl):2989–2994.
71. Smith MR, Halabi S, Ryan CJ, et al. Randomized controlled trial of early zoledronic acid in men with castration-sensitive prostate cancer and bone metastases: results of CALGB 90202 (alliance). *J Clin Oncol*. 2014;32(11):1143–1150.
- **Seminal trial analyzing the utility of zoledronic acid in men with castration-sensitive metastatic disease**
72. Wirth M, Tammela T, Cicalese V, et al. Prevention of bone metastases in patients with high-risk nonmetastatic prostate cancer treated with zoledronic acid: efficacy and safety results of the Zometa European Study (ZEUS). *Eur Urol*. 2015;67(3):482–491.
73. Denham JW, Joseph D, Lamb DS, et al. Short-term androgen suppression and radiotherapy versus intermediate-term androgen suppression and radiotherapy, with or without zoledronic acid, in men with locally advanced prostate cancer (TROG 03.04 RADAR): an open-label, randomised, phase 3 factorial trial. *Lancet Oncol*. 2014;15(10):1076–1089.
74. Petrylak DP, Tangen CM, Hussain MH, et al. Docetaxel and estramustine compared with mitoxantrone and prednisone for advanced refractory prostate cancer. *N Engl J Med*. 2004;351(15):1513–1520.
75. Tannock IF, de Wit R, Berry WR, et al. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. *N Engl J Med*. 2004;351(15):1502–1512.
76. de Bono JS, Logothetis CJ, Molina A, et al. Abiraterone and increased survival in metastatic prostate cancer. *N Engl J Med*. 2011;364(21):1995–2005.
77. Scher HI, Fizazi K, Saad F, et al. Increased survival with enzalutamide in prostate cancer after chemotherapy. *N Engl J Med*. 2012;367(13):1187–1197.
78. Beer TM, Armstrong AJ, Rathkopf DE, et al. Enzalutamide in metastatic prostate cancer before chemotherapy. *N Engl J Med*. 2014;371(5):424–433.
79. de Bono JS, Oudard S, Ozguroglu M, et al. Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: a randomised open-label trial. *Lancet*. 2010;376(9747):1147–1154.
80. Parker C, Nilsson S, Heinrich D, et al. Alpha emitter radium-223 and survival in metastatic prostate cancer. *N Engl J Med*. 2013;369(3):213–223.
81. Kantoff PW, Higano CS, Shore ND, et al. Sipuleucel-T immunotherapy for castration-resistant prostate cancer. *N Engl J Med*. 2010;363(5):411–422.
82. Sweeney CJ, Chen YH, Carducci M, et al. Chemohormonal Therapy in metastatic hormone-sensitive prostate cancer. *N Engl J Med*. 2015;373(8):737–746.
83. Gravis G, Fizazi K, Joly F, et al. Androgen-deprivation therapy alone or with docetaxel in non-castrate metastatic prostate cancer (GETUG-AFU 15): a randomised, open-label, phase 3 trial. *Lancet Oncol*. 2013;14(2):149–158.
84. James ND, Sydes MR, Clarke NW, et al. Addition of docetaxel, zoledronic acid, or both to first-line long-term hormone therapy in prostate cancer (STAMPEDE): survival results from an adaptive, multiarm, multistage, platform randomised controlled trial. *Lancet*. 2016;387(10024):1163–1177.
- **Important trial examining utility of docetaxel and zoledronic acid in combination**
85. Vale CL, Burdett S, Ryzdzewska LHM, et al. Addition of docetaxel or bisphosphonates to standard of care in men with localised or metastatic, hormone-sensitive prostate cancer: a systematic review and meta-analyses of aggregate data. *Lancet Oncol*. 2016;17(2):243–256.

86. 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. *J Clin Oncol*. 2001;19(2):558–567.
87. Lewiecki EM, Miller PD. Renal safety of intravenous bisphosphonates in the treatment of osteoporosis. *Expert Opin Drug Saf*. 2007;6(6):663–672.
88. Chang JT, Green L, Beitz J. Renal failure with the use of zoledronic acid. *N Engl J Med*. 2003;349(17):1676–1679. discussion –9.
89. Coleman R, Woodward E, Brown J, et al. Safety of zoledronic acid and incidence of osteonecrosis of the jaw (ONJ) during adjuvant therapy in a randomised phase III trial (AZURE: BIG 01-04) for women with stage II/III breast cancer. *Breast Cancer Res Treat*. 2011;127(2):429–438.
90. Hoff AO, Toth BB, Altundag K, et al. Frequency and risk factors associated with osteonecrosis of the jaw in cancer patients treated with intravenous bisphosphonates. *J Bone Miner Res*. 2008;23(6):826–836.
91. Ortega C, Montemurro F, Faggiuolo R, et al. Osteonecrosis of the jaw in prostate cancer patients with bone metastases treated with zoledronate: a retrospective analysis. *Acta Oncol*. 2007;46(5):664–668.
92. Cipriani C, Castro C, Curione M, et al. Acute effect of zoledronic acid on the risk of cardiac dysrhythmias. *Intern Emerg Med*. 2015;10(2):151–156.
93. Demirtas D, Bilir C, Demirtas AO, et al. The effects of zoledronic acid on ECG: a prospective study on patients with bone metastatic cancer. *Clin Cases Miner Bone Metab*. 2017;14(1):35–39.
94. John Camm A. Review of the cardiovascular safety of zoledronic acid and other bisphosphonates for the treatment of osteoporosis. *Clin Ther*. 2010;32(3):426–436.
95. Markowitz GS, Fine PL, Stack JI, et al. Toxic acute tubular necrosis following treatment with zoledronate (Zometa). *Kidney Int*. 2003;64(1):281–289.
96. White SL, Jacob A, Gregson C, et al. Severe polyarthritis secondary to zoledronic acid: a case report and literature review. *Clin Cases Miner Bone Metab*. 2015;12(1):69–74.
97. Kennedy T, Sellar PW, Vaideanu-Collins D, et al. Two case reports of zoledronic acid-induced uveitis. *Age Ageing*. 2018;47(5):754–755.
98. Colucci A, Modorati G, Miserocchi E, et al. Anterior uveitis complicating zoledronic acid infusion. *Ocul Immunol Inflamm*. 2009;17(4):267–268.
99. Sharma NS, Ooi JL, Masselos K, et al. Zoledronic acid infusion and orbital inflammatory disease. *N Engl J Med*. 2008;359(13):1410–1411.
100. Shane E, Burr D, Abrahamsen B, et al. Atypical subtrochanteric and diaphyseal femoral fractures: second report of a task force of the American Society for Bone And Mineral Research. *J Bone Miner Res*. 2014;29(1):1–23.
101. Thangavelu T, Johnson-Rabbett B, Magar RR, et al. Severe systemic inflammatory response syndrome with multi-organ failure following zoledronic acid infusion. *AACE Clin Case Rep*. 2018;4(1):e26–e9.