



program in
evidence-based care
a cancer care ontario program

programme de soins
fondé sur des preuves
un programme de action cancer ontario

The Use of Bisphosphonates in Men with Hormone-Refractory Prostate Cancer Practice Guideline Report #3-14

*S. Berry, T. Waldron, E. Winquist, H. Lukka, and the Members of the Genitourinary Cancer
Disease Site Group*

Report Date: January 10, 2005

SUMMARY

Guideline Questions

Should bisphosphonates be used in men with hormone-refractory prostate cancer to:

1. Delay or prevent bone metastases in men without metastases?
2. Reduce the likelihood of skeletal-related events (e.g., bone fracture, spinal cord compression, requirement for radiotherapy or surgery to bone) in men with bone metastases?
3. Reduce pain in men with painful bone metastases?
4. Improve survival and quality of life?

Target Population

These recommendations apply to patients with hormone-refractory prostate cancer. Hormone-refractory is defined as the progression of stage IV disease or a rising prostate-specific antigen with a castrate testosterone level.

Recommendations

Evidence on the use of bisphosphonates in hormone-refractory prostate cancer is limited to 10 randomized trials examining five different bisphosphonates in different patient populations. Six of those trials were small, including less than 100 patients. In contrast to other disease sites where bisphosphonates have been more extensively evaluated, the limited available evidence in hormone-refractory prostate cancer makes it difficult to derive treatment recommendations for bisphosphonates as a class of agents. Therefore, the recommendations that follow apply to different bisphosphonates in specific clinical situations.

- ***In men with hormone-refractory prostate cancer and asymptomatic or minimally symptomatic¹ bone metastases***, it is reasonable to consider zoledronic acid (4mg intravenously every three weeks) to reduce skeletal-related events. Practitioners and

¹ This recommendation is limited to the asymptomatic or minimally symptomatic population of men with hormone-refractory prostate cancer studied in the zoledronic acid trial (1). The trial specifically excluded men with bone pain requiring strong narcotic therapy; the mean baseline pain scores of patients in this trial ranged from 2.0 to 2.5 on the Brief Pain Inventory (10-point pain scale).

patients need to be aware of the benefits and risks of treatment, together with the limitations of the zoledronic acid trial when considering zoledronic acid in this setting.

- Zoledronic acid is associated with an 8% absolute reduction (from 44% to 36%) in skeletal-related events. This reduction translates to a number-needed-to-treat value of 12 in order to prevent a single skeletal-related event.
 - The palliative benefits of reducing skeletal-related events by zoledronic acid should be considered in light of its toxicities, minimal effect on pain prevention, and neutral effect on overall quality of life.
- ***In men with hormone-refractory prostate cancer and moderately² painful bone metastases***, clodronate (1600mg to 3200mg orally once daily or 1500mg intravenously every three weeks) can be considered as an adjunct to other palliative therapies (i.e., chemotherapy, radiotherapy) for reducing pain, along with traditional measures for pain management.
 - Three randomized trials of clodronate showed trends toward improvement in pain control and two trials showed pain improvement in subgroups of patients with moderate pain at baseline. On the basis of those observations, it is reasonable to consider clodronate for pain relief from moderately painful bone metastases.
 - Improvement in pain was observed with intravenous, oral, and combined intravenous and oral clodronate. Individual patient preference, tolerance, and convenience should inform the choice of route of administration. Clodronate is contraindicated in patients with a serum creatinine value greater than 440 µmol/L.
 - Bisphosphonates should not be used with the intent of improving the overall survival of men with hormone-refractory prostate cancer.
 - There is no evidence from randomized trials on the use of bisphosphonates to delay or prevent bone metastases in men with hormone-refractory prostate cancer without bone metastases.

Qualifying Statements

- The optimal duration of bisphosphonate treatment in men with hormone-refractory prostate cancer has not been evaluated in randomized trials. In the trial that demonstrated a reduction in skeletal-related events, zoledronic acid was given for 15 months. Extension data from that trial indicates that some men (122/643) were able to continue their assigned therapy for 24 months (86 men on the zoledronic acid arms of the trial, 36 men on the placebo arm). Among the five trials of clodronate, treatment duration ranged from two weeks to 12 months and was discontinued at the time of symptomatic progression in the largest trial.
- For men with hormone-refractory prostate cancer and bone pain, other palliative measures such as external beam radiotherapy, radioisotope therapy, and chemotherapy have demonstrated unequivocal patient benefits in randomized trials. The value of using bisphosphonates in this context should be considered in relation to the proven benefits of these other palliative treatment options.

Key Evidence

- Ten randomized trials met the eligibility criteria of this review. All 10 trials examined bisphosphonate use in patients who had documented bone metastases at the time of

² The definition of moderate pain was a score of 3.0 or 4.0 on the Present Pain Intensity Scale of the McGill-Melzack Pain Questionnaire in the Ernst et al trial (2), or a score of ≥50mm on a 10cm-long visual analogue scale in the Strang et al trial (3).

randomization. Five trials of clodronate, two trials of pamidronate, and one trial each of alendronate, etidronate, and zoledronic acid form the evidence base of this review.

- Pain was the most frequently reported outcome. The reduction of pain or analgesic use was the primary outcome in eight trials but was reported in nine of 10 trials. Other important endpoints reported included reduction in skeletal-related events (three trials), survival (three trials), quality of life (five trials), and adverse effects (eight trials).
- Of the nine trials reporting on pain, only one detected a statistically significant improvement in pain favouring bisphosphonate treatment. That trial, which evaluated intravenous clodronate, was small (n=13) and had questionable trial methodology. Three trials showed trends toward improved pain relief with clodronate compared with placebo, but those differences did not reach statistical significance. In subgroup analyses, two trials of clodronate showed pain improvement in patients who had moderate pain at baseline (improvement was statistically significant in one trial). The largest trial to assess pain relief (a pooled analysis of the two pamidronate trials, n=350) found no difference in pain scores between pamidronate and placebo trial arms at nine and 27 weeks of treatment. Zoledronic acid, the most potent bisphosphonate, has not been evaluated in the context of pain reduction.
- Three trials evaluated the use of bisphosphonates for the reduction of skeletal-related events. In the zoledronic acid trial, skeletal-related events were significantly less with zoledronic acid versus placebo (absolute reduction in skeletal related events with zoledronic acid was 8%). No difference in skeletal-related events was observed in the pooled analysis of the two pamidronate trials.
- Two trials prospectively evaluated quality of life outcomes associated with bisphosphonate treatment. In both trials, quality of life outcomes were similar between bisphosphonate (clodronate, zoledronic acid) and placebo.
- Three trials (two of clodronate, one of zoledronic acid) assessed whether bisphosphonate treatment prolonged survival compared with placebo. None of those trials detected a survival benefit with bisphosphonate treatment.

Future Research

Further large, well-designed trials with appropriate endpoints are needed to assess the role of bisphosphonates for pain reduction in men with hormone-refractory prostate cancer and bone metastases.

Related Guidelines

Practice Guideline Initiative Practice Guideline Reports:

- #3-6: *Use of Strontium89 in Patients with Endocrine-Refractory Carcinoma of the Prostate Metastatic to Bone*
- #14-1: *Radiopharmaceuticals for the Palliation of Painful Bone Metastases*
- #13-2: *Radiotherapy Fractionation for the Palliation of Uncomplicated Painful Bone Metastases*
- #1-11: *Use of Bisphosphonates in Women with Breast Cancer*
- #6-4: *The Role of Bisphosphonates in the Management of Skeletal Complications for Patients with Multiple Myeloma*

References

1. Saad F, Gleason DM, Murray R, Tchekmedyian S, Venner P, Lacombe L, et al. A randomized, placebo-controlled trial of zoledronic acid in patients with hormone-refractory metastatic prostate carcinoma. *J Natl Cancer Inst* 2002;94:1458-68. [24]

2. Ernst DS, Tannock IF, Winqvist EW, Venner PM, Reyno L, Moore MJ, et al. Randomized, double-blind, controlled trial of mitoxantrone/prednisone and clodronate versus mitoxantrone/prednisone and placebo in patients with hormone-refractory prostate cancer and pain. *J Clin Oncol* 2003;21:3335-42. [13]
3. Strang P, Nilsson S, Brandstedt S, Sehlin J, Borghede G, Varenhorst E, et al. The analgesic efficacy of clodronate compared with placebo in patients with painful bone metastases from prostatic cancer. *Anticancer Res* 1997;17:4717-21. [10]

For further information about this practice guideline report, please contact Dr. Himu Lukka, Chair, Genitourinary Cancer Disease Site Group, Juravinski Cancer Centre, 699 Concession Street, Hamilton, ON, L8V 5C2; TEL (905) 387-9711 ext. 67699; FAX (905) 575-6326.

*The Practice Guidelines Initiative is sponsored by:
Cancer Care Ontario & the Ontario Ministry of Health and Long-term Care.*

*Visit http://www.cancercare.on.ca/access_PEBC.htm
for all additional Practice Guidelines Initiative reports.*

PREAMBLE: About our Practice Guideline Reports

The Practice Guidelines Initiative (PGI) is a project supported by Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care, as part of the Program in Evidence-based Care. The purpose of the Program is to improve outcomes for cancer patients, to assist practitioners to apply the best available research evidence to clinical decisions, and to promote responsible use of health care resources. The core activity of the Program is the development of practice guidelines by multidisciplinary Disease Site Groups of the PGI using the methodology of the Practice Guidelines Development Cycle.¹

This draft practice guideline report, which is based on a systematic review of evidence, is the result of the first three steps of the guideline development cycle. One of the 14 Provincial Disease Site Groups has discussed the best evidence available on the clinical topic in question and has developed clinical recommendations based on this evidence.

In the current step of the cycle, the practice guideline report has been sent to practitioners across Ontario for feedback. The Disease Site Group will review this feedback and modify the clinical recommendations where necessary. The resulting practice guideline report will then be submitted to the Practice Guidelines Coordinating Committee for formal approval.

Reference:

¹ Browman GP, Levine MN, Mohide EA, Hayward RSA, Pritchard KI, Gafni A, et al. The practice guidelines development cycle: a conceptual tool for practice guidelines development and implementation. *J Clin Oncol* 1995;13(2):502-12.

**For the most current versions of the guideline reports and information about the PGI and the Program, please visit the CCO Internet site at:
http://www.cancercare.on.ca/access_PEBC.htm
For more information, contact our office at:
Phone: 905-525-9140, ext. 22055
Fax: 905-522-7681**

Copyright

This guideline is copyrighted by Cancer Care Ontario; the guideline and the illustrations herein may not be reproduced without the express written permission of Cancer Care Ontario. Cancer Care Ontario reserves the right at any time, and at its sole discretion, to change or revoke this authorization.

Disclaimer

Care has been taken in the preparation of the information contained in this document. Nonetheless, any person seeking to apply or consult the practice guideline is expected to use independent medical judgment in the context of individual clinical circumstances or seek out the supervision of a qualified clinician. Cancer Care Ontario makes no representation or warranties of any kind whatsoever regarding their content or use or application and disclaims any responsibility for their application or use in any way.

FULL REPORT

I. QUESTION

Should bisphosphonates be used in men with hormone-refractory prostate cancer (HRPC) to:

1. Delay or prevent bone metastases in men without metastases?
2. Reduce skeletal-related events (e.g., bone fracture, spinal cord compression, requirement for radiotherapy or surgery to bone) in men with bone metastases?
3. Reduce pain or analgesic consumption in men with painful bone metastases?
4. Improve survival and quality of life?

II. CHOICE OF TOPIC AND RATIONALE

Prostate cancer is the most frequently diagnosed cancer in Ontario. It is the fourth most common cause of cancer death in Ontario and the third most common cause of cancer death in men (1). Bone metastases, the most common site of prostate cancer spread, occur in up to 75% of men with prostate cancer and produce significant morbidity including pain, pathologic fractures, and spinal cord compression (2). Docetaxel-based chemotherapy modestly improves survival and provides palliation for men with HRPC and metastases (3,4). In addition to chemotherapy, external beam radiotherapy, and radiopharmaceuticals (5) can also be used to palliate symptoms. Despite the presence of some palliative treatments with proven efficacy, the palliation and treatment of HRPC needs to be improved through the investigation of new agents and approaches.

Bisphosphonates, potent inhibitors of osteoclast function, have a major role in reducing the morbidity from bone metastases in breast cancer and multiple myeloma, tumours that produce predominantly lytic metastases (6,7). While prostatic bone lesions are predominantly osteoblastic, increased osteoclast activity and bone resorption play a major role in the skeletal morbidity of prostate cancer (8). A number of clinical trials examining the role of bisphosphonates in reducing the morbidity of prostatic bone metastases have now been completed. Therefore, the Genitourinary Cancer Disease Site Group (GU DSG) thought it was timely to conduct a systematic review of the evidence on bisphosphonate use in HRPC to derive appropriate recommendations for treatment.

III. METHODS

Guideline Development

This practice guideline report was developed by the Practice Guidelines Initiative (PGI) of Cancer Care Ontario's Program in Evidence-based Care (PEBC), using the methods of the Practice Guidelines Development Cycle (9). Evidence was selected and reviewed by two members of the PGI's GU DSG and methodologists. Members of the GU DSG disclosed potential conflict of interest information.

The practice guideline report is a convenient and up-to-date source of the best available evidence on the use of bisphosphonates for hormone-refractory prostate cancer, developed through systematic reviews and evidence synthesis. The body of evidence in this report is primarily comprised of mature randomized controlled trial data; therefore, recommendations by the DSG are offered. The report is intended to promote evidence-based practice. The Practice Guidelines Initiative is editorially independent of Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care.

External review by Ontario practitioners is obtained for all practice guideline reports through a mailed survey consisting of items that address the quality of the draft practice guideline report and recommendations, and whether the recommendations should serve as a

practice guideline. Final approval of the practice guideline report is obtained from the Practice Guidelines Coordinating Committee.

The PGI has a formal standardized process to ensure the currency of each guideline report. This process consists of the periodic review and evaluation of the scientific literature and, where appropriate, integration of this literature with the original guideline information.

Literature Search Strategy

The MEDLINE (OVID) (1980 through July 2004), EMBASE (1980 through 2004, week 32), CANCERLIT (OVID) (1980 through October 2002), and Cochrane Library databases (OVID) (2004, Issue 2) were searched using the following medical subject headings (MeSH) and text words (tw): “exp neoplasms” (MeSH), “cancer” (tw), “carcinoma” (tw), “tumo?r” (tw), “malignan:” (tw), “bone neoplasms/sc” (secondary), “bone metast:” (tw), “osseous metast:” (tw), “bone pain” (tw), combined with “exp diphosphonates” (MeSH), “bisphosphonate” (tw), “exp alendronate” (MeSH), “alendronate” (tw), “alendronic acid” (tw), “exp clodronic acid” (MeSH), “clodronic acid” (tw), “clodronate” (tw), “dichloromethylene” (tw), “exp etidronic acid” (MeSH), “etidronic acid” (tw), “etidronate” (tw), “exp ibandronate” (MeSH), “ibandronate” (tw), “ibandronic acid” (tw), “pamidronate” (tw), “aredia” (tw), “exp zoledronic acid” (MeSH), “zoledronic acid” (tw), “zoledronic acid” (tw), “zolendronate” (tw), and “zometa” (tw). Those terms were then combined with the search terms for the following publication types and study designs: practice guidelines, systematic reviews, meta-analyses, reviews, randomized controlled trials, and controlled clinical trials. The literature search was not restricted by language.

In addition, conference proceedings from the annual meetings of the American Society of Clinical Oncology (ASCO) (1995-2004) and the American Urological Association (AUA) (1995-2003) were searched for abstracts of relevant trials. The Canadian Medical Association Infobase (<http://mdm.ca/cpgsnew/cpgs/index.asp>) and the National Guidelines Clearinghouse (<http://www.guideline.gov/index.asp>) were also searched for existing evidence-based practice guidelines.

Relevant articles and abstracts were selected and reviewed by three reviewers, and the reference lists from those sources were searched for additional trials, as were the reference lists from relevant review articles.

Inclusion Criteria

Articles were selected for inclusion in this systematic review of the evidence if they met any of the following criteria:

1. They were published reports or abstracts of randomized controlled trials (RCTs) or meta-analyses that compared treatment with a bisphosphonate to placebo or no treatment (open control). RCTs or meta-analyses that compared different bisphosphonates (e.g., different doses, schedules, or routes of administration of the same bisphosphonate), or treatment with a bisphosphonate plus a co-intervention (i.e., hormonal therapy or chemotherapy) to the same treatment without bisphosphonate, were also eligible for inclusion.
2. They included patients with HRPC, where hormone-refractory was defined as the progression of stage IV disease or a rising prostate-specific antigen (PSA) with a castrate testosterone level. Trials that included multiple tumour types were eligible if they included HRPC patients and analyzed outcomes for those patients separately.
3. Results were reported by treatment group for at least one of the following outcomes: incidence of bone metastases in patients without bone metastases at the time of randomization, reduction of skeletal-related events, reduction in bone pain, or reduction in analgesic consumption in patients with bone metastases at the time of randomization, survival, or quality of life. Adverse effects were also an outcome of interest.

4. They were systematic reviews or evidence-based practice guidelines that addressed any of the four guideline questions.

Exclusion Criteria

Articles were excluded from this systematic review if they were RCTs that did not compare bisphosphonate treatment to a placebo or no treatment control arm (i.e., trials with active control arms were excluded).

Synthesizing the Evidence

The most frequently reported outcome in trials of bisphosphonates for HRPC was pain. Wong and Wiffen (10) describe two methods of pooling pain data: 1) in trials that report mean pain scores and standard deviations, the scores can be standardized and used as a summary statistic for quantitative synthesis, and 2) for trials that report proportions of patients with pain relief, odds ratios (OR) can be calculated and then pooled. Since a number of the trials included in this review were small and likely underpowered to detect significant differences in pain outcomes between trial arms, the GU DSG considered pooling the available pain data in a meta-analysis. Unfortunately, the trials included in this report were not amenable to pooling due to considerable variability in the measurement of pain across trials. Among the eight trials that evaluated pain relief, four trials (11-13) (total n=366, 301 from one trial) reported mean pain scores, three trials (14-16) (total n=335, 209 from one trial) reported proportions of patients with pain response, and one trial (17) (n=55) reported pain outcomes by both methods. Because it is not possible to statistically combine trials that report pain by different methods, only two meta-analyses of two different subsets of bisphosphonate trials would have resulted. The GU DSG did not view this approach to pooling as a reasonable option since the largest bisphosphonate trials (13,14) used different pain evaluation methods.

IV. RESULTS

Literature Search Results

Eighteen reports identified by the literature search met the inclusion criteria of this guideline and included three systematic reviews (two of which contained meta-analyses) (10,18,19), one practice guideline (20), and 14 reports (two in abstract form) describing 12 randomized trials (11-17,21-27). One of the systematic reviews (19) was omitted from this review because it included only one prostate cancer trial already captured by the literature search. Two trials were also excluded: one trial closed prematurely due to poor patient accrual (written communication with A. Heidenreich, January, 2003) (26), and a second trial had only accrued two patients at the time the abstract of that trial was published (27). Attempts were made to contact the authors of the second trial to obtain information regarding its status but those efforts were unsuccessful. Table 1 summarizes the 10 randomized trials included in this practice guideline report.

Six additional randomized trials were identified that evaluated bisphosphonates in multiple tumour types (28-33), but none of those reports presented outcome data separately for prostate cancer patients. The number of patients included in those trials ranged from four to 16. Trial authors were contacted to inquire about whether they had analyzed prostate cancer patient data separately but omitted those analyses from trial publications. For four of the six trials (28-30,33) authors confirmed that outcome data were not analyzed separately; therefore, the six trial publications were excluded from this report. Other notable randomized trials excluded from this review include three trials that did not contain a no-treatment or placebo-control arm (34-36).

Table 1. Randomized controlled trials included in this practice guideline report.

Bisphosphonate and comparison evaluated	Number of trials	Number of reports	First author, year (reference number)
Alendronate vs. no treatment	1	1	Dahut, 2001 (21)
Clodronate vs. placebo	5	7	Ernst, 2003 (14) Strang, 1997 (11) Kylmälä, 1997 (17)/Taube, 1994 (23) Adami, 1989 (12) Elomaa, 1992 (15)/Kylmälä, 1993 (24)
Etidronate vs. placebo	1	1	Smith, 1989 (16)
Pamidronate vs. placebo	2	1	Small, 2003 (13)
Zoledronic acid vs. placebo	1	2	Saad, 2002 (25)/Saad, 2004 (22)

Note: vs. – versus.

Previous Systematic Reviews and Meta-analyses

Two previous systematic reviews have reviewed evidence on bisphosphonate use in patients with HRPC. In 1998, Bloomfield (18) published a systematic review that examined the evidence for bisphosphonates to alleviate pain and reduce skeletal complications from bone metastases. The review summarized two small RCTs in patients with HRPC: one of oral clodronate (15) and one of oral and intravenous etidronate (16). From his review of those two trials, Bloomfield concluded that there was no evidence to support the use of either bisphosphonate to reduce skeletal complications or relieve bone pain and that bisphosphonates in prostate cancer required further clinical investigation.

A more recent systematic review and meta-analysis by Wong and Wiffen for the Cochrane Pain, Palliative Care and Supportive Care Group (10), also summarized evidence on bisphosphonates for bone metastases from multiple tumour types. The scope of their review was limited to the effectiveness of bisphosphonates for pain relief. Wong and Wiffen identified 25 eligible RCTs. Of those, four dealt specifically with prostate cancer (11,15-17) and included the two trials reviewed by Bloomfield (18). Three trials evaluated clodronate (11,15,17), and one trial evaluated etidronate (16). Although the primary meta-analysis pooled pain data across trials including patients with any primary neoplasm, subgroup analyses were pre-planned to examine the robustness of the primary meta-analysis results according to disease site. The proportion of patients with pain relief within 12 weeks of treatment was the outcome analyzed. Three of the four prostate cancer trials provided usable data for pooling (15-17). The review reported a non-significant difference in pain relief within 12 weeks between bisphosphonate and control arms (OR, 1.81; 95% confidence interval [CI], 0.82 to 4.02; p=0.5) among the three trials. Because those results reflect subgroup analyses and comprise a small number of patients (n=155), Wong and Wiffen appropriately did not derive any conclusions from that analysis regarding the effectiveness of bisphosphonates for pain relief in prostate cancer. The meta-analysis was updated in 2004, but no additional prostate cancer trials were included in the updated report (37).

Previous Evidence-based Practice Guidelines

In 2000, the Science Committee of the Association for Palliative Medicine of Great Britain and Ireland (APM) published a practice guideline addressing several aspects of bisphosphonate use, including the management of pain from bone metastases (20). The same four trials (11,15-17) included in the Wong and Wiffen review (10) also served to inform the APM guideline. Based on their review of those four trials, the guideline authors stated there was little evidence to support the use of bisphosphonates in prostate cancer for bone pain.

However, the final guideline recommendations supported using bisphosphonates in patients with any primary neoplasm suffering from pain due to bone metastases, where treatment with conventional analgesics, radiotherapy, or surgery is unsuccessful or inappropriate.

Randomized Controlled Trials

The 10 RCTs and the outcomes evaluated in each of those trials are listed in Table 2. All 10 RCTs evaluated bisphosphonate use in patients who had documented bone metastases at the time of randomization. The primary outcome evaluated in the majority of trials was the reduction of pain or analgesic consumption (eight trials). Other endpoints reported included the reduction of skeletal-related events, survival, quality of life, and adverse effects. A number of trials reported outcomes that assessed biochemical markers of bone metabolism (13,15,17,25). Although those endpoints provide useful information about the metabolic action of bisphosphonates, they were considered insufficient for determining treatment recommendations; therefore, outcomes of that nature were excluded from Table 2.

Table 2: Randomized controlled trials included in this practice guideline report: outcomes evaluated.

Trial First author, year (ref)	Trial evaluates the following:					Primary Outcome	Other Outcomes
	Delay or prevention of bone metastases	Reduction in SRE	Reduction of pain or analgesic consumption	Survival	QOL		
Dahut, 2001(21)	No	No	No	No	No	PSA response	Adverse effects
Ernst, 2003 (14)	No	No	Yes	Yes	Yes	Palliative response	Duration of palliative response Time-to-symptomatic progression PSA response Adverse effects
Kylmä, 1997 (17)	No	No	Yes	No	No	Pain	Clinical response Bone response Performance status change Adverse effects
Strang, 1997 (11)	No	No	Yes	No	No	Pain	None
Elomaa, 1992 (15)	No	No	Yes	Yes	Yes*	Pain	Response rate Adverse effects
Adami, 1989 (12)	No	No	Yes	No	No	Pain	None
Smith, 1989 (16)	No	No	Yes	No	No	Pain	Adverse effects
Small, 2003 (13)† [INT-05 and CGP 032]	No	Yes	Yes	No	Yes*	Pain	Skeletal morbidity rate Adverse effects

Trial First author, year (ref)	Trial evaluates the following:					Primary Outcome	Other Outcomes
	Delay or prevention of bone metastases	Reduction in SRE	Reduction of pain or analgesic consumption	Survival	QOL		
Saad, 2002 (25)	No	Yes	No†	Yes	Yes	SRE	Time-to-first SRE Skeletal morbidity rate Time-to-disease progression Bone response Adverse effects

Note: PSA – prostate-specific antigen, QOL – quality of life, ref – reference, SRE – skeletal-related events.

*This trial assessed patient mobility. The guideline authors considered this outcome an aspect of quality of life.

†This report represents two randomized trials, International Trial INT-05 and US Trial CGP 032.

‡This trial excluded patients with pain requiring strong narcotics at baseline. The guideline authors categorized this trial as assessing pain prevention.

Randomized Trials of Bisphosphonates in Men with Hormone-Refractory Prostate Cancer and Bone Metastases

Descriptions of the 10 RCTs are provided in Table 3. Five trials of clodronate (11,12,14,15,17), two trials of pamidronate (13), and one trial each of alendronate (21), etidronate (16), and zoledronic acid (25) form the evidence base of this review.

Trial Quality

Important aspects of trial quality, including method of randomization, degree of blinding, adequate description of treatment and control arms, completeness of follow-up, and analyses performed according to intent-to-treat (ITT) were examined for each randomized trial. Of the 10 RCTs, one trial was reported in abstract form only (21). That trial was a randomized phase II trial. Phase II trials are generally not designed or powered to test the effectiveness of interventions (38). Seven of the nine placebo-controlled trials stated a double-blind trial design, and one reported a single-blind design (Table 3). Two trials adequately described the method of patient randomization (14,25). Patient eligibility criteria were clearly stated in all but one trial (12), and six trials presented baseline demographic and clinical characteristics for treatment and control arms (13-15,17,25). Four of those trials commented that the randomization procedure achieved balance in the distribution of important baseline characteristics between trial arms (13,14,25). The statistical basis for the estimation of sample size and trial power was described in four trials (13,14,25), and two trials stated analyses were performed based on ITT (14,25). Another report also stated ITT analyses were performed; however, 28 patients were excluded from analyses due to protocol violations (13). In general, the reporting of the follow-up of patients in the trials was poor. Few trials provided detailed information on the numbers of patients who received the intended treatment and completed the trial protocol, and details explaining patient withdrawals or dropouts were rarely reported.

Trial Characteristics

The majority of trials recruited patients with HRPC, bone metastases, and pain (Table 3). There were only two trials where pain was not a trial entry eligibility criterion (21,25). Patient accruals ranged from 13 patients in the smallest trial (12) to 643 in the largest trial (25) and totalled 1497 evaluable patients.

Clodronate has been the most studied bisphosphonate in HRPC in terms of the number of trials; however, the five clodronate trials were relatively small, altogether including 404 evaluable patients. The largest clodronate trial by Ernst et al (14) was a multicentre, double-blind trial that randomized 209 patients to either intravenous clodronate every three weeks or

placebo. All patients in that trial received mitoxantrone-prednisone combination therapy. Strang et al (n=52) (11) and Adami and Mian (n=13) (12) have also assessed the short-term use of clodronate. Longer-term clodronate use has been examined in two trials conducted by the Finnish Prostate Cancer Group (15,17). Kylmäla et al (n=55) (17) and Elomaa et al (n=75) (15) both examined clodronate combined with estramustine phosphate. Alendronate and etidronate have been examined in one phase II trial (n=49) (21) and one small, placebo-controlled trial (n=51) (16), respectively.

The remaining two trials include the largest trials of bisphosphonates in HRPC conducted to date. Those trials evaluated the more potent bisphosphonates pamidronate (13) and zoledronic acid (25). Between February 1998 and November 1999, two multicentre randomized trials, International trial INT-05 and US trial CGP 032, recruited 140 and 238 patients, respectively, to assess the effectiveness of pamidronate in reducing bone pain and analgesic consumption from painful bone metastases. Both trials failed to accrue their target sample size. Because the trial eligibility criteria, route, dose, and scheduling of pamidronate, and the outcomes assessed in both trials, were almost identical, data from the trials were combined, and the published results were based on pooled data analyses (13). Between the two trials, 378 patients (350 evaluable) were randomized to either 90mg of intravenous pamidronate every three weeks for 27 weeks or placebo. Patients receiving hormonal therapy or chemotherapy at the time of randomization were allowed to continue this therapy after randomization so long as it had not been modified within six weeks prior to randomization.

In the zoledronic acid trial (25), 643 patients with bone metastases were randomly assigned to one of three trial arms: 4mg of intravenous zoledronic acid, 8mg of intravenous zoledronic acid, or placebo. Patients received zoledronic acid every three weeks for up to 15 months. Halfway through the trial treatment period, some patients in the 8mg zoledronic acid treatment arm developed renal toxicity. As a result, all patients in that arm received zoledronic acid at a reduced dose of 4mg (that trial arm is referred to as the 8/4mg arm in succeeding text). The proportion of patients experiencing at least one skeletal-related event was the primary endpoint of the trial. Two hundred and eight patients completed the study. Of those patients, 186 opted to continue in the trial for an additional nine months (total study time of 24 months). One hundred and twenty-two patients completed the extension phase of the trial (49 in 4mg arm, 37 in 8/4mg arm, and 36 in placebo arm). The longer-term efficacy results were presented in a subsequent trial report (22)

Table 3: Randomized trials of bisphosphonates in men with hormone-refractory prostate cancer and bone metastases: trial descriptions.

First author, year (ref)	Design	Patient population	No. of patients randomized/evaluable	Treatment groups	Route, dose, and frequency	Planned duration of treatment
<i>Alendronate</i>						
Dahut, 2001 (21) (abstract)	Randomized phase II	HRPC + bone metastases	52/49	I. Alendronate + H + KT II. H + KT	40mg oral od	Until disease progression or unacceptable toxicity
<i>Clodronate</i>						
Ernst, 2003 (14)	Placebo/ double blind	HRPC + bone metastases + pain	209/209	I. Clodronate + mito/pred II. Mito/pred + placebo	1500mg iv q 3 weeks	21 weeks*
Kylmäälä, 1997 (17)	Placebo/ double blind	HRPC + bone metastases + pain	57/55	I. Clodronate + EMP II. EMP + placebo	300mg iv x 5d, then 1600mg oral od	12 months
Strang, 1997 (11)†	Placebo/ double blind	HRPC + bone metastases + pain despite analgesic treatment	55/52	I. Clodronate II. Placebo	300mg iv x 3d, then 3200mg oral (1600mg bid)	4 weeks
Elomaa, 1992 (15)	Placebo/ no blinding	HRPC + bone metastases + pain despite daily analgesic use	75/NR	I. Clodronate + EMP II. EMP + placebo	3200mg oral od x 1mo, then 1600mg oral od	5 months
Adami, 1989 (12)	Placebo/ single blind	HRPC + bone metastases + pain, some received EMP	13/13	I. Clodronate II. Placebo	300mg iv od	2 weeks

First author, year (ref)	Design	Patient population	No. of patients randomized/evaluable	Treatment groups	Route, dose, and frequency	Planned duration of treatment
<i>Etidronate</i>						
Smith, 1989 (16)	Placebo/ double blind	HRPC + bone metastases + pain requiring analgesics	57/51	I. Etidronate‡ II. Etidronate‡ III. Etidronate‡ IV. Placebo‡	7.5 mg/kg iv x 3d, then 200mg oral bid 7.5 mg/kg iv x 3d, then placebo oral bid placebo iv x 3d, then etidronate 200mg oral bid iv and oral placebo	1 month§
<i>Pamidronate</i>						
Small, 2003 (13) [INT-05 and CGP 032]	Placebo/ double blind	HRPC + bone metastases + pain	378/350	I. Pamidronate II. Placebo	90mg iv q 3 weeks	27 weeks
<i>Zoledronic acid</i>						
Saad, 2002 (25)	Placebo/ double blind	HRPC + bone metastases not producing pain requiring strong narcotics	643/643	I. Zoledronic acid¶ II. Zoledronic acid¶ III. Placebo	4mg iv q 3 weeks# 8/4mg iv q 3 weeks#	15 months

Note: bid – twice daily, d – day, EMP – estramustine phosphate, H – hydrocortisone, HRPC – hormone-refractory prostate cancer, iv – intravenous, KT – ketoconazole, kg – kilogram, mg – milligram, mito – mitoxantrone; mo – month; No. – number, NR – not reported, od – once daily, pred – prednisone, PSA – prostate-specific antigen, q – every, ref – reference, x – times.

*In responding patients, prednisone and clodronate were continued until disease progression; mitoxantrone was discontinued after a cumulative dose of 140mg/m².

†This trial was closed prematurely due to difficulties in recruiting patients.

‡Six patients (one in group I, two in group II, one in group III, and two in group IV) were considered unevaluable because they failed to complete one month of treatment.

§Patients remained on original randomized treatment for at least one month. After one month, those who had not responded had the option of repeat treatment with open-label therapy (intravenous etidronate followed by oral etidronate). Patients with a response to initial randomized treatment remained on that therapy for up to six months, as long as they maintained evidence of response.

||This report represents a combined analysis of two randomized trials, International Trial INT-05 and US Trial CGP 032.

¶Three patients (one in group I and two in group II) never received zoledronic acid. These patients were included in the efficacy analysis according to intention-to-treat but were excluded from the safety analysis. One patient in the 8/4mg zoledronic acid treatment arm incorrectly received zoledronic acid at 4mg for the duration of the trial; this patient was included in the 8/4mg treatment group for the efficacy analysis and included in the 4mg treatment group for the safety analysis.

#Patient enrolment and treatment in this trial took place between June 1998 and January 2001. Initially, patients received zoledronic acid via a 5-minute 50ml iv infusion; however, this was amended to a 15-minute 100ml infusion in June 1999 to increase renal safety. A subsequent protocol amendment in June 2000 reduced the dose of the 8mg zoledronic acid treatment arm to 4mg because of renal toxicity (8/4mg treatment group).

Outcomes

The results of the 10 RCTs are summarized by outcome in Tables 4 through 7.

Pain

Nine trials involving 1399 evaluable patients assessed bisphosphonates for relieving pain or reducing analgesic consumption in men with HRPc and bone metastases (11-17,25) (Table 4). In all but one of those trials (25), pain was the primary efficacy variable. The means by which pain was measured was variable across trials. Pain outcomes were assessed using visual or linear analogue scales (11,12,16,17), the Present Pain Intensity (PPI) scale (14), and the Brief Pain Inventory (BPI) (13,25); the method of assessment was not specified in one trial (15). The frequency of pain assessment was also variable. Two trials assessed pain at a single time point after bisphosphonate treatment (12,16), while the remaining trials assessed pain at various multiple time points during and after treatment. For seven trials, trial reports indicated pain outcomes were patient reported (11,13,14,16,17,25). Analgesic use was evaluated in addition to pain in eight trials (12-17,25). One other trial reported assessing analgesic use; however, results for that outcome were not provided in the published trial report (11). Analgesic use was either measured by patient diaries and then converted to oral morphine equivalents (OME) (13,14) or by nominal scales that described the type and/or frequency of analgesic use (17,25). Four trials did not indicate how analgesic consumption was measured (11,12,15,16).

Clodronate

Four (11,14,15,17) of five clodronate trials found no significant difference in pain outcomes between clodronate and placebo trial arms.

In the largest trial (n=209), Ernst et al (14) 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 (or a greater than 50% decrease in analgesic score without an increase in PPI), in patients treated with mitoxantrone-prednisone and either clodronate or placebo. No significant difference in palliative response rates was detected between the two arms after seven cycles of treatment. When the PPI and analgesic scores were analyzed as separate outcomes and not as a composite measure, the change in both outcomes compared with baseline scores was also similar between arms. In an exploratory analysis, palliative response was analyzed while controlling for baseline PPI score. Results from a logistic regression analysis showed that among the 23% (n=49) of patients with moderate baseline pain (PPI of 3 or 4), patients treated with clodronate were more likely to achieve a palliative response compared with patients receiving placebo (OR, 4.6; 95% CI, 1.3 to 15.5; p=0.04). The palliative response rate for patients with moderate pain in the clodronate arm was 58% compared with 26% in the placebo arm.

Kylmäälä et al (17), Strang et al (11), and Elomaa et al (15) also did not detect significant improvements in pain with clodronate compared with placebo. Kylmäälä et al (17) (n=55) reported that the proportion of patients experiencing complete pain relief at one month after treatment was 25% in both clodronate and placebo trial arms. At three months, the proportion of those patients was 10% higher in the clodronate arm but the difference was not statistically significant. Strang et al (11) (n=52) found similar pain scores among patients treated with clodronate versus placebo. Changes in mean pain, and mean least and worst pain were similar in both arms at every time point that pain was assessed during the follow-up period of 32 days. Strang et al (11) also found a trend towards improved pain scores in patients with moderate pain. In a post hoc subgroup analysis, patients in both clodronate (n=6) and placebo arms (n=14) with a visual analogue score ≥ 50 mm showed significant reductions in mean pain from baseline (p<0.01). The reduction in mean pain was greater with clodronate than with placebo but the difference was not statistically significant. A similar trend was observed for mean worst pain. Elomaa et al (15) (n=75) reported that a greater proportion of patients receiving

clodronate in their trial were free of pain at one, three, and six months compared with patients allocated to placebo, with the most marked difference between trial arms occurring at one month (34% versus 18% of patients); however, none of those differences were statistically significant. A similar pattern of response was noted for the proportion of patients requiring no analgesics.

The only trial to report statistically significant improvements in pain relief with clodronate was the trial by Adami and Mian (n=13) (12). Both pain relief and analgesic consumption were significantly reduced ($p<0.01$) after two weeks in patients receiving intravenous clodronate (n=7) compared with patients receiving placebo (n=6). The trial was terminated early due to the trial findings, and patients assigned to the placebo arm were then put on maintenance therapy consisting of intravenous clodronate.

Etidronate

Smith (16) (n=51) 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. The number of patients with significant subjective pain improvement, minor pain improvement, and reductions in analgesic use at one month were comparable between the four treatment groups.

Pamidronate

The pooled analysis of the two pamidronate trials by Small et al (13) represents the largest bisphosphonate trial assessing pain relief. The trial measured BPI pain score changes from baseline at nine (n=301) and 27 weeks (n=218) and considered a three-point difference in BPI pain score clinically significant. No statistically or clinically significant differences in BPI pain scores (i.e., least, average, and worst BPI score) were detected at either time point between evaluable patients receiving pamidronate and placebo. Analgesic consumption was also comparable at both evaluation time points.

Zoledronic Acid

Patient eligibility in the zoledronic acid trial (n=643) (25) did not require patients to have pain at trial entry, and patients were excluded if they had pain requiring strong narcotic therapy. However, pain was measured at baseline and every six weeks during the trial as part of a quality of life assessment. At the start of the trial, the proportion of patients with pain was 73% for both the 4mg zoledronic acid and placebo trial arms and 79% for the 8/4mg zoledronic acid arm. Mean baseline BPI scores in each treatment group were low, 2.0 in the 4mg arm, 2.5 in the 8/4mg arm, and 2.1 in the placebo arm. Over the 15-month follow-up period, BPI pain scores increased in all trial arms except at three months, where both zoledronic acid arms showed a decrease in pain scores compared with placebo. 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 4mg and 8/4mg zoledronic acid arms, respectively. For patients who completed the extension phase of the trial (n=122), at 24 months the mean change in BPI scores from baseline for the 4mg and 8/4mg zoledronic acid arms were 0.58 ($p=0.024$) and 0.54 ($p=0.013$) versus 1.05 with placebo (22).

Table 4: Pain – Randomized trials of bisphosphonates versus placebo in men with hormone-refractory prostate cancer and bone metastases.

First author, year (ref), total n	Measurement tool for pain and analgesic use	Pain/analgesic use assess't interval	Definition of pain reduction/relief	Treatment groups (n)	Baseline pain/analgesic use			Results									
					% of patients with:	Clodronate	Placebo	% of patients with:	Clodronate			Placebo					
Ernst, 2003 (14), n=209	Pain: 6-pt PPI,* assessed by patient Analgesic use: diary, assessed by patient	q 3 weeks	Palliative response: 2 pt reduction in PPI without increase in analgesic score or disease progression†; or ≥ 50% decrease in analgesic score without increase in PPI	I. Clodronate iv (104) II. Placebo (105)	% of patients with:			% of patients with:	Clodronate	Placebo	Palliative response	45	39	≥ 2-pt reduction in PPI	33	26	
					PPI 1 or 2	75	78										50% decrease in analgesic score
					PPI 3 or 4	25	22										
					Median OME	70	57										
								No significant difference between groups in palliative response, PPI, or analgesic scores compared with baseline.									
Kylmäla, 1997 (17), n=55	Pain: 5-pt VOS‡, assessed by physician; 5-pt VAS‡, assessed by patient Analgesic use: 4-pt scale§	At 1, 3, 6, and 12 months	Pain: change from baseline in VAS pain scores at 1, 3, 6, and 12 months Analgesic use: change from baseline in analgesic use at 1, 3, 6, and 12 months	I. Clodronate iv + oral (28) II. Placebo (27)	% of patients with VAS score of :			% of patients with VAS score of:	Clodronate	Placebo	0	36	32	21	22	22	19
					0	21	7										
					1	46	44				1	32	14	14	37	19	11
					2	18	44				2	11	7	4	26	30	19
					3	11	4				3	7	18	14	11	15	4
					4	0	0				4	0	0	7	0	0	4
					Analgesic score of:			% of patients with analgesic score of:	Clodronate	Placebo	0	46	29	21	30	19	19
					0	36	11										
					1	39	48				1	21	21	14	26	19	11
					2	21	37				2	18	11	11	33	30	11
					3	4	4				3	4	14	14	7	15	11
								At 1 month, 25% of patients were free of pain in both groups; at 3 months, proportion of patients free of pain was 10% higher in the clodronate group; at 1 month, proportion of patients without analgesics was 11% higher in the clodronate group; none of the observed differences between groups were statistically significant.									

First author, year (ref), total n	Measurement tool for pain and analgesic use	Pain/analgesic use assess't interval	Definition of pain reduction/relief	Treatment groups (n)	Baseline pain/analgesic use			Results
Strang, 1997 (11), n=52	Pain: 10cm VAS, assessed by patient Analgesic use: NR	At d1-4, 11, 18, 25, and 32	Mean pain intensity and mean pain intensity during the best and worst periods	I. Clodronate iv + oral (25) II. Placebo (27)	Clodronate	Placebo	NR No significant difference in mean pain intensity or mean pain intensity during best and worst periods between groups during 32-day follow-up period	
					Mean pain: 39 Mean least pain: 13 Mean worst pain: 53	53 18 68		
Elomaa, 1992 (15), n=75	Pain: NR Analgesic use: NR	At 1, 3, and 6 months	Pain: proportion of patients with and without pain at 1, 3, and 6 months Analgesic use: proportion of patients without analgesics at 1, 3, and 6 months	I. Clodronate Oral + EMP (36) II. EMP + placebo (39)	All patients had pain at the start of the trial, degree of baseline pain was NR			% of patients with no pain at 1, 3, and 6 months: 1 34 18 3 29 4 6 18 15 No analgesia at: 1 38 18 3 23 12 6 18 23 No significant difference in pain or analgesic use between groups at 1, 3, or 6 months.
Adami, 1989 (12), n=13	Pain: 20cm VAS Analgesic use: NR	2 weeks	Pain: mean change in pain score from baseline at 2 weeks Analgesic use: mean change in analgesic use from baseline at 2 weeks	I. Clodronate iv (7) II. Placebo (6)	Clodronate	Placebo	Mean pain score at 2 weeks: 2.1¶¶ 11.9¶¶ Mean analgesic score at 2 weeks: 0.2¶¶ 3.6¶¶ Significant difference between groups in both mean pain score (p<0.01) and mean analgesic score (p<0.01) at 2 weeks.	
					Mean pain score: 15.7¶¶ Mean analgesic score: 4.1¶¶	13.2¶¶ 3.1¶¶		

First author, year (ref), total n	Measurement tool for pain and analgesic use	Pain/analgesic use assess't interval	Definition of pain reduction/relief	Treatment groups (n)	Baseline pain/analgesic use			Results
Saad, 2002 (25), n=643	Pain: BPI††, assessed by patient Analgesic use: 4-pt§§ nominal scale, assessed by physician	q 6 weeks	Pain: mean increase in BPI pain score from baseline at 15 months Analgesic use: change from baseline in analgesic score at 15 months	I. Zoledronic acid iv 4mg (214) II. Zoledronic acid iv 8/4mg (221) III. Placebo (208)	Mean BPI score: % of patients with pain at baseline:	Zoledronic acid I. 2.0 II. 2.5 I. 73 II. 79	Placebo III. 2.1 III. 73	Mean increase (95% CI) from baseline in BPI: 4mg vs. placebo 0.58 (0.29-0.87) No significant difference 8/4mg vs. placebo 0.43 (0.16-0.70) Significant difference (p=0.026) Placebo 0.88 (0.61-1.15)

Note: assess't – assessment, BPI – Brief Pain Inventory, cm – centimetre, d – day, EMP – estramustine phosphate, iv – intravenous, LAS – linear analogue scale, mg – milligram, n – number, NR – not reported, OME – oral morphine equivalent, PPI – Present Pain Intensity scale, pt – point, q – every, ref – reference, VAS – visual analogue scale, VOS – visual ordinal scale, vs. – versus.

*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 VOS/VAS: 0=no pain to 4=intolerable pain.

§4-point analgesic score: 0=no analgesic drugs, 1=non-narcotic analgesic drugs < 3 times per day, 2=non-narcotic analgesic drugs > 3 times per day, 3=narcotic analgesic drugs.

||Mean pain intensity was significantly higher (p=0.02) in the placebo group at baseline.

¶Estimated from curve.

#This report represents a combined analysis of two randomized trials, International Trial INT-05 and US Trial CGP 032.

**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.

§§4-pt analgesic scale: 0=none, 1=minor analgesics, 2=tranquilizers and antidepressants, 3=mild narcotic, 4=strong narcotic.

Skeletal-Related Events

Skeletal-related events have been evaluated in three trials involving 993 patients (13,25) (Table 5), one testing zoledronic acid and two testing pamidronate. In the zoledronic acid trial (25), skeletal-related events were reported as a composite measure and prospectively 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 (13) employed a similar definition but also included hypercalcemia and the need for a spinal orthotic brace.³ Change in antineoplastic therapy was not included as a skeletal-related event in the pamidronate trials.

Zoledronic Acid

Saad et al (25) (n=643) detected a statistically significant reduction in the occurrence of skeletal-related events after 15 months of zoledronic acid treatment, but the observed benefit was only significant when zoledronic acid was given at a dose of 4mg. Compared with placebo, where the incidence of skeletal-related events was approximately 44%, 33% (p=0.02) and 39% (p=0.2) of patients in the 4mg and 8/4mg zoledronic acid trial arms, respectively, had a skeletal-related event during the trial. Similar results were observed for the incidence of all pathological fractures, although there were no differences in the incidence of vertebral and non-vertebral fractures by treatment group. In terms of non-fracture skeletal-related events, except for a change in antineoplastic treatment, which was required more frequently in the 8/4mg zoledronic acid arm, the proportions of patients needing radiation or surgery to bone, and having spinal cord compression, were less with either dose of zoledronic acid than placebo. None of those differences, however, were statistically significant. Saad et al (25) also assessed time-to-first skeletal-related event. The median time-to-first skeletal-related event was not reached for patients in the 4mg zoledronic acid arm and therefore was estimated to be 14 months, which was a significantly longer time period compared with placebo (10.7 months, p=0.01). Patients in the 8/4mg zoledronic acid arm had a median time-to-first skeletal-related event that was not significantly different from placebo. At 24 months, the percentage of patients with an event during the trial was 38% in the 4mg arm (p=0.028) and 41% in the 8/4 mg arm (p=0.129) versus 49% with placebo; the mean annual incidence of events in each of those arms was 0.77 (p=0.005), 1.05 (p=0.098) and 1.47, respectively (based on 122 patients completing the extension phase of the trial) (22). Median time-to-first skeletal-related event was reached for both treatment groups during the extension phase of the study and was significantly longer for patients treated with 4mg of zoledronic acid (but not 8/4mg) than placebo (p=0.009) (488 days [4mg], 363 days [8/4mg], 321 days [placebo]).

Pamidronate

In contrast to the zoledronic acid trial, Small et al (13) (n=350) detected no difference in the proportion of patients with skeletal-related events at nine or 27 weeks between pamidronate and placebo. At nine weeks, 12% and 11% of patients in the pamidronate and placebo arms had a skeletal-related event. At 27 weeks, the proportion of patients experiencing a skeletal-related event was 25% in both trial arms.

³ Because only one of the two pamidronate trials considered the need for an orthotic brace as a skeletal-related event, rates for that event were not provided in the trial publication (13) and therefore are missing from Table 5.

Table 5: Skeletal-related events - Randomized trials of bisphosphonates versus placebo in men with hormone-refractory prostate cancer and bone metastases.

First author, year (ref), total n	Treatment groups (n)	Any SRE as defined by trial* (% of patients)	Median time-to-first SRE* (months)	% of patients with type of skeletal-related event*:							
				Pathologic fracture			Radiation to bone	Surgery to bone	Spinal cord compression	Change in antineoplastic therapy	Hypercalcaemia
				All	vertebral	non-vertebral					
Saad, 2002 (25), n=643	Zoledronic acid iv 4mg (n=214)	33 (p=0.021)	14† (p=0.011)	13 (p=0.015)	4	10	23	2	4	5	NR
	Zoledronic acid iv 8/4mg (n=221)	39	12.1	15	8	10	24	3	5	8	
	Placebo (n=208)	44	10.7	22	8	16	29	3	7	7	
Small, 2003 (13), n=350‡ [INT-05 and CGP 032]	Pamidronate iv (n=169)	9 wks: 12 27 wks: 25	NR	NR	9 wks: 3 27 wks: 7	9 wks: 4 27 wks: 8	For pain relief: 9 wks: 7 27 wks: 15 To prevent fracture: 9 wks: 4 27 wks: 5	9 wks: 1 27 wks: 3	9 wks: 2 27 wks: 3	NR	9 wks: 0 27 wks: <1
	Placebo (n=181)	9 wks: 11 27 wks: 25	NR	NR	9 wks: 1 27 wks: 6	9 wks: 3 27 wks: 7	For pain relief: 9 wks: 6 27 wks: 16 To prevent fracture: 9 wks: 2 27 wks: 4	9 wks: 2 27 wks: 3	9 wks: 0 27 wks: 2		9 wks: <1 27 wks: 1

Note: iv – intravenous, mg – milligram, n – number, NR – not reported; ref – reference, SRE – skeletal-related event, wks – weeks.

*Statistical comparison is treatment group vs. placebo; only statistically significant differences are presented in table.

†The time-to-first skeletal-related event was not reached for patients who received zoledronic acid at 4mg; therefore time-to-first skeletal-related event was considered to be at least 420 days (based on the estimated event rate of <50% at day 420, which was the end of treatment).

‡This report represents a combined analysis of two randomized trials, International Trial INT-05 and US Trial CGP 032.

Survival

Three trials have evaluated whether treatment with a bisphosphonate improves overall survival in patients with HRPC and bone metastases (14,15,25). Survival was studied as a secondary endpoint in all three trials; results from those trials are summarized in Table 6.

Clodronate

Both Ernst et al (14) and Elomaa et al (15) have reported on survival outcomes in patients treated with clodronate versus placebo. In both trials, median survival times with clodronate were not significantly different from placebo. Ernst et al (14) also assessed median time-to-disease progression and found no difference in that outcome between arms.

Zoledronic Acid

In the zoledronic acid trial (25), median survival time was longer in patients receiving 4mg of zoledronic acid but was not statistically different compared with patients in both the 8/4mg zoledronic acid and placebo trial arms. Median time-to-disease progression was also equivalent in the three trial arms. Survival data were not presented for the extension phase of the trial (22).

Table 6: Survival - Randomized trials of bisphosphonates versus placebo in men with hormone-refractory prostate cancer and bone metastases.

First author, year (ref), total n	Treatment groups (n)	Median survival in months*		Median time-to-disease progression in months*	
Ernst, 2003 (14), n=209	Clodronate iv (n=104)	10.8	HR = 0.95 (95% CI, 0.71-1.28) (p=0.73)	5†	HR = 1.24 (95% CI, 0.93-1.64) (p=0.14)
	Placebo (n=105)	11.5		4†	
Elomaa, 1992 (24)‡, n=75	Clodronate oral + EMP (n=36)	10 (p=NS)		NR	
	Placebo + EMP (n=39)	12			
Saad, 2002 (25), n=643	Zoledronic acid iv 4mg (n=214)	18.2 (p=0.09)		2.8 (p=NS)	
	Zoledronic acid iv 8/4mg (n=221)	13.6 (p=0.39)		2.8 (p=NS)	
	Placebo (n=208)	15.5		2.8	

Note: CI – confidence interval, EMP – estramustine phosphate, HR – hazard ratio, iv – intravenous, mg – milligram, n – number, NR – not reported, NS – not significant, ref – reference, vs. – versus.

*Statistical comparison is treatment vs. placebo.

†Symptomatic disease progression, defined as the time from the date of randomization to the date of progression from pain or other symptoms.

‡Median survival data for the trial were taken from the Kylmäla et al, 1993 publication (24).

Quality of Life

Two trials have prospectively examined quality of life associated with bisphosphonate treatment in HRPC using validated questionnaires or instruments. Both trials assessed quality of life at baseline and during and post-bisphosphonate treatment (14,25). Three other trials have reported on mobility outcomes (13,15).

Clodronate

In the Ernst et al trial (n=209) (14), quality of life was assessed using the validated Prostate Cancer-Specific Quality of Life Instrument (PROSQOLI). The PROSQOLI is comprised of nine linear analogue scales that measure different aspects of patient quality of life including pain, physical activity, fatigue, appetite, constipation, passing urine, family/marital relationships, mood, and overall well-being. A quality of life response to clodronate was defined by the authors as a 1cm improvement from baseline on the 10cm visual analogue scale for overall well-being, with a response maintained for at least two successive visits not less than three weeks apart. Quality of life assessment was carried out until symptomatic (pain or other symptoms) progression. During the trial, a quality of life 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 quality of life domains with the exception of pain. Improvement in quality of life domains was observed in both treatment groups; however, for the pain domain, scores were improved significantly with clodronate compared with placebo (p=0.02).

In the trial by Elomaa et al (n=75) (15), improvements in mobility were observed after one month of clodronate therapy. At one month, 30% and 20% of patients, respectively, in the clodronate and placebo arms were evaluated as ambulatory; however, that improvement was only temporary, with 40% of patients achieving ambulatory status at three months in each treatment group.

Pamidronate

Small et al (13) also assessed patient mobility (n=350). Mobility was measured by the number of seconds it took patients to walk 10 feet and the number of steps required to turn left 360 degrees. At nine and 27 weeks, there were no significant differences in the change from baseline in mobility measurements between the pamidronate and placebo trial arms.

Zoledronic Acid

Quality of life assessment in the zoledronic acid trial (25) consisted of patient performance status (Eastern Cooperative Oncology Group [ECOG]), two quality of life questionnaires, including the Functional Assessment of Cancer Therapy-General (FACT-G) and the Euro Quality of Life (EuroQol) EQ-5D, as well as pain scores and analgesic consumption, which have been previously discussed. Performance status assessment and quality of life questionnaires were completed at enrolment and every three months during the trial. The efficacy of bisphosphonate treatment on those indicators was measured by comparing changes from baseline in mean FACT-G and EuroQol scores and performance status between the three treatment groups (n=643) at 15 months. Saad et al (25) reported that performance status scores increased and quality of life questionnaire scores decreased over the duration of the trial from baseline, with no statistically significant differences observed among the treatment groups. Quality of life data were not presented for the extension phase of the trial (22).

Adverse Effects

Table 7 lists the adverse effects reported in randomized trials of bisphosphonates in men with HRPC and bone metastases. Toxicity data were provided in eight of the 10 randomized

trials (13-17,21,25) and were generally not reported by grade of severity in trial reports. Overall, bisphosphonates were generally well tolerated in patients, with the majority of trials reporting only mild toxicity occurring in equal proportions of patients treated with bisphosphonate and placebo. The most frequently reported adverse event was nausea and/or vomiting, which occurred in 9% to 33% of patients in three trials of clodronate (14,15,17) and 18% of patients in the etidronate trial (16). Higher rates of nausea/vomiting were seen with pamidronate (45%) and zoledronic acid (4mg, 58%; 8/4mg, 82%); however, in all of those trials, the rates of nausea/vomiting in the treatment arms were comparable with placebo (13,25). Other common adverse effects associated with both pamidronate and zoledronic acid treatment were bone pain, anorexia, constipation, anemia, and fatigue. 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. Nephrotoxicity was also increased with zoledronic acid. Grade 3 serum creatinine increases and renal function deterioration (15%, 21%, and 12% in the zoledronic acid 4mg, 8/4mg, and placebo arms, respectively) occurred in a greater proportion of patients treated with zoledronic acid compared with placebo, although the differences were statistically non-significant. Three trials reported that the percentage of patients discontinuing treatment because of toxicity was similar among trial arms (13,14,25). No toxic deaths were reported in any of the bisphosphonate trials. Saad et al reported that the incidence of adverse effects and the rates of study discontinuation due to those effects were similar between trial arms during the extension phase of the trial (22).

Table 7: Adverse effects - Randomized trials of bisphosphonates versus placebo or no treatment in men with hormone-refractory prostate cancer and bone metastases.

First author, year (ref)	Reported toxicity	Treatment groups % of patients unless otherwise specified	
Dahut, 2001 (21)	Nausea/vomiting Edema Fatigue Dry skin/mouth Sticky skin syndrome Headache Esophagitis	Alendronate* yes/no	No treatment* yes/no
		yes	yes
		yes	yes
		yes	yes
		yes	yes
		yes	yes
		yes	yes
		yes	no
Ernst, 2003 (14)	Grade 3/4 Granulocytopenia Anemia Thrombocytopenia Cardiovascular Nausea/vomiting Headache Shortness of breath Infection	Clodronate	Placebo
		13	13
		8	5
		2	4
		0	3
		9	7
		4	<1
		4	7
		7	3
Kylmälä, 1997 (17)	Nausea	Clodronate†	Placebo†
		33	40
Elomaa, 1992 (15)	Nausea, diarrhea	Clodronate	Placebo
		8	18

First author, year (ref)	Reported toxicity	Treatment groups % of patients unless otherwise specified	
Smith, 1989 (16)	Mild stomach cramping and nausea	Etidronate	Placebo
		18‡	25
Small, 2003 (13)§ [INT-05 and CGP 032]	Anemia	Pamidronate	Placebo
	Fever	21	20
	Nausea	18	8
	Vomiting	28	22
	Diarrhea	17	16
	Constipation	12	9
	Fatigue	22	21
	Weakness	23	19
	Anorexia	14	13
	Weight decrease	23	23
	Dizziness	18	11
	Dyspnea	7	5
	Urinary tract infection	12	14
	Bone pain	7	11
		43	39
Saad, 2002 (25)		Zoledronic acid	Placebo
	Anemia	4mg	8/4mg
	Fever	27	28
	Nausea	20	22
	Vomiting	36	53
	Diarrhea	22	29
	Constipation	17	16
	Fatigue	34	39
	Myalgia	33	31
	Weakness	25	24
	Anorexia	21	23
	Weight decrease	20	25
	Edema, lower limb	17	17
	Dizziness	19	22
	Bone pain	18	10
	Grade 3/4 hypocalcemia	51	61
	Grade 3/4 decrease in hemoglobin	2	2
	Grade 3 increases in creatinine	5	10
		3	2
			NR
			4
			1

Note: mg – milligram, NR – not reported, ref – reference.

*The adverse events reported in this trial were generally considered mild and occurring in both trial arms; the percentage of patients experiencing specific adverse events in each trial arm was not reported.

†7% and 4% of patients in the clodronate and placebo arms discontinued treatment due to nausea.

‡ Nausea was reported for the three etidronate trial arms combined.

§This report represents a combined analysis of two randomized trials, International Trial INT-05 and US Trial CGP 032.

V. INTERPRETIVE SUMMARY

Interpreting the 10 RCTs of bisphosphonates for HRPC is complex due to the heterogeneity in patient populations, the bisphosphonates studied, and the outcomes assessed, as well as the methodological limitations of some of the trials.

Pain

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 (11-17). The largest randomized trial of bisphosphonates (n=643), the zoledronic acid trial (25), included pain as a secondary outcome but specifically excluded men with pain requiring strong narcotics at baseline. As a result, the baseline level of pain in that trial was low. Therefore, the zoledronic acid trial was essentially a trial of pain prevention.

Pain Prevention

In the zoledronic acid trial (25), men in the 8/4mg zoledronic acid arm (n=221) had a statistically significant lower rise in their mean pain scores from baseline at 15 months compared with men receiving placebo (n=208). At 24 months the rise in mean pain scores was statistically significantly lower for men in both the 4 mg and 8/4 mg arms. Although statistically significant, the actual difference in rise on a 10-point scale was less than one point at both 15 and 24 months. Large trials examining pain can show statistically significant differences when mean pain scores are considered, even when there are no clinically significant differences (10). This seems to be the case in the zoledronic acid trial, where the efficacy of zoledronic acid in preventing pain appears to be clinically insignificant.

Pain Reduction

The eight trials that examined pain reduction by bisphosphonates were highly heterogeneous in their methodologies for measuring pain and analgesic consumption, the duration and frequency of pain assessment, baseline levels of pain, and in whether bisphosphonates were administered alone or in combination with chemotherapy. Only one trial, the small trial by Adami and Mian (n=13) (12), which evaluated intravenous clodronate, showed a statistically and clinically significant reduction in pain in the bisphosphonate arm. The positive findings of that trial should be interpreted cautiously, however, as important details about the conduct of the trial (e.g., patient recruitment and eligibility, outcome measures, randomization procedures, and methods of statistical analysis) were not reported. Parameters such as those provide an indication of trial quality and the robustness of trial results. That fact, combined with the trial's single-blind design, small sample size, and short duration of follow-up (two weeks) casts doubt on the validity of the trial's findings.

The combined analysis of the two pamidronate trials represents the largest randomized trial of a bisphosphonate for pain reduction (n=350) (13). That analysis failed to demonstrate a statistically or clinically significant reduction in pain with pamidronate. Although the trial was negative, trial limitations should be noted. First, whether an appropriate ITT analysis occurred is unclear, since only 350 of 378 patients randomized were included in the ITT efficacy analysis. Second, co-intervention with chemotherapy could have had a major influence on the pain outcomes of patients in the trial. Unfortunately, the trial report does not indicate how often chemotherapy was used or whether attempts were made to control for this potentially confounding co-intervention.

Despite the fact that seven of the eight pain reduction trials did not show any statistically significant benefits, the following points should also be considered:

1. Two clodronate trials, Strang et al (11) and Ernst et al (14), have both demonstrated improvements in pain in the bisphosphonate arms of their trials in subsets of men with moderate pain at baseline (the improvement was statistically significant in the Ernst et al

trial). Those findings were not based on pre-planned subgroup analyses in either trial, but in the Ernst et al trial the subgroup analysis was based on an a priori stratification.

2. Overall quality of life estimates in the Ernst et al trial (14) were not significantly different between clodronate and placebo arms (see below), but the pain domain of quality of life was significantly better with clodronate.
3. Of the seven negative bisphosphonate trials, four had fewer than 100 patients (11,15-17), and three (14,15,17) demonstrated interesting trends suggesting a benefit for clodronate that was not statistically significant. The negative trials were likely underpowered; therefore, treatment effects possibly existed but the trials were too small to detect them.

To summarize the data from the five clodronate trials, one was positive but methodologically flawed (12), three showed statistically non-significant trends for clodronate providing better pain relief (14,15,17), and two showed pain improvement in subgroups of patients with moderate pain at baseline (11,14). The subgroup analyses involved a small number of patients (17% [69/404] of evaluable patients from the five clodronate trials, and 9% [69/756] if all eight trials evaluating pain relief are considered); however, *all* the clodronate trials showed some trend indicating that this bisphosphonate could improve pain in men with HRPC and painful bone metastases.

Skeletal-Related Events

Three trials have addressed the impact of bisphosphonates on skeletal-related events (13,25). The large zoledronic acid trial (n=643) (25) demonstrated a statistically significant reduction in the proportion of patients experiencing a skeletal-related event, and median time-to-first skeletal-related event was significantly longer with zoledronic acid than placebo. The important question is whether those reductions in events were clinically significant. This question can be answered by considering the magnitude of the reduction observed and the types of skeletal-related events that were prevented.

The magnitude of reduction in the rate of skeletal-related events is dependent on the method of statistical analysis used. In the zoledronic acid trial (25), there was an 11% absolute reduction in skeletal-related events (44% → 33%, number needed to treat [NNT] = 9), or a 25% relative risk reduction when the 4mg zoledronic acid arm was compared with the placebo arm. However, if the 4mg and 8/4mg trial arms are considered together, which improves the statistical power of the comparison (39), the absolute reduction in skeletal-related events is actually 8% (44% → 36%, NNT=12); at 24 months, the absolute reduction in skeletal-related events is 9% (49% → 40%) (22). The delay in median time-to-first skeletal-related event when both zoledronic acid arms are combined is 102 days (321 days → 423 days). Those reductions are clinically significant when considered in isolation, but they must be viewed within the context of the toxicities associated with treatment and the lack of a quality of life benefit (see the discussion below on quality of life).

The other relevant question is whether the types of skeletal-related events that were prevented were actually clinically meaningful. Vertebral fractures, whether clinically significant or only apparent on imaging studies, were considered a skeletal-related event in the zoledronic acid trial (25). In the initial trial report, the authors addressed the issue that reduction in vertebral fractures observed only in radiographs would be of limited clinical significance (25). However, subsequent to this report, Saad et al (40) determined that, compared with placebo, zoledronic acid at 4mg reduced the number of bone fractures requiring medical intervention from 10% to 3%. When only those fractures were considered in the analysis of skeletal-related event rates there was still a statistically significant reduction (p=.029). Indeed, when all vertebral fractures were excluded from the analysis the absolute reduction in skeletal-related events remained exactly the same at 8% (placebo 42%, zoledronic acid 4mg and 8/4mg 34%,

p=0.048, data on file with Novartis).⁴ Therefore, the inclusion of vertebral fractures as a skeletal-related event did not affect the clinical significance of the findings of the trial.

The combined analysis of the two randomized trials of pamidronate did not demonstrate a reduction in skeletal-related events (13). The patients included in those two trials had more advanced prostate cancer (i.e., higher rates of previous skeletal-related events and higher mean PSA levels), and the lack of a reduction was possibly related to the patient population.

Quality of Life

The two trials that had a formal analysis of quality of life (14,25) were both large randomized trials. In the Saad et al trial (n=643) (25), the quality of life of patients on zoledronic acid did not differ from those on placebo. That finding may be attributable to a number of toxicities such as nephrotoxicity, fatigue, anemia, myalgia, fever, and lower limb edema that were increased in the zoledronic acid arm at a rate comparable to the reduction of skeletal-related events (39) or may be an indication that the quality of life instruments used in the trial were not adequate for that patient population. The use of available validated prostate cancer-specific quality of life instruments (e.g., PROSQOLI) might have given a better representation of quality of life changes than the generic instruments used in the trial. In the Ernst et al (14) trial (n=209), overall quality of life was not significantly improved with clodronate.

Survival

The three trials that presented survival data did not detect a survival benefit with bisphosphonates. There was a non-significant trend toward increased survival in the 4mg zoledronic acid arm of the Saad et al trial (25). Survival was not the primary outcome of any of these trials, and although two of the trials were large (14,25), they were likely underpowered to detect a survival difference even if it existed.

VI. ONGOING TRIALS

The Physician Data Query (PDQ) clinical trials database on the Internet (http://www.cancer.gov/search/clinical_trials/) was searched for reports of new or ongoing trials. The GU DSG did not identify any ongoing RCTs evaluating bisphosphonates in men with HRPC.

VII. DISEASE SITE GROUP CONSENSUS PROCESS

Developing a recommendation for the use of bisphosphonates in HRPC posed particular challenges for the GU DSG. Unlike other disease sites such as breast cancer (41) and myeloma (42), where the evidence base for bisphosphonate use is much larger and relatively consistent, the evidence base for bisphosphonate use in HRPC is comparatively smaller and more conflicting. Evidence from those other sites suggests that there is likely a class effect of bisphosphonates in reducing pain and skeletal-related events in patients with bone metastases. However, it is difficult to justify a similar class effect for men with HRPC and bone metastases from the available evidence. Consequently, the recommendations formed by the GU DSG were restricted to the use of different bisphosphonates in particular groups of patients. The GU DSG derived a set of draft recommendations out of discussions of the following issues:

a) Choice of bisphosphonate: Because randomized trials have evaluated bisphosphonate use in two distinct groups of men, the GU DSG felt strongly that separate recommendations for those groups of patients were required versus extrapolating the evidence to all patients with HRPC. Zoledronic acid has only been evaluated in patients with asymptomatic or minimally

⁴ The trial data was provided by Novartis in response to a request made by the guideline authors for clarification regarding the analysis of skeletal-related events.

symptomatic bone metastases; in those patients, zoledronic acid was associated with clinically significant reductions in skeletal-related events. Therefore, the GU DSG thought it was reasonable to recommend zoledronic acid for reducing skeletal-related events but with the qualification that it be considered in light of its minimal effect on pain, neutral effect on quality of life outcomes, and associated toxicity. Clodronate has only been evaluated in patients with painful bone metastases. The GU DSG spent considerable time discussing whether the strength of the evidence on clodronate was sufficient to recommend its use in these patients. Considering the possibility that some of the clodronate trials were underpowered to detect differences in treatment effect (four of the five clodronate trials included less than 100 patients), a meta-analysis synthesizing the data from those trials would have been ideal but was not technically possible. However, given that *all* the clodronate trials showed a trend indicating clodronate could improve pain, the GU DSG was comfortable with recommending clodronate to be used as an adjunct to other palliative therapies used for pain management (i.e., chemotherapy and radiotherapy).

b) Dose, scheduling, and duration of therapy: The GU DSG agreed that the dosing and scheduling of zoledronic acid in patients with asymptomatic or minimally symptomatic bone metastases should resemble the administration received by patients in the 4mg arm of the zoledronic acid trial. However, how long patients should continue receiving this treatment is currently unknown. For patients with moderately painful bone metastases, benefits were observed with intravenous, oral, and combined intravenous and oral clodronate; therefore, the choice of administration should be informed by patient preference and tolerance. GU DSG members felt that it was important for treating physicians to be aware that the optimal duration of bisphosphonate therapy in either group of patients has not been evaluated in a randomized trial. Several DSG members suggested that recommendations for both patient populations be qualified with a statement about the uncertainty of bisphosphonate treatment duration.

c) Bisphosphonates use in the context of other palliative therapies: Docetaxel-based chemotherapy modestly improves survival and provides palliation for men with HRPC and metastases (3,4). In addition to chemotherapy, external beam radiotherapy and radiopharmaceuticals (5) can also be used to palliate pain related to HRPC. The GU DSG agreed that the value of bisphosphonates for relieving the pain of men with HRPC and bone metastases needs to be considered in relation to the proven benefits of other palliative treatment options.

VIII. IMPLICATIONS FOR POLICY

An earlier version of this guideline was submitted to the Policy Advisory Committee (PAC) of Cancer Care Ontario in September 2003. The guideline was submitted in draft form and had not been disseminated for practitioner feedback. The purpose of the submission was to inform the PAC of the current state of the evidence regarding bisphosphonate treatment in patients with HRPC, and more specifically, to prompt a discussion regarding a funding policy for zoledronic acid. In December of 2003, the Ontario Ministry of Health approved new drug funding for zoledronic acid; however, in January of 2004, implementation of zoledronic acid reimbursement was delayed indefinitely due to funding restrictions. Reimbursement was reinstated in July of 2004.

IX. EXTERNAL REVIEW OF THE PRACTICE GUIDELINE REPORT

Draft Recommendations

Based on the evidence reviewed, the GU DSG drafted the following recommendations:

Target Population

These recommendations apply to adult male patients with hormone-refractory prostate cancer. Hormone-refractory is defined as the progression of stage IV disease or a rising prostate-specific antigen with a castrate testosterone level.

Draft Recommendations

Evidence on the use of bisphosphonates in hormone-refractory prostate cancer is limited to 10 randomized trials that examined five different bisphosphonates in different patient populations. Six of these trials were small, including less than 100 patients. In contrast to other disease sites where bisphosphonates have been more extensively evaluated, the limited available evidence makes it difficult to derive treatment recommendations for bisphosphonates as a class of agents for hormone-refractory prostate cancer. Therefore, the recommendations that follow apply to different bisphosphonates in specific clinical situations.

- ***In men with hormone-refractory prostate cancer and asymptomatic or minimally symptomatic⁵ bone metastases***, it is reasonable to consider zoledronic acid (4mg intravenously every three weeks) to reduce skeletal-related events. Practitioners and patients need to be aware of the benefits and risks of treatment, together with the limitations of the zoledronic acid trial when considering zoledronic acid in this setting.
 - Zoledronic acid is associated with an 8% absolute reduction (from 44% to 36%) in skeletal-related events. This reduction translates to a number-needed-to-treat value of 12 in order to prevent a single skeletal-related event.
 - The palliative benefits of reducing skeletal-related events by zoledronic acid in asymptomatic or minimally symptomatic patients should be considered in light of its toxicities, minimal effect on pain prevention, and neutral effect on overall quality of life.
- ***In men with hormone-refractory prostate cancer and moderately⁶ painful bone metastases***, clodronate (1600mg to 3200mg orally once daily or 1500mg intravenously every three weeks) can be considered as an adjunct to other palliative therapies (i.e., chemotherapy, radiotherapy) for reducing pain, along with traditional measures for pain management.
 - Three randomized trials of clodronate showed trends toward improvement in pain control and two trials showed pain improvement in subgroups of patients with moderate pain at baseline. On the basis of these observations, it is reasonable to consider clodronate for pain relief from moderately painful bone metastases.
 - Improvement in pain was observed with intravenous, oral, and combined intravenous and oral clodronate. Individual patient preference, tolerance, and convenience should inform the choice of route of administration. Clodronate is contraindicated in patients with a serum creatinine value greater than 440 µmol/L.
- Bisphosphonates should not be used with the intent of improving the overall survival of men with hormone-refractory prostate cancer.

⁵ This recommendation is limited to the asymptomatic or minimally symptomatic population of men with hormone-refractory prostate cancer studied in the zoledronic acid trial (25). The trial specifically excluded men with bone pain requiring strong narcotic therapy; the mean baseline pain scores of patients in this trial ranged from 2.0 to 2.5 on the Brief Pain Inventory (10-point pain scale).

⁶ The definition of moderate pain was a score of 3.0 or 4.0 on the Present Pain Intensity Scale of the McGill-Melzack Pain Questionnaire in the Ernst et al trial (14), or a score of ≥50mm on a 10cm-long visual analogue scale in the Strang et al trial (11).

- There is no evidence from randomized trials on the use of bisphosphonates to delay or prevent bone metastases in men with hormone-refractory prostate cancer without bone metastases.

Qualifying Statements

- The optimal duration of bisphosphonate treatment in men with hormone-refractory prostate cancer has not been evaluated in randomized trials. In the trial that demonstrated a reduction in skeletal-related events, zoledronic acid was given for 15 months. Among the five trials of clodronate, treatment duration ranged from two weeks to 12 months and was discontinued at the time of symptomatic progression in the largest trial.
- For men with hormone-refractory prostate cancer and bone pain, other palliative measures such as external beam radiotherapy, radioisotope therapy, and chemotherapy have demonstrated unequivocal patient benefits in randomized trials. The value of using bisphosphonates in this context should be considered in relation to the proven benefits of these other palliative treatment options.

Practitioner Feedback

Based on the evidence and the draft recommendations presented above, feedback was sought from Ontario clinicians.

Methods

Practitioner feedback was obtained through a mailed survey of 102 practitioners in Ontario (33 medical oncologists, 19 radiation oncologists, 30 urologists, and 20 pharmacists). The survey consisted of items evaluating the methods, results, and interpretive summary used to inform the draft recommendations, and whether the draft recommendations above should be approved as a practice guideline. Written comments were invited. The practitioner feedback survey was mailed out on May 3, 2004. Follow-up reminders were sent at two weeks (post card), four weeks (complete package mailed again), and six weeks (complete package mailed again). The GU DSG reviewed the results of the survey.

Results

Fifty-five responses were received out of the 102 surveys sent (53.9% response rate). Responses include returned completed surveys as well as phone, fax, and email responses. Of the practitioners who responded, 32 indicated that the report was relevant to their clinical practice and completed the survey. Key results of the practitioner feedback survey are summarized in Table 8.

Table 8. Practitioner responses to eight items on the practitioner feedback survey.

Item	Number (%)		
	Strongly agree or agree	Neither agree nor disagree	Strongly disagree or disagree
The rationale for developing a clinical practice guideline, as stated in the “ <i>Choice of Topic</i> ” section of the report, is clear.	29 (93.5)	2 (6.5)	0
There is a need for a clinical practice guideline on this topic.	29 (93.5)	1 (3.2)	1 (3.2)
The literature search is relevant and complete.	30 (96.7)	1 (3.2)	0
The results of the trials described in the report are interpreted according to my understanding of the data.	28 (93.3)	0	2 (6.7)
The draft recommendations in this report are clear.	29 (95.8)	2 (6.5)	0
I agree with the draft recommendations as stated.	25 (80.6)	3 (9.7)	3 (9.7)
This report should be approved as a practice guideline.	27 (84.4)	2 (6.3)	3 (9.4)
If this report were to become a practice guideline, how likely would you be to make use of it in your own practice?	Very likely or likely	Unsure	Not at all likely or unlikely
	17 (53.1)	4 (12.5)	11 (34.4)

Summary of Written Comments

Sixteen respondents (50%) provided written comments. The main points contained in the written comments were:

1. Two practitioners commented that the zoledronic acid trial has created controversy due to uncertainty surrounding its actual benefit and the strong lobbying by the pharmaceutical industry. Both practitioners remarked that they thought the evidence from this trial was weak and did not justify a guideline.
2. One practitioner commented that the lack of funding for zoledronic acid puts oncologists and administration in a very difficult position. This practitioner voiced frustration about approving a recommendation when there are no financial resources to support it.
3. Four practitioners wrote that they strongly disagreed or disagreed with the guideline recommendations. One practitioner felt that the recommendation for clodronate in symptomatic patients was in fact not evidence-based because every clodronate trial conducted to date has been negative; this practitioner questioned the GU DSG for developing a recommendation based on data showing trends and from subgroup analyses. A second practitioner also disagreed with the clodronate recommendation, citing patients do not tolerate clodronate and its approval for this indication would be costly given the size of the patient population. The other two practitioners strongly disagreed with the zoledronic acid recommendation and voiced similar concerns; they believed that a favourable risk-benefit ratio has not been established with zoledronic acid and therefore a recommendation for its use would be a very poor use of resources given its expensive cost. The one practitioner also noted that while there may be an occasional patient who might benefit from bisphosphonate treatment (and maybe slightly more may benefit when on long-term androgen deprivation), overall, the evidence is weak for using any of the bisphosphonates in HRPC.
4. One practitioner thought the guideline was too long and suggested it be simplified and shortened. A second practitioner commented that trials showing a benefit in pain control in patients with prostate cancer and osteoporosis had been excluded from the guideline.
5. Four practitioners evaluated the guideline as a good/fair summary of the available evidence. One of those practitioners also commented that the choice of topic was relevant, the data were well summarized, and the conclusions of the report were

consistent with the evidence. Patients with chemorefractory disease for whom NSAID/steroid and opioid use have produced suboptimal results, and non-metastatic patients undergoing androgen deprivation were identified by these practitioners as patient populations where the role of bisphosphonates is also relevant.

6. One practitioner described the guideline as an excellent document, albeit conservative with respect to the recommendations. This practitioner mentioned that at his/her centre, bisphosphonates are used in all patients with bone metastases (not just patients with HRPC).
7. One practitioner noted that although it was likely outside the scope of the report, he/she would have found the inclusion of a cost-benefit analysis helpful.

Modifications/Actions

Practitioner responses summarized in Table 8 suggest that practitioners generally view the guideline content and recommendations very positively. However, despite the strong approval, approximately only half of practitioners would be very likely to make use of the guideline in practice. A review of some of the data not summarized in Table 8 suggests that practitioners would not make use of the guideline due to issues regarding cost implications of the recommendations as opposed to weaknesses in the guideline; 37% of practitioners thought the recommendations would be too expensive to apply. The GU DSG acknowledges the importance of cost and funding issues; however, addressing this type of feedback is beyond the scope of the GU DSG's mandate but is accepted to be within the mandate of the PAC. Accordingly, those comments have been forwarded to the PAC for their consideration. The GU DSG has responded to all written comments unrelated to cost or funding:

1. Regarding the comments that evidence from the zoledronic acid trial is “weak” — the GU DSG critically reviewed the evidence from that trial and believes that its limitations are adequately reflected in the guideline recommendations.
2. To address the comments that the recommendations for clodronate were not “evidence-based” — the GU DSG critically reviewed all of the data from the clodronate trials and attempted a “qualitative synthesis” (details in the interpretive summary) of the evidence from those trials since a quantitative synthesis or meta-analysis was not possible. The qualitative synthesis recognized that, although all trials except one had been negative, all the clodronate trials demonstrated some form of trend suggesting clodronate may be of some benefit. The limitations of the clodronate evidence led to a qualified recommendation with the wording “clodronate can be considered as an adjunct to other palliative therapies”.
3. Regarding the comment that “patients do not tolerate clodronate” — the recommendation to use clodronate highlights the need to assess individual patient's tolerance of clodronate in deciding on the route of administration. In fact, all randomized trials that reported adverse effects of clodronate reported similar or lower adverse event rates in the clodronate arms of their trials (see Table 7).
4. Regarding the comment that the guideline is too long — the GU DSG felt that a careful description, explanation, and interpretation of the evidence were required to adequately support the guideline recommendations.
5. Regarding the comment that “trials showing a benefit in pain control in patients with prostate cancer and osteoporosis had been excluded from the guideline” — the GU DSG is not aware of any other randomized trials of bisphosphonates for pain control in men with HRPC and is unaware of the existence of any randomized trials addressing the impact of bisphosphonates on osteoporosis.
6. Regarding the comments on the relevancy of bisphosphonate use in subgroups of patients (those with chemorefractory disease for whom NSAID/steroid and opioid use have produced suboptimal results, and non-metastatic patients undergoing androgen

deprivation) — the GU DSG is unaware of any trials that address men with chemorefractory disease but the recommendations for men with moderately painful bone metastases could guide treatment for such men. The role of bisphosphonates in non-metastatic men on androgen deprivation is beyond the scope of this guideline.

Practice Guidelines Coordinating Committee Approval Process

The practice guideline report was circulated to members of the PGCC for review and approval. Nine of 15 members of the PGCC returned ballots. All nine PGCC members approved the practice guideline report as written.

X. PRACTICE GUIDELINE

The GU DSG reviewed all the feedback obtained from the external review process. After careful consideration, the GU DSG decided not to modify the draft recommendations in response to practitioner feedback. The practice guideline has been approved by the GU DSG and by the Practice Guidelines Coordinating Committee.

Target Population

These recommendations apply to patients with hormone-refractory prostate cancer. Hormone-refractory is defined as the progression of stage IV disease or a rising prostate-specific antigen with a castrate testosterone level.

Recommendations

Evidence on the use of bisphosphonates in hormone-refractory prostate cancer is limited to 10 randomized trials examining five different bisphosphonates in different patient populations. Six of those trials were small, including less than 100 patients. In contrast to other disease sites where bisphosphonates have been more extensively evaluated, the limited available evidence in hormone-refractory prostate cancer makes it difficult to derive treatment recommendations for bisphosphonates as a class of agents. Therefore, the recommendations that follow apply to different bisphosphonates in specific clinical situations.

- ***In men with hormone-refractory prostate cancer and asymptomatic or minimally symptomatic⁷ bone metastases***, it is reasonable to consider zoledronic acid (4mg intravenously every three weeks) to reduce skeletal-related events. Practitioners and patients need to be aware of the benefits and risks of treatment, together with the limitations of the zoledronic acid trial when considering zoledronic acid in this setting.
 - Zoledronic acid is associated with an 8% absolute reduction (from 44% to 36%) in skeletal-related events. This reduction translates to a number-needed-to-treat value of 12 in order to prevent a single skeletal-related event.
 - The palliative benefits of reducing skeletal-related events by zoledronic acid should be considered in light of its toxicities, minimal effect on pain prevention, and neutral effect on overall quality of life.
- ***In men with hormone-refractory prostate cancer and moderately⁸ painful bone metastases***, clodronate (1600mg to 3200mg orally once daily or 1500mg intravenously

⁷ This recommendation is limited to the asymptomatic or minimally symptomatic population of men with hormone-refractory prostate cancer studied in the zoledronic acid trial (1). The trial specifically excluded men with bone pain requiring strong narcotic therapy; the mean baseline pain scores of patients in this trial ranged from 2.0 to 2.5 on the Brief Pain Inventory (10-point pain scale).

⁸ The definition of moderate pain was a score of 3.0 or 4.0 on the Present Pain Intensity Scale of the McGill-Melzack Pain Questionnaire in the Ernst et al trial (2), or a score of ≥ 50 mm on a 10cm-long visual analogue scale in the Strang et al trial (3).

every three weeks) can be considered as an adjunct to other palliative therapies (i.e., chemotherapy, radiotherapy) for reducing pain, along with traditional measures for pain management.

- Three randomized trials of clodronate showed trends toward improvement in pain control and two trials showed pain improvement in subgroups of patients with moderate pain at baseline. On the basis of those observations, it is reasonable to consider clodronate for pain relief from moderately painful bone metastases.
 - Improvement in pain was observed with intravenous, oral, and combined intravenous and oral clodronate. Individual patient preference, tolerance, and convenience should inform the choice of route of administration. Clodronate is contraindicated in patients with a serum creatinine value greater than 440 µmol/L.
- Bisphosphonates should not be used with the intent of improving the overall survival of men with hormone-refractory prostate cancer.
 - There is no evidence from randomized trials on the use of bisphosphonates to delay or prevent bone metastases in men with hormone-refractory prostate cancer without bone metastases.

Qualifying Statements

- The optimal duration of bisphosphonate treatment in men with hormone-refractory prostate cancer has not been evaluated in randomized trials. In the trial that demonstrated a reduction in skeletal-related events, zoledronic acid was given for 15 months. Extension data from that trial indicates that some men (122/643) were able to continue their assigned therapy for 24 months (86 men on the zoledronic acid arms of the trial, 36 men on the placebo arm). Among the five trials of clodronate, treatment duration ranged from two weeks to 12 months and was discontinued at the time of symptomatic progression in the largest trial.
- For men with hormone-refractory prostate cancer and bone pain, other palliative measures such as external beam radiotherapy, radioisotope therapy, and chemotherapy have demonstrated unequivocal patient benefits in randomized trials. The value of using bisphosphonates in this context should be considered in relation to the proven benefits of these other palliative treatment options.

XI. JOURNAL REFERENCE

Berry S, Waldron T, Winqvist E, Lukka H; Genitourinary Cancer Disease Site Group. The use of bisphosphonates in men with hormone-refractory prostate cancer: a systematic review of randomized trials. *Can J Urol.* 2006;13(4):3034-43.

XII. CONFLICTS OF INTEREST

The members of the GU DSG disclosed potential conflicts of interest relating to this practice guideline. One author reported receipt of honoraria from the pharmaceutical company that manufactures zoledronic acid.

XIII. ACKNOWLEDGEMENTS

The Genitourinary Cancer Disease Site Group would like to thank Drs. Scott Berry, Eric Winqvist, and Himu Lukka and Ms. Tricia Waldron for taking the lead in drafting and revising this practice guideline report.

For a complete list of the Genitourinary Cancer Disease Site Group members and the Practice Guidelines Coordinating Committee members, please visit the PEBC the CCO Web site at:
http://www.cancercare.on.ca/access_PEBC.htm

REFERENCES

1. National Cancer Institute of Canada. Canadian Cancer Statistics 2003. Toronto, Canada: 2003.
2. Coleman RE. Skeletal complications of malignancy. *Cancer*. 1997;80:1588-94.
3. Petrylak DP, Tangen CM, Maha PH, Hussain HA, Lara PN, Jones JA, et al. Docetaxel and estramustine compared with mitoxantrone and prednisone for advanced refractory prostate cancer. *N Engl J Med*. 2004;351:1513-20.
4. Tannock IF, De Wit R, Berry WR, Horti J, Pluzanska A, Chi K, et al. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. *N Engl J Med*. 2004;351:1502-12.
5. Brundage MD, Crook JM, Lukka H, and Members of the Genitourinary Cancer Disease Site Group. Use of strontium89 in patients with endocrine-refractory carcinoma of the prostate metastatic to bone. Practice Guideline Report #3-6 [summary and full report on the Internet]. Toronto (Canada): Cancer Care Ontario; 2001 Oct [cited 2004 Oct 8]. Available from: <http://www.cancercare.on.ca/pdf/pebc3-6f.pdf>.
6. Plunkett TA, Rubens RD. Bisphosphonate therapy for patients with breast carcinoma. Who to treat and when to stop. *Cancer*. 2003;97(3 Suppl):854-8.
7. Kanis JA, McCloskey EV. Bisphosphonates in multiple myeloma. *Cancer*. 2000;88:3022-32.
8. Berruti A, Dogliotti L, Tucci M, Tarabuzzi R, Fontana D, Angeli A. Metabolic bone disease induced by prostate cancer: rationale for the use of bisphosphonates. *J Urol*. 2001;166(6):2023-31.
9. Browman GP, Levine MN, Mohide EA, Hayward RSA, Pritchard KI, Gafni A, et al. The practice guidelines development cycle: a conceptual tool for practice guidelines development and implementation.. *J Clin Oncol*. 1995;13(2):502-12.
10. Wong R, Wiffen PJ. Bisphosphonates for the relief of pain secondary to bone metastases (Cochrane Review). The Cochrane Library. Oxford: Update Software; 2002.
11. Strang P, Nilsson S, Brandstedt S, Sehlin J, Borghede G, Varenhorst E, et al. The analgesic efficacy of clodronate compared with placebo in patients with painful bone metastases from prostatic cancer. *Anticancer Res*. 1997;17(6D):4717-21.
12. Adami S, Mian M. Clodronate therapy of metastatic bone disease in patients with prostatic carcinoma. *Recent Results Cancer Res*. 1989;116:67-72.
13. Small EJ, Smith MR, Seaman JJ, Kowalski MO. A multicenter, randomized, placebo-controlled study of pamidronate disodium for the palliation of bone pain in men with metastatic prostate cancer. *J Clin Oncol*. 2003;21(23):1-9.
14. Ernst DS, Tannock IF, Winqvist EW, Venner PM, Reyno L, Moore MJ, et al. Randomized, double-blind, controlled trial of mitoxantrone/prednisone and clodronate versus mitoxantrone/prednisone and placebo in patients with hormone-refractory prostate cancer and pain. *J Clin Oncol*. 2003;21:3335-42.
15. Elomaa I, Kylmälä T, Tammela T, Viitanen J, Ottelin J, Ruutu M, et al. Effect of oral clodronate on bone pain. A controlled study in patients with metastatic prostatic cancer. *Int Urol Nephrol*. 1992;24(2):159-66.
16. 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):85-7.
17. Kylmälä T, Taube T, Tammela TL, Risteli L, Risteli J, Elomaa I. Concomitant i.v. and oral clodronate in the relief of bone pain--a double-blind placebo-controlled study in patients with prostate cancer. *Br J Cancer*. 1997;76(7):939-42.

18. Bloomfield DJ. Should bisphosphonates be part of the standard therapy of patients with multiple myeloma or bone metastases from other cancers? An evidence-based review. *J Clin Oncol.* 1998;16(3):1218-25.
19. Ross JR, Saunders Y, Edmonds PM, Patel S, Broadley KE, Johnston SRD. Systematic review of the role of bisphosphonates on skeletal morbidity in metastatic cancer. *BMJ.* 2003;327:1-6.
20. Mannix K, Ahmedzai SH, Anderson H, Bennett M, Lloyd-Williams M, Wilcock A. Using bisphosphonates to control the pain of bone metastases: evidence-based guidelines for palliative care. *Palliat Med.* 2000;14(6):455-61.
21. Dahut WL, Dyer V, Arlen P, Gulley J, Fedenko K, Chen C, et al. A randomized phase II trial of ketoconazole (KT) and alendronate (AL) versus ketoconazole in androgen independent prostate cancer (AIPC) [abstract]. *Proc Am Soc Clin Oncol.* 2001;20:185a.
22. Saad F, Gleason D, Murray R, Tchekmedyian S, Venner P, Lacombe L, 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):879-82.
23. Taube T, Kylmäälä T, Lamberg-Allardt C, Tammela TL, Elomaa I. The effect of clodronate on bone in metastatic prostate cancer. Histomorphometric report of a double-blind randomised placebo-controlled study. *Eur J Cancer.* 1994;30A(6):751-8.
24. Kylmäälä T, Tammela T, Risteli L, Risteli J, Taube T, Elomaa I. Evaluation of the effect of oral clodronate on skeletal metastases with type 1 collagen metabolites. A controlled trial of the Finnish Prostate Cancer Group. *Eur J Cancer.* 1993;29A(6):821-5.
25. Saad F, Gleason DM, Murray R, Tchekmedyian S, Venner P, Lacombe L, 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):1458-68.
26. Heidenreich A. Treatment of hormone-refractive prostatic carcinoma with painful bone metastasis. Epirubicin vs. clodronate vs. epirubicin plus clodronate [German]. *Urologe.* 1997;36(6):568.
27. Farooqui M, Weinreb S, and Higby D. A clinical trial to compare the efficacy of strontium89 with cisplatin vs strontium89 with pamidronate in palliative treatment of metastatic prostate cancer [abstract]. *Proc Am Soc Clin Oncol.* 1996;15:539.
28. Coleman RE, Purohit OP, Black C, Vinholes JJ, Schlosser K, Huss H, et al. Double-blind, randomised, placebo-controlled, dose-finding study of oral ibandronate in patients with metastatic bone disease. *Ann Oncol.* 1999;10(3):311-6.
29. Vinholes JJ, Purohit OP, Abbey ME, Eastell R, Coleman RE. Relationships between biochemical and symptomatic response in a double-blind randomised trial of pamidronate for metastatic bone disease. *Ann Oncol.* 1997;8(12):1243-50.
30. Ernst DS, Brasher P, Hagen N, Paterson AH, MacDonald RN, Bruera E. A randomized, controlled trial of intravenous clodronate in patients with metastatic bone disease and pain. *J Pain Symptom Manage.* 1997;13(6):319-26.
31. Robertson AG, Reed NS, Ralston SH. Effect of oral clodronate on metastatic bone pain: a double-blind, placebo-controlled study. *J Clin Oncol.* 1995;13(9):2427-30.
32. O'Rourke N, McCloskey E, Houghton F, Huss H, Kanis JA. Double-blind, placebo-controlled, dose-response trial of oral clodronate in patients with bone metastases. *J Clin Oncol.* 1995;13(4):929-34.
33. Ernst DS, MacDonald RN, Paterson AH, Jensen J, Brasher P, Bruera E. A double-blind, crossover trial of intravenous clodronate in metastatic bone pain. *J Pain Symptom Manage.* 1992;7(1):4-11.
34. Lipton A, Glover D, Harvey H, Grabelsky S, Zelenakas K, Macerata R, et al. Pamidronate in the treatment of bone metastases: results of 2 dose-ranging trials in patients with breast or prostate cancer. *Ann Oncol.* 1994;5 Suppl 7:S31-S35.

35. Jagdev SP, Purohit P, Heatley S, Herling C, Coleman RE. Comparison of the effects of intravenous pamidronate and oral clodronate on symptoms and bone resorption in patients with metastatic bone disease. *Ann Oncol.* 2001;12(10):1433-8.
36. Koeberle D, Bacchus L, Thuerlimann B, Senn HJ. Pamidronate treatment in patients with malignant osteolytic bone disease and pain: a prospective randomized double-blind trial. *Support Care Cancer.* 1999;7(1):21-7.
37. Wong, R., Shukla, V. K., Mensinkai, S., and Wiffen, P. Bisphosphonate agents for the management of pain secondary to bone metastases: a systematic review of effectiveness and safety. Ottawa: Canadian Coordinating Office for Health Technology Assessment, 2004.
38. Jadad AR. Types of randomised controlled trials. *Randomised Controlled Trials.* London, UK: BMJ Books; 1998: p. 10-27.
39. Canil CM, Tannock IF. Should bisphosphonates be used routinely in patients with prostate cancer metastatic to bone? *J Natl Cancer Inst.* 2002;94(19):1422-3.
40. Saad F, Gleason D. Response RE: a randomized placebo-controlled trial of zoledronic acid in patients with hormone-refractory metastatic prostate carcinoma. *J Natl Cancer Inst.* 2003;95(4):333-4.
41. Warr D, Johnston M; Breast Cancer Disease Site Group. Use of bisphosphonates in women with breast cancer. Practice Guideline Report #1-11 Version 2.2002 [summary and full report on the Internet]. Toronto (Canada): Cancer Care Ontario; 2004 Apr [cited 2004 Oct 8]. Available from: <http://www.cancercare.on.ca/pdf/pebc1-11f.pdf>.
42. Imrie K, Stevens A, Makarski J, Esmail R, Meharchand J, Meyer R; Hematology Disease Site Group. The role of bisphosphonates in the management of skeletal complications for patients with multiple myeloma. Practice Guideline Report #6-4 [summary and full report on the Internet]. Toronto (Canada): Cancer Care Ontario; 2004 Mar [cited Jan 10 2005]. Available from: <http://www.cancercare.on.ca/pdf/pebc6-4f.pdf>.