Long term zoledronic acid during androgen blockade for prostate cancer

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Objectives: *To evaluate the effect of zoledronic acid on androgen deprivation therapy in patients with hormone-sensitive prostate cancer by measuring the percentage change in lumbar-spine bone mineral density (BMD) at 12 and 24 months.*

Materials and methods: *An open-label, multicenter, randomized, two-phase study was conducted in patients with hormone-sensitive prostate cancer (N = 200) receiving 10.8 mg goserelin acetate with or without zoledronic acid (4 mg intravenously) every 3 months. In phase I, patients were randomized to goserelin acetate alone or goserelin acetate plus zoledronic acid for 12 months. In phase II, patients receiving goserelin acetate plus zoledronic acid continued treatment for up to a total of 24 months, whereas patients receiving goserelin acetate alone were randomized to goserelin acetate alone or goserelin acetate plus zoledronic acid for an additional 12 months. Lumbar-spine, femoral-neck, and total-hip BMD were assessed at 6, 12, and 24 months. Additional assessments included height change, laboratory studies, bone scans, radiographs, and computed tomography scans.*

Results: *Significant BMD differences between patients receiving goserelin acetate alone and goserelin acetate plus zoledronic acid were observed at the 12-month ($p \leq .01$ for each site) and 24-month ($p < .05$ for each site) assessments. Initiating zoledronic acid after 12 months of goserelin acetate alone provided BMD benefits but was insufficient to completely restore BMD. Combining goserelin acetate and zoledronic acid was generally well tolerated.*

Conclusions: *Two years of zoledronic acid is well tolerated and can prevent bone loss in patients with prostate cancer undergoing androgen deprivation therapy.*

Key Words: bone density, bone density conservation agents, clinical trial, gonadotropin-releasing hormone, goserelin, prostate cancer, zoledronic acid

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Introduction

Prostate cancer accounts for approximately 20% to 25% of all cancer diagnoses and is the most commonly diagnosed cancer in men.[1] Moreover, prostate cancer accounts for approximately 10% of all cancer-related deaths in European men. Early stage prostate cancer typically responds to hormone-based therapies; therefore, patients commonly receive androgen deprivation therapy (ADT) by orchiectomy or luteinizing hormone-releasing hormone analogues as standard first-line therapy.[2] Goserelin acetate, a commonly used luteinizing hormone-releasing hormone analogue, effectively inhibits testosterone and estrogen production by more than 95% and more than 80%, respectively, compared with untreated patients.[2] Goserelin acetate alone and combined with radiation therapy can inhibit disease progression, reduce disease recurrence, improve survival, and reduce tumor burden.[3-5] Side effects commonly

associated with ADT include but are not limited to general pain, hot flashes, and sexual dysfunction.[6,7] In addition, because testosterone and estrogen play key roles in maintaining normal bone metabolism,[2] ADT can also result in bone loss.[2,7]

The annual bone loss rate in men receiving ADT is 4.6%, which is more than nine times greater than that reported in normal men.[2] This bone loss can be apparent within 6 months of treatment initiation[8] and can increase fracture risk.[2] Indeed, a large database study of patients diagnosed with prostate cancer (N = 50,613) revealed that after 5 years fracture rates were significantly higher for patients receiving ADT compared with no ADT (19.4% versus 12.6%, respectively; $p < .001$).[9] Similarly, a medical claims database study of patients with nonmetastatic prostate cancer (n = 11,661) revealed that gonadotropin-releasing hormone agonist therapy significantly increased the risk of fracture ($p < .001$), and this risk increased with longer duration of treatment.[10] Furthermore, fractures have been associated with significantly shortened overall survival in patients receiving ADT ($p = .04$).[11] Therefore, preserving bone health should be a treatment consideration to prevent ADT-induced bone loss and to reduce the risk of potentially life-limiting fractures.

Bisphosphonates have demonstrated efficacy in preventing ADT-induced bone loss in patients with prostate cancer.[12,13] For example, in a multicenter, double-blind, randomized, placebo-controlled trial in patients with hormone-sensitive prostate cancer receiving ADT (N = 106), zoledronic acid (4 mg via 15-minute intravenous infusion every 3 months) increased bone mineral density (BMD) in the lumbar spine, femoral neck, trochanter, and total hip compared with patients receiving ADT alone for 12 months ($p < .001$).[13] These findings provide the rationale to assess the long term efficacy and safety of zoledronic acid for the prevention of ADT-induced bone loss.

Patients and methods

Patients

Hormone-therapy–naive men with locally advanced prostate cancer initiating goserelin acetate were recruited between June 2003 and June 2004. Adult patients (≥ 18 years of age) were required to have histologically or cytologically confirmed diagnosis of locally advanced, lymph node-positive, or recurrent prostate cancer with no metastases. Absence of bone metastases was verified by negative bone scan (or additional radiographic measures to exclude bone metastases if the bone scan was positive). Eligible patients were scheduled to receive goserelin acetate for at least 1 year, with the first scheduled study drug treatment within 30 days of goserelin acetate initiation. The protocol and amendments were reviewed by Trafalgar Ethics Board, Inc. (Oakville, Ontario, Canada), and the study was conducted in accordance with Canada's Good Clinical Practice–Consolidated Guidelines. Written informed consent was provided by all patients enrolled.

Exclusion criteria included presence of bone or visceral metastases; prior ADT, calcitriol, or bisphosphonate treatment; thyroxine treatment in the previous year; concomitant or prior long term systemic glucocorticoid therapy; diagnosis of Paget's disease, hyperthyroidism, Cushing's disease, hyperprolactinemia, chronic liver disease, or chronic renal insufficiency (serum creatinine > 2.0 mg/dL). Patients with known hypersensitivity to luteinizing hormone-releasing hormone, luteinizing hormone-releasing hormone agonists or analogues, or any component of goserelin acetate or zoledronic acid were not included in this study. Per investigators' discretion, patients who had concomitant conditions that could undermine safety or compliance were excluded.

Study design

This was an open-label, randomized, controlled, multicenter, two-phase study of patients from 25 sites across Canada. In phase I, patients were randomized 1:1 (based on a central randomization scheme) to receive goserelin acetate (10.8 mg) alone or goserelin acetate plus zoledronic acid (4 mg via 15-minute intravenous infusion) every 3 months for 12 months. The protocol was subsequently amended to lengthen the treatment duration for an additional 12 months, and phase II was initiated at 18 sites across Canada. In phase II, patients treated with goserelin acetate plus zoledronic acid were given the opportunity to continue treatment every 3 months for an additional 12 months (for a total of 24 months), and were classified as the "upfront zoledronic acid" group. Patients treated with goserelin acetate alone who chose to continue the study were randomized to receive goserelin acetate alone or goserelin acetate plus zoledronic acid every 3 months for the next 12 months. Patients who received goserelin acetate alone for 12 months then goserelin acetate plus zoledronic acid for the following 12 months were classified as the "delayed-zoledronic acid" group. All patients received a minimum of 400 International Units of vitamin D and 500-mg calcium supplements daily for the entire length of the study.

Study endpoints

The primary endpoint was percentage change from baseline in lumbar spine BMD at 12 and 24 months. Secondary endpoints included percentage changes from baseline in BMD at femoral neck and total hip, height change from baseline, and safety.

Safety was assessed throughout the study by continuous adverse event (AE) monitoring, physical examinations, vital signs, and laboratory evaluations.

Assessments

Efficacy evaluations were performed at baseline and at 12 and 24 months. Serial BMD was assessed by dual-energy x-ray absorptiometry; standing height was measured using commonly available measurement scales; blood samples were analyzed at each site's local laboratory; and bone or visceral metastases were diagnosed via bone, x-ray, or computed tomography scans.

Statistical analysis

Baseline BMD at lumbar spine, femoral neck, and total hip was analyzed by unpaired t-tests. Posttreatment BMD was analyzed by region and treatment group using analysis of covariance with baseline BMD as the covariate.

All BMD measurements from the two types of dual-energy x-ray absorptiometry bone mineral densitometers (ie, Hologic and Lunar) were standardized to Lunar equivalents.[14,15]

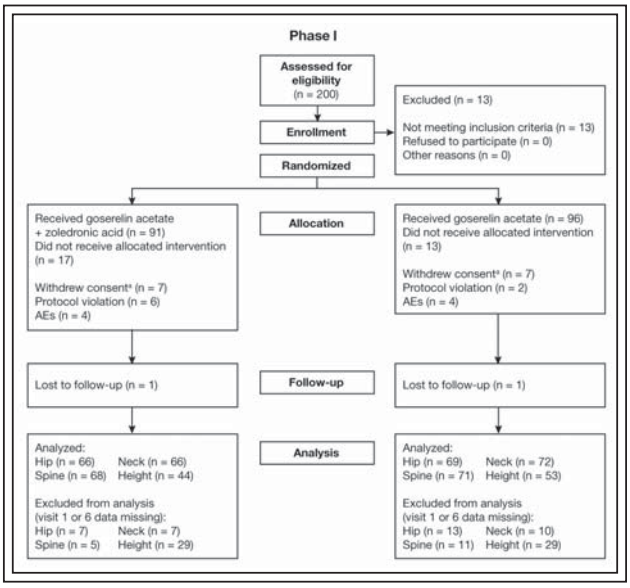

Figure 1. Phase I-Trial patient disposition at 12 months. CONSORT diagram of phase I of the trial. One hundred fifty-five patients completed the 12-month study.
ADT = androgen deprivation therapy;
AE = adverse event.
[a]Patients withdrew consent to seek alternative therapy or research studies, they were not indicated for ADT for 1 year, or they wished to discontinue ADT to resume sexual activity.

Determination of sample size

A previous 1-year study of pamidronate in patients receiving the gonadotropin-releasing hormone agonist leuprolide for treatment of advanced or recurrent prostate cancer was used to assess necessary sample size.[12]

Results revealed a group marginal means difference of 3.0% between patients who received leuprolide alone versus leuprolide plus pamidronate. The standard deviation obtained in this study was estimated to be 1% to 2%. The mean matrix was used to generate power estimates based on varying combinations of standard deviations (1, 2, 3, 5, 10) and correlation coefficients (0.2, 0.5, 0.7) between the two time points.

A sample size of 100 patients per group yielded a power estimate above 99% for detection of a significant treatment effect and time for all scenarios involving standard deviations up to 5%.

Results

Efficacy of zoledronic acid in patients receiving goserelin acetate for prostate cancer

Phase I

In phase I of the study, 200 patients were screened; 187 patients who met the inclusion criteria were randomized to receive goserelin acetate alone (n = 96) or goserelin acetate plus zoledronic acid (n = 91), Figure 1. Patient demographics and baseline BMD assessments were similar between groups, Table 1.

At the 12-month assessment, BMD decreased from baseline in patients who received goserelin acetate alone by 1.5% (n = 71), 1.7% (n = 72), and 2.0% (n = 69) at lumbar spine, femoral neck, and total hip, respectively. In contrast, BMD increased from baseline in patients treated with goserelin acetate plus zoledronic acid by 3.3% (n = 68), 1.8% (n = 66), and 0.9% (n = 66) at lumbar spine, femoral neck, and total hip, respectively, Figure 2. Differences in BMD between the two patient groups were significant at 12 months ($p \leq .01$ for each site). There was no significant difference in height change between groups.

TABLE 1. **Demographics and baseline BMD assessments: phase I**

	Goserelin acetate alone	Goserelin acetate + zoledronic acid
Screened, n	100	100
Randomized, n	96	91
Completed 12-month study, n	82	73
Mean age, years (range)	75 (56-93)	74 (57-86)
Mean height, cm	172	171
Mean baseline BMD ± SEM,[a] g/cm^2		
Lumbar spine	1.27 ± 0.03	1.26 ± 0.03
Total hip	1.03 ± 0.02	1.02 ± 0.02
Femoral neck	0.91 ± 0.02	0.92 ± 0.02

BMD = bone mineral density; SEM = standard error of the mean.
[a]Not all patients had baseline assessments at each site; lumbar spine: goserelin acetate alone n = 71, goserelin acetate + zoledronic acid n = 68; total hip: goserelin acetate alone n = 69, goserelin acetate + zoledronic acid n = 66; femoral neck: goserelin acetate alone n = 72, goserelin acetate + zoledronic acid n = 66

Phase II

Of 153 patients eligible for phase II of the study, 62 declined enrollment. Of the 91 patients who enrolled in phase II, 76 completed the 24-month trial, and 73 were evaluable for BMD, Figure 3. Patients who declined to participate in phase II of the trial either participated in another study, were not indicated to receive goserelin acetate beyond 1 year, or wished to discontinue goserelin acetate. Patient baseline BMD assessments for phase II of the trial, measured at the initiation of phase I, were similar between the three groups, Table 2.

At the 24-month assessment, BMD decreased from baseline in patients who received goserelin acetate alone by 2.5% (n = 14), 2.3% (n = 14), and 3.0% (n = 14) at lumbar spine, femoral neck, and total hip, respectively. In contrast, BMD increased from baseline in patients treated with goserelin acetate plus upfront zoledronic acid by 2.8% (n = 47), 1.1% (n = 48), and 0.2% (n = 48) at lumbar spine, femoral neck, and total hip, respectively,

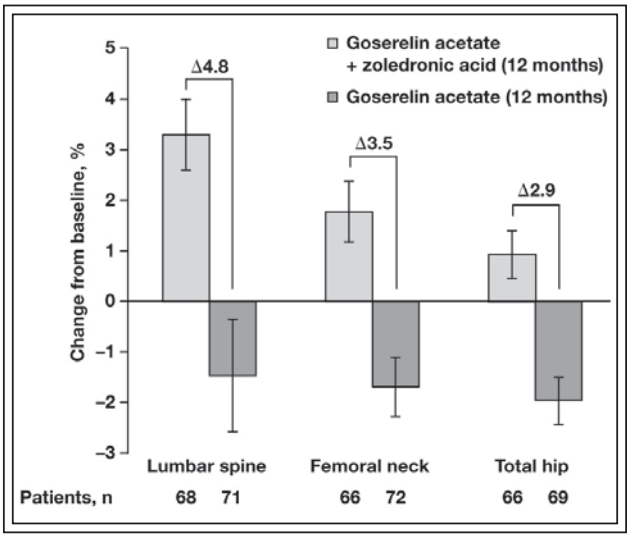

Figure 2. Phase I-Mean percentage changes in bone mineral density from baseline after 12 months of treatment. The bone mineral density differences between groups are represented by Δs. Error bars represent standard error of the mean.

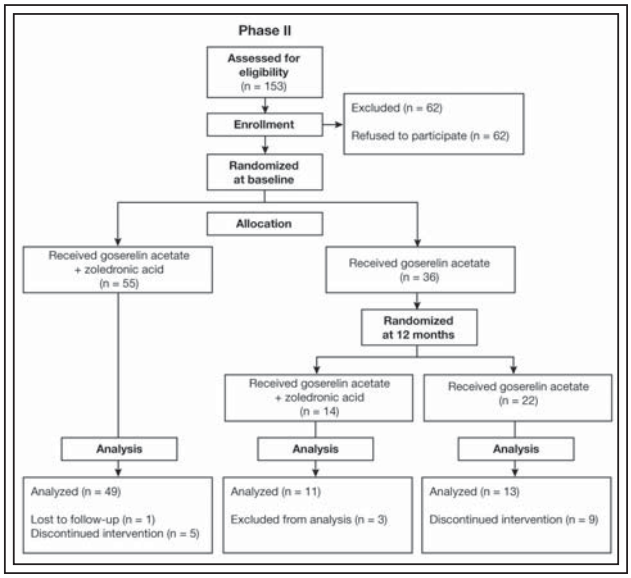

Figure 3. Phase II-Trial patient disposition at 24 months. CONSORT diagram of phase II of the trial.

TABLE 2. **Baseline BMD assessments: phase II**

	Goserelin acetate alone		Goserelin acetate + zoledronic acid
	Goserelin acetate alone (n = 22)	**Goserelin acetate + zoledronic acid (n = 14)**	**Goserelin acetate + zoledronic acid (n = 55)**
Mean baseline BMD ± SEM, g/cm^2			
Lumbar spine	1.26 ± 0.03	1.25 ± 0.03	1.25 ± 0.03
Total hip	1.02 ± 0.03	1.02 ± 0.03	1.02 ± 0.02
Femoral neck	0.92 ± 0.02	0.93 ± 0.02	0.92 ± 0.03

BMD = bone mineral density; SEM = standard error of the mean

Figure 4. Although the results were not significant for an increase in BMD, these results demonstrated preservation of bone.

In patients who received goserelin acetate alone for 12 months then goserelin acetate plus zoledronic acid for an additional 12 months (ie, the delayed-zoledronic acid group), BMD decreased by 0.9% (n = 11), 1.9% (n = 11), and 2.0% (n = 11) from baseline at lumbar spine, femoral neck, and total hip, respectively, Figure 4. However, these decreases were not as large as those in the goserelin acetate-alone group, consistent with an intermediate BMD benefit, although statistical power is limited.

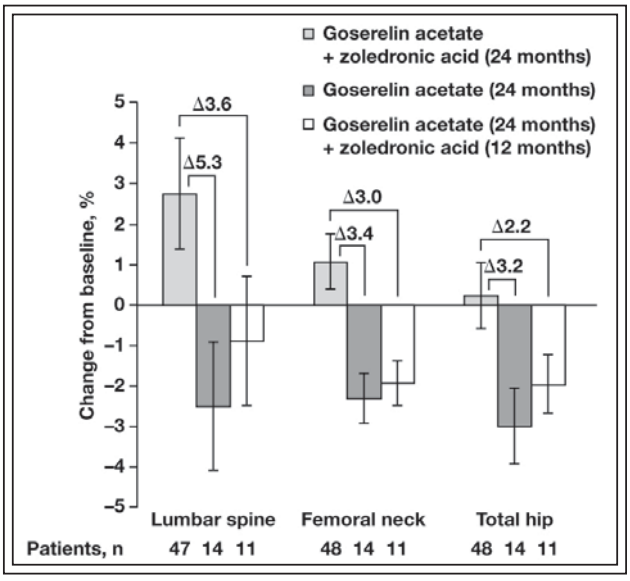

Figure 4. Phase II-Mean percentage changes in bone mineral density from baseline after 24 months of treatment. The bone mineral density differences between groups are represented by Δs. Error bars represent standard error of the mean.

Tolerability of zoledronic acid in patients receiving goserelin acetate for prostate cancer

The combination of goserelin acetate plus zoledronic acid was generally well tolerated. As expected, hot flashes were frequently reported after goserelin acetate administration, Table 3. The transient flu-like AEs (eg, fatigue, nausea) common after the first infusion of nitrogen-containing bisphosphonates were mild to moderate. Serious AEs (SAEs) were reported in 22 patients during phase I of the trial: 13 occurred in 11 patients receiving goserelin acetate plus zoledronic acid and 11 occurred in 11 patients receiving goserelin acetate alone. None of the SAEs was suspected to be related to the study medication. No SAEs were reported in phase II. Of the 187 patients randomized in this study, one patient who received goserelin acetate alone experienced acute renal failure that was suspected to be prostate cancer related, and no cases of osteonecrosis of the jaw were reported. Three deaths occurred during phase I of the study; however, none of these deaths was suspected by the principal investigators to be related to the study medication.

Discussion

In addition to preventing BMD loss with zoledronic acid, this study demonstrates that goserelin acetate plus zoledronic acid was generally well tolerated in patients with hormone-sensitive prostate cancer for up to 24 months. The combination of zoledronic acid and goserelin acetate did not increase toxicity relative to goserelin acetate alone. The most frequent AEs were consistent with the established safety profiles of these agents. Adverse events associated with zoledronic acid were transient, mild to moderate in severity, and manageable with supportive care. Notably, no SAEs were reported in phase II. It is possible that the requirement to obtain consent for phase II

TABLE 3. **Common nonserious adverse events**[a]

Adverse event	Phase I		Phase II[b]	
	Goserelin acetate alone (n = 93)	Goserelin acetate + zoledronic acid (n = 92)	Goserelin acetate alone (n = 22)	Goserelin acetate + zoledronic acid (n = 69)
Hot flashes, n (%)	27 (29)	23 (25)	4 (18)	16 (23)
Fatigue, n (%)	12 (13)	6 (7)	3 (14)	4 (6)
Body aches, n (%)	2 (2)	3 (3)	2 (9)	2 (3)
Bone/joint pain, n (%)	5 (5)	3 (3)	0	1 (1)
Nausea, n (%)	2 (2)	3 (3)	2 (9)	3 (4)

[a]Common nonserious adverse events related to study medication
[b]Adverse events reported from months 12 to 24

introduced a selection bias for healthier prostate cancer patients, thereby eliminating patients who may have experienced a non–drug-related SAE. In general, zoledronic acid combined with adjuvant hormonal therapies in other long term studies has also been considered well tolerated.[16-18]

Previous trials of ADT and bisphosphonates assessed BMD changes in patients with hormone-sensitive prostate cancer over 12 months, a relatively short period of time considering that patients with hormone-sensitive prostate cancer may receive ADT for longer than 12 months and can survive well over 10 years.[19] Because patients with hormone-sensitive prostate cancer can survive for many years despite their disease, early, effective bone-targeted therapies to prevent ADT-induced bone loss and associated skeletal morbidity are necessary.[7]

The results presented herein confirm and extend previous 12-month zoledronic acid studies in patients with hormone-sensitive prostate cancer receiving ADT.[13,20] In a prospective, double-blind, randomized, placebo-controlled trial in patients with hormone-sensitive prostate cancer receiving ADT for 48 weeks (N = 222), zoledronic acid increased lumbar spine and total hip BMD by 4.7% and 1.6%, respectively, compared with baseline.[20] In contrast, patients who received ADT alone had approximately 2% decreases in lumbar spine and total hip BMD compared with baseline ($p < .0001$ between groups).[20]

The current study evaluated long term (2-year) zoledronic acid use for preventing ADT-induced bone loss in patients with nonmetastatic hormone-sensitive prostate cancer. A few small studies in patients with hormone-sensitive prostate cancer receiving ADT also demonstrated the long term benefits of bisphosphonate treatment. A small pilot study randomized patients receiving ADT to placebo (n = 31), clodronate (n = 39), or zoledronic acid (n = 24) for 36 months.[21] This study demonstrated BMD stabilization with bisphosphonate treatment compared with placebo ($p < .0001$). A small retrospective study of alendronate (70 mg/week) in men receiving ADT (N = 47) with a mean follow-up of 17.6 months demonstrated BMD increases at lumbar spine, total hip, femoral neck, and trochanter compared with patients who received ADT alone ($p \leq .05$).[22]

A more complete comparison between upfront and delayed zoledronic acid in the current study might have been achieved had a greater proportion of eligible patients from phase I enrolled in phase II of the study. Because less than 60% of phase I completers chose to continue, the sample size required to detect significant treatment group differences in BMD was not attained. For potential future prospective studies, a 2-year trial design would ensure that patients and investigators agree with the trial concept and duration from the inception.

Hormonal therapy is a commonly used first-line treatment for patients with prostate cancer or breast cancer to reduce tumor burden; however, it is associated with increased bone loss and reduced skeletal integrity.[2,7] As presented in this study, concomitant zoledronic acid treatment can prevent ADT-induced bone loss and may be most effective if patients receive zoledronic acid at ADT initiation. Studies have also demonstrated significant BMD preservation with zoledronic acid in patients with early stage breast cancer receiving hormonal therapy.[16,17] Bone loss in that setting is similar to that occurring during ADT. The Zometa-Femara Adjuvant Synergy Trials (Z-FAST and ZO-FAST) are parallel studies of zoledronic acid (4 mg intravenously every 6 months) in postmenopausal patients (N = 1667) receiving adjuvant

letrozole (2.5 mg/day orally) for 5 years.[16,17] In these studies, women with early postmenopausal breast cancer received adjuvant letrozole therapy and were randomized to receive zoledronic acid immediately (upfront zoledronic acid) or only after they experienced a T-score < –2.0 or a nontraumatic fracture (delayed zoledronic acid).[16,17] Results from Z-/ZO-FAST indicate that upfront zoledronic acid more effectively preserves BMD compared with delayed zoledronic acid. In addition, in the Austrian Breast and Colorectal Cancer Study Group trial 12 (ABCSG-12), goserelin acetate (3.6 mg every 28 days) was administered with tamoxifen (20 mg/day) or anastrozole (1 mg/day), both with or without zoledronic acid (4 mg every 6 months) in 1803 premenopausal women with early breast cancer. Zoledronic acid was found to have benefits beyond BMD preservation.[23] At 48 months, zoledronic acid produced a 36% relative reduction in risk of disease-free survival events (log-rank p = .01) and a 35% relative reduction in risk of recurrence-free survival events (log-rank p = .01) compared with endocrine therapy alone.[18,23] These results suggest that zoledronic acid may have treatment benefits beyond regulating bone homeostasis.

The results from the study presented herein demonstrated that zoledronic acid (4 mg every 3 months) safely and effectively preserves BMD in patients with hormone-sensitive prostate cancer initiating ADT. Corresponding data from other tumor types suggest that zoledronic acid may provide additional treatment benefits to patients with cancer; however, prospective data are needed to extend these treatment outcomes to the prostate cancer setting. Ongoing trials, such as ZEUS, RADAR, and STAMPEDE, will provide further insight into the role of zoledronic acid in patients with prostate cancer. The ZEUS trial will assess event-free survival in patients with high risk early prostate cancer and no distant metastases (accrual complete: N = 1498) during 4 years of standard therapy with or without zoledronic acid (4 mg intravenously every 3 months).[24] Secondary endpoints include time to bone metastasis, prostate-specific antigen doubling time, BMD loss, and overall survival. Similarly, RADAR (enrolled: N = 1071) and STAMPEDE (planned: N = 3300) will assess survival endpoints in patients with prostate cancer. RADAR is investigating overall survival and bone-metastases–free survival in patients receiving zoledronic acid with or without intermittent or short term ADT for nonmetastatic prostate cancer, whereas STAMPEDE is assessing failure-free survival and overall survival in patients with or without bone metastases from prostate cancer who are receiving ADT. The results from these studies will provide further evidence for the bone-protective and antitumor benefits of bisphosphonates, and the role of bisphosphonates in both the early and advanced cancer settings is likely to expand.

Disclosure

AstraZeneca Canada Inc. and Novartis Canada Inc. provided CMX with a grant to conduct the study. For phase II, Novartis also provided zoledronic acid packaged as an investigational product. Financial support for medical editorial assistance was provided by Novartis. The authors have no other conflicts of interest to report. □

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