The use of bisphosphonates in men with hormone-refractory prostate cancer: a systematic review of randomized trials

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Purpose: *A systematic review of randomized controlled trials (RCTs) was performed to assess the benefits of bisphosphonate therapy in men with hormone-refractory prostate cancer (HRPC).*
Methods: *The literature was searched to identify RCTs or meta-analyses comparing treatment with bisphosphonates to placebo or no treatment.*
Results: *Ten trials that studied clodronate (five trials, 404 patients), pamidronate (two trials, 350 patients), alendronate (one trial, 49 patients), etidronate (one trial, 51 patients), and zoledronic acid (one trial, 643 patients) in men with HRPC and bone metastases met the eligibility criteria. Pain response was the most frequently reported primary outcome (eight trials). Only the smallest trial demonstrated a statistically significant improvement in pain, but other non-statistically significant trends and subgroup analyses showing improvement in pain were observed in six clodronate and pamidronate trials. Three trials reported skeletal-related events (SREs). A trial studying zoledronic acid reported a statistically and clinically significant reduction in the number of patients having at least one SRE; however, there were higher rates of some adverse effects, and quality of life was not improved.*
Conclusion: *Zoledronic acid appears to reduce the number of patients having at least one SRE in men with bone metastases from HRPC that are causing minimal or no pain. This benefit should be weighed against the associated toxicities, and the neutral effect on quality of life. Bisphosphonates may reduce bone pain in men with HRPC, but the evidence is less robust. Further investigations to identify the role of bisphosphonates alone and in combination with other therapies proven effective for men with HRPC are warranted.*

Key Words: prostatic neoplasms, diphosphonates, bone neoplasms

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Introduction

Bone is the most common site of prostate cancer spread. Metastases occur in up to 90% of men with hormone-refractory prostate cancer (HRPC) with sequelae including pain, pathologic fractures, and spinal cord compression.[1] Bisphosphonates are potent inhibitors of osteoclast function and have established roles in reducing the morbidity of bone metastases from breast cancer and multiple myeloma, tumors that produce predominantly lytic metastases.[2,3] While prostatic bone lesions are predominantly osteoblastic, increased

osteoclast activity and bone resorption play a major role in the skeletal morbidity of prostate cancer.[4] A number of clinical trials studying the efficacy of bisphosphonates on skeletal morbidity outcomes in HRPC have now been completed. The intent of this systematic review was to identify and review the results of published randomized controlled trials (RCTs) to determine the benefits of bisphosphonates in men with HRPC.

Methods

Inclusion criteria

Studies of interest were RCTs or meta-analyses of RCTs studying men with HRPC and comparing treatment with a bisphosphonate to placebo or no treatment (open control), comparing different bisphosphonates or routes of administration of the same bisphosphonate, or comparing treatment with a bisphosphonate plus a co-intervention (i.e., hormonal therapy or chemotherapy) to the same treatment without bisphosphonate. Eligible studies reported results for at least one of the following outcomes: incidence of new bone metastases, skeletal-related events (SREs), palliative or symptom response rates, survival, and/or quality of life (QoL). Adverse effects were also of interest.

Search strategy

The MEDLINE (1980 through July 2004), EMBASE (1980 through 2004, week 32), CANCERLIT (1980 through October 2002), and Cochrane Library databases (2004, Issue 2) were searched for relevant trials using disease-specific, treatment-specific, and design-specific medical subject headings and text words. Conference proceedings from the annual meetings of the American Society of Clinical Oncology (1995-2004) and the American Urological Association (1995-2004) were also searched. Relevant articles and abstracts were selected and reviewed by three reviewers; the reference lists from those sources were searched for additional trials, as were the reference lists from relevant review articles.

Data extraction and trial appraisal

Information on trial characteristics, including patient population, number of randomized and evaluable patients, treatment regimens, and outcomes, were extracted from each trial report. Information indicative of trial quality, including methods of randomization and blinding, adequacy of the description of treatment and control arms, completeness of follow-up, and whether intent-to-treat (ITT) analyses were performed, were also examined for each RCT.

Statistical methods

If deemed appropriate, an objective of the review was to statistically pool outcome data. If not, an interpretive synthesis was planned.

Results

Search results

Seventeen reports were identified as eligible, including three systematic reviews[5-7] and 14 reports (two in abstract form) describing 12 RCTs.[8-21] Three of those reports were excluded: one systematic review included a single prostate cancer trial already identified,[7] one RCT closed prematurely due to inadequate patient accrual,[20] and another RCT had accrued two patients at the time of publication.[21]

Systematic reviews and meta-analyses

Two previous systematic reviews considered evidence on bisphosphonates in HRPC.[5,6] The scope of those reports was broad, including multiple tumor types and a small subset of trials involving HRPC patients.[10,11,14,16] Neither review included four recently published, larger trials.[9,17,18]

Randomized controlled trials

Trial characteristics

Five trials of clodronate,[9-11,13,14] two trials of pamidronate,[17] and one trial each of alendronate,[8] etidronate,[16] and zoledronic acid[18] form the evidence base of this review and are summarized in Table 1.

Trial quality

Nine RCTs were placebo-controlled, and seven of those described double-blinding; one RCT reported a single-blind design. Two trials described the method of patient randomization.[9,18] Six trials presented baseline characteristics for treatment and control arms,[9,11,14,17,18] and four of those reported that treatment arms were balanced for important prognostic variables.[9,17,18] The statistical basis for the estimation of sample size and trial power were described in four trials,[9,17,18] and two trials performed statistical analyses according to ITT.[9,18] A third trial also stated ITT analyses were performed, however, approximately 20% of patients were excluded from statistical analyses of the primary outcome.[17] The reporting of patient follow-up in the trials was poor; few provided detailed information on the numbers of patients who received intended treatment and completed trial protocol, and details explaining patient withdrawals or dropouts were rarely reported.

TABLE 1. **Eligible randomized trials of bisphosphonates in men with hormone-refractory prostate cancer**

Trial	Design	Patient population	No. randomized/ evaluable	Treatment regimens
Alendronate				
Dahut[8] 2001 (abstract)	Randomized phase II	Bone metastases	52/49	i. Alendronate 40 mg po od + hydrocortisone/ketoconazole ii. Hydrocortisone/ketoconazole
Clodronate				
Ernst[9] 2003	Placebo double blind	Bone metastases + pain	209/209	i. Clodronate 1500 mg iv q 3 weeks + mitoxantrone/prednisone ii. Mitoxantrone/prednisone + placebo
Kylmälä[11] 1997	Placebo double blind	Bone metastases + pain	57/55	i. Clodronate 300 mg iv x 5d, then 1600 mg po od + EMP ii. EMP + placebo
Strang[10] 1997†	Placebo double blind	Bone metastases + pain despite analgesic treatment	55/52	i. Clodronate 300 mg iv x 3d, then 3200 mg po (1600 mg bid) ii. Placebo
Elomaa[14] 1992	Placebo no binding	Bone metastases + pain despite daily analgesic use	75/NR	i. Clodronate 3200 mg po od x 1 mo, then 1600 mg po od + EMP ii. EMP + placebo
Adami[13] 1989	Placebo single blind	Bone metastases + pain, some received EMP	13/13	i. Clodronate 300 mg iv od ii. Placebo
Etidronate				
Smith[16] 1989	Placebo double blind	Bone metastases + pain requiring analgesics	57/51	i. Etidronate‡ 7.5 mg/kg iv x 3d, then 200 mg po bid ii. Etidronate‡ 7.5 mg/kg iv x 3d, then placebo po bid iii. Etidronate‡ placebo iv x 3d, then etidronate 200 mg po bid iv. Placebo‡ iv and po placebo
Pamidronate				
Small[17] 2003‖ [INT-05 and CGP 032]	Placebo double blind	Bone metastases + pain	378/350	i. Pamidronate 90 mg iv q 3 weeks ii. Placebo
Zoledronic acid				
Saad[18] 2002	Placebo/ double blind	Bone metastases not producing pain requiring strong narcotics	643/643	i. Zoledronic acid 4 mg iv q 3 weeks# ii. Zoledronic acid 8/4 mg iv q 3 weeks# iii. Placebo

bid – twice daily; d – day; EMP – estramustine phosphate; iv – intravenous; kg – kilogram; mg – milligram; No. – number; NR – not skeletal-related event; x – times.

*in responding patients, prednisone and clodronate were continued until disease progression and mitoxantrone was discontinued prematurely due to difficulties in recruiting patients; ‡six patients were considered unevaluable because they failed to complete 1 treatment for at least 1 month, those not responding were given the option of repeat treatment with open-label therapy (intravenous remained on the same therapy for up to 6 months as long as they maintained evidence of response; ‖this report represents a INT-05 and US Trial CGP 032; ¶patient enrolment and treatment in this trial took place between June 1998 and January 2001. 50 ml iv infusion, however, this was amended to a 15-minute 100 ml infusion in June 1999 to increase renal safety. A subsequent 8 mg zoledronic acid treatment arm to 4 mg because of renal toxicity (8/4 mg treatment group).

Planned duration of treatment	Primary outcome
Until disease progression or unacceptable toxicity	PSA response
7 cycles*	Palliative response
12 months	Pain
4 weeks	Pain
5 months	Pain
2 weeks	Pain
1 month§	Pain
27 weeks	Pain
15 months	SRE

reported; od – once daily; po – per oral; q – every; SRE –

after a cumulative dose of 140 mg/m^2; †this trial was closed month of treatment; §patients remained on original randomized etidronate followed by oral etidronate). Responding patients combined analysis of two randomized trials, International Trial Patients initially received zoledronic acid via a 5-minute protocol amendment in June 2000 reduced the dose of the

Outcomes

Pain

Nine trials involving 1399 evaluable patients have assessed bisphosphonates for relieving pain or reducing analgesic consumption,[9-11,13,14,16-18] Table 2. The method and frequency of pain measurement varied across trials; pain was assessed using visual or linear analogue scales,[10,11,13,16] the Present Pain Intensity (PPI) scale,[9] and the Brief Pain Inventory (BPI),[17,18] and the method of assessment was not specified in one trial.[14]

The majority of trials were underpowered to detect modest but clinically significant differences in pain outcomes between trial arms, thereby making meta-analysis an ideal approach to synthesizing their data. Unfortunately, statistical pooling could not be performed due to the variability in the methods of measuring pain across trials. Among the eight trials that evaluated pain relief, four trials[10,13,17] (total n = 366, 301 from one trial) reported mean pain scores, three trials[9,14,16] (total n = 335, 209 from one trial) reported proportions of patients with pain response, and one trial[11] (n=55) reported pain outcomes by both methods. The largest trials[9,17] used different pain evaluation methods that could not be mathematically combined.

Four[9-11,14] of the five clodronate trials did not detect significant differences in pain outcomes between clodronate and placebo trial arms. The statistically significant results of Adami and Mian's[13] trial are suspect because important details about the conduct of the trial were not reported, and the trial's single-blind design, small sample size, and short duration of follow-up (2 weeks). Ernst et al[9] compared the proportion of patients achieving a palliative response (defined as a two-point reduction in the PPI score without an increase in analgesic score or disease progression) in patients treated with mitoxantrone-prednisone and either clodronate or placebo. No significant difference in palliative response rate was detected between the two arms after seven cycles of treatment. Among the 23% of patients (n = 49) with moderate baseline pain (PPI of 3 or 4), patients treated with clodronate were more likely to achieve a palliative response (58%) compared with patients receiving placebo (26%) (Odds Ratio, 4.6; 95% Confidence Interval, 1.3 to 15.5; p = 0.04).

Kylmälä et al,[11] Strang et al,[10] and Elomaa et al[14] also did not detect significant improvements in pain with clodronate compared with placebo. However, certain trends and subgroup analyses from these trials are worth noting. Kylmälä et al[11] reported that the proportion of patients experiencing complete pain relief at 1 month after treatment was 25% in both trial

arms; at 3 months, that proportion was 10% higher in the clodronate arm but was not statistically significant. Strang et al[10] reported similar changes from baseline in mean pain, and mean least and worst pain in both arms at every time point assessed during the 32-day follow-up period. In a post hoc subgroup analysis,

TABLE 2. **Pain – randomized trials of bisphosphonates versus placebo in men with hormone-refractory prostate cancer and bone metastases**

Trial, n	Measurement tool	Definition of pain reduction/relief	Results
Clodronate			
Ernst[9] 2003 n = 209	Pain: 6-pt PPI* Analgesic use: diary	Palliative response: 2-pt reduction in PPI (or complete loss of pain if PPI was 1 or 2) without increase in analgesic score or disease progression†; or ≥ 50% decrease in analgesic score without increase in PPI	% of patients with: Clodronate Placebo Palliative response 45 39 ≥ 2-pt reduction in PPI 33 26 50% decrease in analgesic score 33 30 No significant difference between groups in palliative response, PPI, or analgesic scores compared with baseline
Kylmälä[11] 1997 n = 55	Pain: 5-pt VAS‡	Pain change from baseline in VAS pain scores	% of patients with VAS score of: Clodronate (months: 1, 3, 6) Placebo (months: 1, 3, 6) 0: 36, 32, 21, 22, 22, 19 1: 32, 14, 14, 37, 19, 11 2: 11, 7, 4, 26, 30, 19 3: 7, 18, 14, 11, 15, 4 4: 0, 0, 7, 0, 0, 4 No significant difference between groups in VAS pain scores at 1, 3, 6, or 12 months compared with baseline
Strang[10] 1997 n = 52	Pain: 10 cm VAS	Mean pain intensity and mean pain intensity during the best and worst periods	Data NR No significant difference in mean pain intensity or mean pain intensity during the best and worst periods between groups during 32-day follow-up period
Elomaa[14] 1992 n = 75	Pain: NR	Pain: proportion of patients with and without pain	% of patients with no pain at months: Clodronate Placebo 1: 34 18 3: 29 4 6: 18 15 No significant difference in pain between groups at 1, 3, or 6 months.
Adami[13] 1989 n = 13	Pain: 20 cm VAS	Pain: mean change in pain score from baseline	Clodronate Placebo Mean pain score at 2 weeks: 2.1‖ 11.9‖ Significant difference between groups in mean pain score ($p < 0.01$) at 2 weeks
Etidronate			
Smith[16] 1989 n = 51	Pain: numerical and LAS, diary	Pain: proportion of patients with pain improvement at 1 month	No significant difference in subjective or minor pain between groups at 1 month improvement

TABLE 2 (cont'd): **Pain – randomized trials of bisphosphonates versus placebo in men with hormone-refractory prostate cancer and bone metastases**

Pamidronate					
Small[17] 2003 n = 301	Pain: BPI¶	Pain: the difference in pain score (least, average, and worst pain) from baseline	Mean BPI score at 9 and 27 weeks:	Pamidronate	Placebo
			Least		
			9	-0.15	-0.11
			27	-0.15	+0.26
			Average		
			9	-0.61	-0.44
			27	-0.40	-0.27
			Worst		
			9	-0.86	-0.69
			27	-0.60	-0.65
			No significant difference in mean BPI scores between groups at 9 or 27 weeks		
Zoledronic acid					
Saad[18] 2002 n = 643	Pain: BPI#	Pain: mean increase in BPI pain score from baseline at 15 months	Mean increase from baseline in BPI:		
			4 mg versus placebo	0.58 No significant difference	
			8/4 mg versus placebo	0.43 Significant difference (p = 0.026)	
			Placebo	0.88	

BPI – Brief Pain Inventory; cm – centimeter; LAS – linear analogue scale; mg – milligram; NR – not reported; PPI – Present Pain Intensity scale; pt – point; ref – reference; VAS – visual analogue scale

*6-point PPI scale: 0=no pain, 1=mild pain, 2=discomforting pain, 3=distressing pain, 4=horrible pain, 5=excruciating pain; †disease progression defined as one or more of the following: a 1 point or more increase in PPI or a 25% increase in analgesic consumption compared with baseline, need for RT, or evidence of radiologic progression; ‡4-point VAS: 0=no pain to 4=intolerable pain; ||estimated from curve; ¶pain score derived from the BPI; pain score is based on an 11-point scale (0-10): 0=no pain to 10=pain as severe as can be imagined; #Pain score as assessed by the BPI, was a composite score of four pain scores: worst pain, least pain, average pain of the last seven days, and pain right now. An increase in score indicates increased pain.

patients with moderate pain (visual analogue score ≥ 50) showed a greater reduction in mean pain with clodronate (n = 6) than with placebo (n = 14) but the difference did not reach statistical significance. Elomaa et al[14] reported that a greater proportion of patients receiving clodronate in their trial were free of pain at 1, 3, and 6 months compared with patients allocated to placebo, with the most marked difference between trial arms occurring at 1 month (34% versus 18%); however, none of those differences were statistically significant.

The pooled analysis of the two pamidronate trials[17] represents the largest trial to assess pain relief. Those trials measured BPI pain score changes from baseline at 9 and 27 weeks and considered a three-point difference in BPI pain score clinically significant. Overall, no statistically or clinically significant differences in mean BPI pain scores were detected between treatment arms at either time point. For the entire study population, analgesic consumption was also comparable at both evaluation time points, however, in the subgroup of patients with decreasing or stable analgesic use (n = 121), the average and worst BPI scores were statistically improved by pamidronate at 9 weeks (p = 0.008 and p = 0.011, respectively). In the subset of patients with moderate pain at baseline (BPI 4 to 7) and stable analgesic use, patients receiving pamidronate had a statistically significant reduction in pain compared with placebo at 9 weeks (p = 0.004) but this difference was not maintained at 27 weeks. This trial does have a number of limitations that might obscure a modest clinical benefit from pamidronate. It was not stated whether optimization of analgesic use was required prior to trial entry, the use of co-interventions influencing pain control (e.g., chemotherapy) was not controlled or reported, and 20% of randomized patients were excluded from ITT analyses of pain and analgesic use. In addition, the

fact that more patients had stable or decreasing pain in the placebo group (44% in placebo versus 36% in pamidronate) suggests a real baseline imbalance in patient characteristics, effects of patient exclusions, and/or co-interventions significantly affected the results in favor of placebo.

Patient eligibility in the zoledronic acid trial[18] did not require patients to have pain at trial entry (although approximately 70% of patients presented with pain), and patients were excluded if they had pain requiring strong narcotic therapy – this is reflected in the low mean baseline BPI scores in each treatment group: 2.0 in the 4 mg arm, 2.5 in the 8/4 mg arm, and 2.1 in the placebo arm (10-point pain scale). However, pain was measured at baseline and every 6 weeks as part of a QoL assessment. At 15 months, mean increases in pain scores were lower with zoledronic acid; increases of 0.58 (p = 0.13) and 0.43 (p = 0.026) (versus 0.88 with placebo) were seen in the 4 mg and 8/4 mg zoledronic acid arms, respectively. At 24 months, the mean change in BPI scores from baseline for the 4 mg and 8/4 mg zoledronic acid arms were 0.58 (p = 0.024) and 0.54 (p = 0.013) versus 1.05 with placebo.[19]

Smith[16] reported that etidronate was ineffective in relieving pain from bone metastases in a four-arm trial that compared both intravenous etidronate and intravenous and oral etidronate combined treatment with placebo.

Skeletal-related events

SREs have been evaluated in three trials involving 993 patients.[17,18] In the zoledronic acid trial[18] SREs were defined as any one of the following: new pathologic bone fractures (vertebral and non-vertebral), spinal cord compression, the need for surgery or radiation to bone (including radioisotopes), and a change in antineoplastic therapy to treat bone pain. The two pamidronate trials[17] employed a similar definition but also included hypercalcemia and the need for a spinal orthotic brace. Change in antineoplastic therapy was not included as an SRE in the pamidronate trials.

Saad et al[18] detected a significant reduction in the number of patients having at least one SRE after 15 months of zoledronic acid treatment, but the benefit was only significant when given at a dose of 4 mg. Forty-four percent of men in the placebo arm had at least one SRE, while in the 4 mg and 8/4 mg zoledronic acid trial arms, 33% (p = 0.02) and 39% (p = 0.2) of patients, respectively, had at least one SRE during the trial. When the two zoledronic acid arms are combined, the reduction in the number of men having at least one SRE remains statistically significant (36% versus 44% for zoledronic acid and placebo, respectively; p = 0.041).[22] At 24 months, the percentage of patients having a least one SRE during the trial was 38% in the 4 mg arm (p = 0.028) and 41% in the 8/4 mg arm (p = 0.129) versus 49% with placebo, or 40% when the zoledronic arms are combined (versus 49% for placebo; p = 0.031).[19] Median time-to-first SRE was reached for both treatment groups at 24 months and was significantly longer for patients treated with 4 mg of zoledronic acid (but not 8/4 mg) than placebo (p = 0.009) [488 days (4 mg), 363 days (8/4 mg), 321 days (placebo)].

In contrast to the zoledronic acid trial, Small et al[17] detected no difference in the proportion of patients with SREs at 9 or 27 weeks between pamidronate and placebo. At 9 weeks, 12% and 11% of patients in the pamidronate and placebo arms had a SRE; at 27 weeks, the proportion of patients experiencing a SRE was 25% in both arms.

Survival

Three trials, two of clodronate and one of zoledronic acid, have reported whether treatment with a bisphosphonate prolongs survival.[9,14,18] Survival was studied as a secondary endpoint in each trial, and none of the trials detected statistically significant survival differences between trial arms.

Quality of life

Two trials prospectively examined QoL using validated questionnaires or instruments. Both assessed QoL at baseline, during and post-treatment.[9,18] Ernst et al[9] assessed QoL using the validated Prostate Cancer-Specific Quality of Life Instrument (PROSQOLI). QoL response was seen in 38% (39/104) of patients receiving clodronate and 42% (44/105) of patients receiving placebo (p = 0.6). In patients completing at least two PROSQOLI assessments, there were no statistically significant differences between clodronate and placebo in mean changes from baseline on any of the QoL domains with the exception of pain, which was improved with clodronate compared with placebo (p = 0.02).

QoL assessment in the zoledronic acid trial[18] consisted of patient performance status and two QoL questionnaires, the Functional Assessment of Cancer Therapy-General (FACT-G) and the Euro Quality of Life (EuroQol) EQ-5D, completed at enrollment and every 3 months during the trial. Saad et al[18] reported that QoL questionnaire scores decreased over the duration of the trial from baseline to 15 months, with no statistically significant differences between treatment groups.

Adverse effects

Overall, bisphosphonates were generally well tolerated, with the majority of trials reporting only mild toxicity occurring in equal proportions of patients treated with bisphosphonate and placebo. Toxicity data were generally not reported by grade of severity in trial reports. The most frequently reported adverse event was nausea and/or vomiting, which occurred in 9% to 33% of patients in three trials of clodronate[9,11,14] and 18% of patients in the etidronate trial.[16] Higher rates of nausea/vomiting were seen with pamidronate (45%) and zoledronic acid (4 mg, 58%; 8/4 mg, 82%); however, in all of those trials, the rates in the treatment arms were comparable with placebo.[17,18] In the pamidronate trial, fever, weight loss, and nausea were at least 5% higher with pamidronate than placebo. In the zoledronic acid trial, rates of fatigue, anemia, myalgia, fever, and lower-limb edema were at least 5% higher with zoledronic acid than placebo.[18] Grade 3 serum creatinine increases and renal function deterioration occurred in a greater proportion of patients treated with zoledronic acid compared with placebo (15%, 21%, and 12% in the zoledronic acid 4 mg, 8/4 mg, and placebo arms, respectively). Three trials reported that the percentage of patients discontinuing treatment due to toxicity was similar among trial arms.[9,17,18]

Discussion

Interpretation of the data provided by the ten RCTs included in this review is complex due to the heterogeneity in patient populations, the bisphosphonates studied, the outcomes assessed, and the methodological limitations of some of the trial designs.

The most widely studied outcome was pain. Eight trials (n = 756) included men with bone metastases and pain and designated pain reduction as the primary outcome, and all were negative except the smallest trial.[9-11,13,14,16,17] However, among the four negative clodronate trials, three showed trends towards improved pain relief in the bisphosphonate arm that were not statistically significant,[9,11,14] two showed pain improvement in subgroups of patients with moderate pain at baseline,[9,10] and, in one trial, the pain domain of a QoL assessment was significantly better with clodronate.[9] A combined analysis of two pamidronate trials failed to demonstrate overall pain benefits but did report statistically significant benefits in subgroups of patients with moderate pain at baseline and stable analgesic use. Limitations of the trial may have obscured modest benefits of pamidronate in the overall study population.[23] Some of the negative clodronate and pamidronate trials were likely underpowered to detect differences in treatment effect (three of six included less than 100 patients), making a meta-analysis of the data from them ideal. Unfortunately, statistical pooling was not technically possible. Although the subgroup analyses and non-statistically significant trends described above involved a small number of patients, all six of those trials demonstrated some trend indicating that bisphosphonates could improve pain.

The most potent bisphosphonate, zoledronic acid, has not been studied in the context of pain reduction in men with HRPC. Rather, because the baseline level of pain in men in the zoledronic acid trial was low, the trial should be considered a trial of pain prevention. One zoledronic acid arm had a lower rise in mean pain scores from baseline at 15 months compared with men receiving placebo that was statistically significant. However, the absolute difference in rise on a 10-point scale was less than one point, a benefit of doubtful clinical impact.

Three trials addressed the impact of bisphosphonates on SREs.[17,18] Although zoledronic acid was associated with a statistically significant reduction in the proportion of patients having at least one SRE,[18,19] the clinical significance of those findings is more difficult to judge. Zoledronic acid 4 mg was associated with an 11% absolute reduction in the number of patients having at least one SRE at both 15 and 24 months when compared with placebo. However, if both zoledronic acid arms are considered together, which improves the statistical power of the comparison,[24] the absolute reduction in the number of men having at least one SRE at 15 and 24 months is actually 8% and 9%, respectively.[19,22] Although clinically significant, such a reduction still should be viewed within the context of the toxicities associated with treatment and the lack of a QoL benefit given that the population studied in that trial had few or no symptoms. The combined analysis of the two pamidronate trials did not demonstrate a reduction in SREs.[17]

Zoledronic acid is associated with statistically and clinically significant reductions in the number of men having at least one SRE among men with minimally symptomatic or asymptomatic HRPC. The benefits of reducing SREs should be considered in light of zoledronic acid's toxicities, minimal effect on pain prevention, and neutral effect on QoL. Evidence for the use of clodronate or pamidronate to reduce pain in men with HRPC is less robust in that it is derived from trends in smaller trials and subset analyses. The value of using bisphosphonates to reduce pain should

be considered in relation to the proven benefits of other palliative treatment options for men with HRPC and bone pain such as external beam radiotherapy and chemotherapy.[25] The observation of trends and results from subset analyses should be seen primarily as a stimulus to investigations of the role of bisphosphonates alone and in combination with other effective systemic therapies for men with HRPC. □

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