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CED-CCO Special Advice Report 18

Zoledronic Acid for the Treatment of Bone Metastases Secondary to Renal Cell Carcinoma

M. MacKenzie, C. Quinton-Gladstone, A.E. Haynes, and S. Hotte

Report Date: June 16, 2010

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Zoledronic Acid for the Treatment of Bone Metastases Secondary to Renal Cell Carcinoma

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Report Date: June 16, 2010

SUMMARY

QUESTION

Does the use of zoledronic acid in patients with bone metastases secondary to renal cell carcinoma result in patient benefits?

Outcomes of interest include the incidence of skeletal-related events (SRE), time to first SRE, skeletal morbidity rate, progression-free survival (PFS), overall survival (OS), quality of life, and adverse events.

TARGET POPULATION

Adult patients with renal cell carcinoma who have bone metastases.

RECOMMENDATIONS

The following recommendations reflect the opinions of the authors of this special advice report.

- **Zoledronic acid is recommended in the treatment of patients with bone metastases secondary to renal cell carcinoma.**

QUALIFYING STATEMENTS

- Zoledronic acid should be given at a dose of 4 mg every three weeks via 15-minute infusion in 100 mL of infusate for nine months.
- Patients should be closely monitored for osteonecrosis of the jaw and should be counselled on the need for proper oral hygiene during use of zoledronic acid.

KEY EVIDENCE

One randomized controlled trial (RCT) investigating the use of zoledronic acid in patients with bone metastases secondary to lung cancer or other solid tumours not including breast or prostate cancer was identified (1). Of the 773 patients randomized to either placebo, zoledronic acid 4 mg, or zoledronic acid 8 mg, 74 (9.6%) had metastatic renal cell carcinoma. A subset analysis of that trial, published as Lipton et al (2), reported only on the

patients with metastatic renal cell carcinoma. Nineteen patients were randomized to the placebo arm, 27 to the zoledronic acid 4 mg arm, and 28 to the 8 mg arm. The authors only compared the zoledronic acid 4 mg arm to the placebo arm, as patients in the 8 mg arm had a dose reduction to 4 mg due to concerns over decreased renal tolerability. The skeletal-related event rate was significantly less for patients who received zoledronic acid compared to placebo (37% versus [vs.] 74%, respectively; $p=0.015$). The time to first SRE was also significantly better in the zoledronic acid arm compared to placebo (median not yet reached (NYR) vs. 72 days; $p=0.006$), as was the time-to-progression of bone lesions (median 265 days vs. 89 days; $p=0.014$). The skeletal morbidity rate was significantly lower for patients who received zoledronic acid compared to placebo (2.68 events/year vs. 3.38 events/year; $p=0.014$). In a multiple event analysis, the authors reported a 61% reduction in the risk of SREs, with a hazard ratio of 0.394 ($p=0.008$). The authors did not report whether statistical differences were found between treatment arms for adverse events. However, the most commonly reported adverse events were bone pain, nausea, emesis, fatigue, pyrexia, and anemia.

In a small retrospective review of 166 patients, 78 of whom received zoledronic acid, osteonecrosis of the jaw developed in one patient with renal cell carcinoma who received sunitinib and zoledronic acid concurrently (3). The incidence of osteonecrosis of the jaw among all patients with cancer receiving bisphosphonates with or without antiangiogenic agents was 16% and 1.1%, respectively ($p=0.008$).

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2. Lipton A, Zheng M, Seaman J. Zoledronic acid delays the onset of skeletal-related events and progression of skeletal disease in patients with advanced renal cell carcinoma. *Cancer*. 2003 Sep 1;98(5):962-9.
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FULL REPORT

QUESTION

Does the use of zoledronic acid in patients with bone metastases secondary to renal cell carcinoma result in patient benefits?

Outcomes of interest include the incidence of skeletal-related events (SRE), time to first SRE, skeletal morbidity rate, progression-free survival (PFS), overall survival (OS), quality of life, and adverse events.

INTRODUCTION

Approximately 4600 new cases of renal cell carcinoma were diagnosed in Canada in 2009, and 1600 of those patients are likely to die of this disease (1). In recent years, several large randomized phase III trials of new therapies have shown a benefit for patients with metastatic renal cell carcinoma (MRCC). Such therapies include (but are not limited to) sunitinib, sorafenib, temsirolimus, and everolimus (2-5).

A retrospective review of patients with bone metastases from MRCC, which was conducted before the advent of the new treatments described above for MRCC, showed that patients with renal cell carcinoma suffered significant morbidity from bone metastases (6). Over 80% of patients with bone metastases from MRCC in this series required palliative radiation, and 40% suffered pathologic fractures.

Despite the availability of new agents for renal cell carcinoma, high rates of skeletal-related events have still been observed. Secter et al (7) reported a review of 196 patients with MRCC in London, Ontario. Of these 196 patients, 32% had bone metastases. Of the patients with bone metastases, 42% suffered a pathologic fracture, 28% experienced a spinal cord compression or cauda equina syndrome, 87% required radiotherapy, and 22% underwent surgery for bone metastases. Forty percent of patients with bone metastases from MRCC were hospitalized for skeletal-related events, and the mean length of hospital stay was 21 days. This high rate of skeletal morbidity was observed despite the fact that over 75% of patients in this review were treated with newer agents such as sunitinib, sorafenib, and temsirolimus.

In a large phase III trial reported by Rosen et al (8) investigating zoledronic acid to prevent skeletal-related events (SREs), the rate of SRE in the placebo arm was 44%. In the subset of patients with MRCC, the SRE rate was 74%, which was much higher than the rate observed in the placebo arm of the overall trial population. This observation, along with the series from Zekri et al (6) and Secter et al (7), provides ample evidence that patients with bone metastases from MRCC are at very high risk for skeletal-related events that are likely to result in prolonged hospitalizations for surgical fixation, radiotherapy, and other palliative treatments. The objective of this report is to provide advice to the Committee to Evaluate Drugs - Cancer Care Ontario (CED-CCO) Subcommittee on the use of zoledronic acid in patients with bone metastases secondary to MRCC.

METHODS

This advice report, produced by the Program in Evidence-based Care (PEBC) of CCO, is a convenient and up-to-date source of the best available evidence on the use of zoledronic acid in patients with bone metastasis secondary to renal cell carcinoma, developed through a systematic review of the available evidence. Contributing authors disclosed any potential conflicts of interest. The PEBC is editorially independent of the Ontario Ministry of Health and Long-Term Care.

PEBC reports do not search for or review economic data related to the advice report question. Cost and resource implications related to the special advice report are considered

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

Literature Search Strategy

MEDLINE (Ovid) (1996 to March Week 5 2010 [April 8]), EMBASE (Ovid) (1996 to Week 13 2010 [April 8]), and the Cochrane Library (April 2010) databases were searched. The search strategies for MEDLINE and EMBASE are shown in Appendix 1. Search strategies in other databases were similar.

In addition, conference proceedings of the American Society of Clinical Oncology (ASCO; 2005-2009) and the ASCO Genitourinary Cancers Symposium (2008-2010) were searched for abstracts of relevant trials. The Canadian Medical Association Infobase (<http://mdm.ca/cpgsnew/cpgs/index.asp>), the National Guidelines Clearinghouse (<http://www.guideline.gov/index.asp>), and the National Institute for Clinical Excellence (<http://www.nice.org.uk/>) were also searched for existing evidence-based practice guidelines.

Relevant articles and abstracts were selected and reviewed by two reviewers, and the reference lists from these sources were searched for additional trials. Personal files were also searched.

Study Selection Criteria

Inclusion Criteria

Articles were selected for inclusion in this systematic review of the evidence if they were published full-report articles or published meeting abstracts of:

1. Practice guidelines or systematic reviews of zoledronic acid in patients with bone metastasis secondary to renal cell carcinoma.
2. Randomized phase II or phase III clinical trials comparing the use of zoledronic acid to either placebo or no zoledronic acid.

Randomized trials must have included patients with bone metastases secondary to renal cell carcinoma. Trials could include patients with other cancer types; however, the results for patients with renal cell carcinoma must have been reported separately from other types of cancer. Published studies must have reported data on one or more of the following outcomes: incidence of skeletal-related events (SRE), time to first SRE, skeletal morbidity rate, PFS, OS, quality of life, and adverse events.

Exclusion Criteria

Studies were excluded if they were:

1. Letters, comments, books, notes, or editorial publication types.
2. Articles published in a language other than English, because of financial considerations for translation.

Synthesizing the Evidence

A meta-analysis of the trial results was not conducted, as only one RCT was identified.

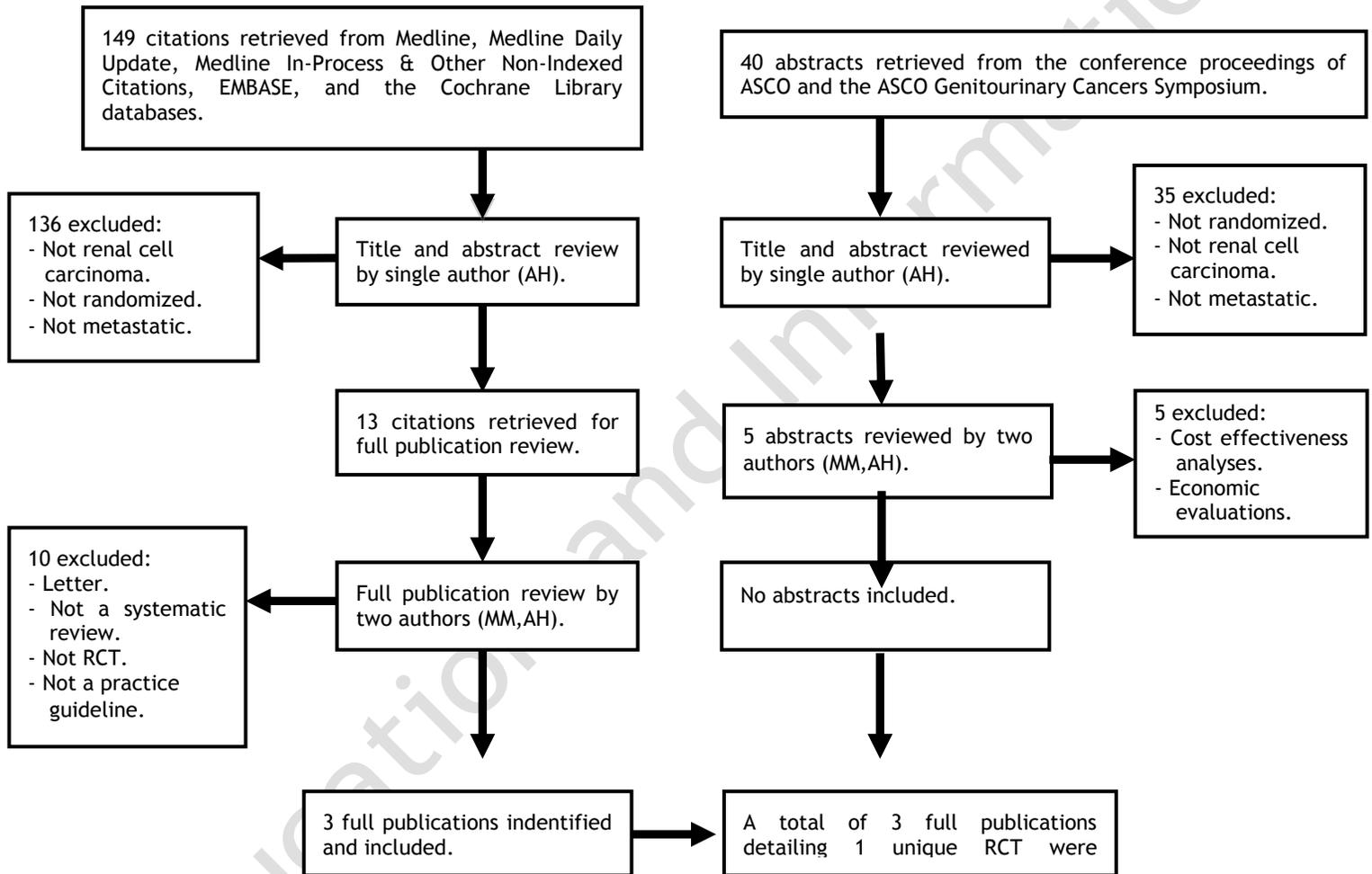
RESULTS

Literature Search Results

A total of 149 citations were identified in the databases of MEDLINE, EMBASE, and the Cochrane Library (Figure 1). Three full publications of one RCT were included. Forty

abstracts were identified from ASCO and the ASCO Genitourinary Cancers Symposium. Of those, four were cost-effectiveness analyses, and one was an economic evaluation of zoledronic acid in patients with bone metastases secondary to renal cell carcinoma. As those abstracts did not report on the outcomes of interest, they were excluded.

Figure 1. Selection of studies investigating zoledronic acid in patients with bone metastases secondary to renal cell carcinoma from the search results of MEDLINE, EMBASE, and the Cochrane Library databases, and the conference proceedings of ASCO and the ASCO Genitourinary Cancers Symposium.



Trial and Patient Characteristics

All three identified full publications (9-11) reported a subset analysis of the same RCT. That trial was originally published as Rosen et al in 2003 (8), with updated results published in 2004 as Rosen et al (12). In that trial, the authors included patients with bone metastases secondary to lung cancer and other solid tumours, not including breast or prostate cancer (8). Seven hundred seventy-three patients were randomized to receive either zoledronic acid 4 mg every three weeks (n=257), zoledronic acid 8 mg every three weeks (n=266), or placebo (n=250) for nine months (8). A protocol amendment due to concerns over decreased renal tolerability at the 8 mg dose level reduced the dose for patients in the 8 mg arm to 4 mg of zoledronic acid. Only 25% of patients in the 8 mg arm were still receiving treatment and were subsequently switched to the lower dose. The remaining patients had all completed nine months of treatment. All patients received calcium supplements (500 mg) and a multivitamin tablet with vitamin D (400 to 500 IU) daily. Of the 773 patients enrolled in the trial, 74 (9.6%) had renal cell carcinoma. Neither of the publications by Rosen et al, 2003 (8) or 2004 (12), reported separate data for patients with renal cell carcinoma. Lipton et al 2003 (9) and 2004 (10) and Shulman (11) reported a subset analysis including only those patients.

Table 1. Trial and patient characteristics of trials investigating the use of zoledronic acid in patients with bone metastases secondary to renal cell carcinoma.

Author, year (ref)	Patient characteristics	Treatment	N	Differences between treatment groups at baseline
Rosen, 2003 (8) Rosen, 2004 (12)	Patients with bone metastases secondary to lung cancer or other solid tumours (excluding breast and prostate cancer), age ≥18 years	Placebo	250 RCC: 19	Overall: arms balanced RCC: arms balanced
		Zoledronic acid 4 mg every 3 weeks	257 RCC: 27	
		Zoledronic acid 8 mg every 3 weeks	266 RCC: 28	

Notes: N=number of patients randomized; RCC=renal cell carcinoma; ref=reference.

Trial Quality

Select quality characteristics of the included RCT can be found in Table 2. The trial met the required sample size, although the authors did not report how patients were randomized or on allocation concealment (8). While the authors reported that the trial was double-blind, the only further mention of blinding was a statement that the central radiologist was blinded to treatment. The primary outcome was the incidence of SREs, defined as pathologic fracture, spinal cord compression, radiation therapy to bone, or surgery to bone. Secondary outcomes were the time to first SRE, skeletal morbidity rate, PFS, and OS. The authors also conducted a multiple event analysis. The authors reported a final intention-to-treat analysis. That final analysis compared the placebo arm to the zoledronic acid 4 mg arm only in terms of efficacy; the authors did not compare the placebo arm to the zoledronic acid 8 mg arm. Overall, the RCT was of high quality.

The subset analysis reported by Lipton et al 2003 (9) and 2004 (10) and Shulman (11) included only 74 patients with renal cell carcinoma, representing approximately 10% of the total number of randomized patients in the trial. The authors reported a retrospective subset analysis of the patients with renal cell carcinoma. Rosen et al (8) reported that patient stratification was based on one of two tumour types: non-small-cell lung cancer or other solid

tumour. Of note, Lipton et al 2003 (9) reported that, although the trial did not include renal cell carcinoma in the stratification, the three arms of the trial had similar numbers of patients with renal cell carcinoma, with similar baseline characteristics. The numbers of patients with renal cell carcinoma were similar in the three treatment arms. Similarly to the main trial report, the authors reported that they did not compare the zoledronic 8 mg arm to the placebo arm; however, for almost all outcomes, the authors reported statistical comparisons, including p-values, for each treatment arm compared to placebo.

Table 2. Quality characteristics of identified RCT.

Author, year (ref)	Primary outcome	Required sample size	Secondary outcomes	Randomization method	Allocation concealment	Blinding	ITT analysis	Final analysis	Early termination	Losses to follow-up	Ethical Approval
Rosen, 2003 (8) Rosen, 2004 (12)	SRE	700 pts req'd to detect a 14% improvement in SRE (zoledronic acid 24% incidence vs. placebo 38% incidence) with a power of 80%.	Time-to first SRE, skeletal morbidity rate, multiple event analysis, PFS, OS	NR	NR	Yes ¹	Yes	Yes	No	<1%	Yes

Notes: ITT=intent-to-treat; NR=not reported; OS=overall survival; PFS=progression-free survival; pts=patients; ref=reference; req'd=required; SRE=skeletal-related event; vs.=versus.

¹Although the term “double-blind” was used, the authors only reported that the radiologist who centrally assessed all patients was blinded to patient assignment. The authors did not report on who else was blinded to treatment assignment.

Efficacy Outcomes

Efficacy outcomes can be found in Table 3.

Disease control

The authors reported that the incidence of SRE in each of the zoledronic acid-treatment arms was significantly less than in the placebo arm (Table 3). A multiple event analysis showed a 61% reduction in risk of SRE (hazard ratio [HR] 0.394; p=0.008) (9). The authors also reported better time to first SRE for each of the two treatment arms versus placebo (Table 3). The skeletal morbidity rate was also significantly lower in each of the treatment arms compared to the placebo arm (2.68 and 1.67 events per year vs. 3.38 events per year, respectively). The authors also reported significantly better time-to-progression of bone lesions for the zoledronic acid 4 mg treatment arm compared to placebo (median 265 days vs. 89 days; p=0.014). No significant difference was reported for the zoledronic acid 8 mg arm compared to placebo.

Survival

The authors reported no significant differences in OS (Table 3) (9).

Quality of life

Quality-of-life data for just the renal cell carcinoma patients were not reported in the subset analysis (9-11) nor in the main trial report (8).

Table 3. Outcomes for patients with renal cell carcinoma in the included RCT.

Author, year (ref)	Treatment	N	SRE (%)	Time-to-first SRE (median, days)	Skeletal morbidity rate (events/year)	Time-to-progression of bone lesions (median, days)	Multiple event analysis	OS (median, days)
Lipton, 2003 (9)	Placebo	19	74	72	3.38	89	61% reduction in risk of SRE	216
Lipton, 2004 (10)	Zoledronic acid 4 mg	27	37 p=0.015	NYR p=0.006	2.68 p=0.014	265 p=0.014	HR=0.394 p=0.008	295 p=0.179
Schulman, 2004 (11)	Zoledronic acid 8 mg	28	50 p=0.108	140 p=0.016	1.67 p=0.026	162 p=0.077	NR	308 p=NR

Notes: N=number randomized; NR=not reported; NYR=not yet reached; OS=overall survival; ref=reference; SRE=skeletal-related event.

Adverse Events

The most common adverse events among patients with renal cell carcinoma, of any grade, included bone pain, nausea, emesis, fatigue, pyrexia, and anemia (Table 4). The authors did not report statistical comparisons between the treatment and placebo arms (9-11). One patient (4.8%) in the zoledronic acid 8 mg arm had acute renal failure, and one patient (5.6%) in the zoledronic acid 4 mg arm had renal failure, not otherwise specified. No patients in the placebo arm had renal failure. Serious adverse events were reported in 48% of patients in the zoledronic acid 4 mg arm and in 68% of patients in the placebo arm. No data were reported on serious adverse events for the 8 mg zoledronic acid arm. The most commonly reported serious adverse events were malignant neoplasm, bone pain, dehydration, dyspnea, and pneumonia. The authors did not include data on the incidence of serious adverse events for the treatment or placebo arms (9-11).

Table 4. Any grade adverse events for patients with renal cell carcinoma in the included RCT.

Author, year (ref)	Treatment	N	Bone pain (%)	Nausea (%)	Emesis (%)	Fatigue (%)	Pyrexia (%)	Anemia (%)
	Placebo	19	63	32	26	16	16	32
Lipton, 2003 (9)	Zoledronic acid 4 mg	27	52	52	33	33	30	26
	Zoledronic acid 8 mg	28	39	36	36	21	29	18

DISCUSSION

Only one RCT comparing zoledronic acid to placebo in patients with bone metastases secondary to renal cell carcinoma was identified. That trial included patients with lung cancer and other solid tumours in addition to renal cell carcinoma. Although a total of 773 patients were enrolled, only 74 (9.6%) had renal cell carcinoma. The primary publication of the trial did not report separate data for patients with renal cell carcinoma, as the investigators did not report that they planned to analyze those patients separately (8). The retrospective analysis of the renal cell carcinoma patients included only 19 patients in the placebo arm, 27 patients in the 4 mg zoledronic acid arm, and 28 patients in the 8 mg zoledronic acid arm (9). The authors made an a priori decision not to compare the zoledronic acid 8 mg arm to the placebo arm for efficacy conclusions, although no rationale was provided other than the dose of zoledronic acid was reduced in that arm to 4 mg due to concerns over renal tolerability. The treatment arms were imbalanced in terms of the number of patients in each arm, with approximately 40% more patients in the zoledronic acid 4 mg arm than in the placebo arm. In addition, during enrolment in the RCT, the

randomization to treatment arm was only stratified by non-small-cell lung cancer and other solid tumours. However, renal cell carcinoma patients would still have had an equal and unbiased chance of being placed in either of the zoledronic acid treatment arms or the placebo arm. In addition, the authors reported that the three treatment arms were balanced for a number of demographic and baseline characteristics (9).

The subset analysis by Lipton et al (9) showed that patients with bone metastases secondary to renal cell carcinoma who received zoledronic acid 4 mg had significantly less SRE than patients who received a placebo (37% vs. 74%; $p=0.015$). The skeletal morbidity rate (annual incidence of SRE) was also significantly lower in the zoledronic acid 4 mg arm compared to placebo (2.68 vs. 3.38; $p=0.014$). Patients who received zoledronic acid 4 mg also had better time to first SRE and time-to-progression of bone lesions (Table 3).

Although the analysis was conducted retrospectively, the data used in that analysis were collected prospectively as part of a larger RCT. It is difficult to generalize the subset analysis of MRCC patients by Lipton et al to the larger population given its small sample size. However, the much higher rate of SREs in the renal cell carcinoma placebo population (74%) compared to the general placebo trial population (44%) provides a rationale for the targeting of the agent, in this case zoledronic acid, to the patient population that it is most likely to benefit. Indeed, the absolute benefit of zoledronic acid in preventing SREs in the MRCC population (37%) is much higher than the absolute reduction in risk seen in prostate cancer (11%) (13). In addition, given the relative rarity of metastatic renal cell carcinoma, it is unlikely that another RCT will be conducted in this patient population.

Osteonecrosis of the jaw (ONJ) is a well-known albeit uncommon complication of bisphosphonate therapy. In one retrospective review of 166 patients of whom 78 had zoledronic acid, ONJ developed in one patient with renal cell carcinoma receiving sunitinib and zoledronic acid concurrently (14). The incidence of ONJ among patients (all cancers) receiving bisphosphonates with or without antiangiogenic agents was 16% and 1.1%, respectively ($p=0.008$). Although small and retrospective in nature, this study should be kept in consideration when treating patients with inhibitors of angiogenesis [see PEBC Evidence-based Series #3-8-4, *The Use of Inhibitors of Angiogenesis in Patients with Inoperable Locally Advanced or Metastatic Renal Cell Cancer* (15)] and zoledronic acid and proper oral hygiene, close monitoring and a high index of suspicion should be maintained.

CONCLUSIONS

The opinion of the authors is that zoledronic acid is recommended in the treatment of patients with bone metastases secondary to renal cell carcinoma.

ONGOING TRIALS

The National Cancer Institute clinical trials database on the Internet (http://www.cancer.gov/search/clinical_trials/) and the National Institutes of Health Clinical Trials database (<http://clinicaltrials.gov/>) were searched for reports of new or ongoing randomized trials investigating the use of zoledronic acid in patients with bone metastases secondary to renal cell carcinoma. No new or ongoing randomized trials were identified.

CONFLICT OF INTEREST

The authors of this special advice report disclosed potential conflicts of interest relating to the topic of this special advice report. One author has received honouraria for speaking engagements for Novartis (MM), and one author has received grant/research support from Novartis (SH). The remaining authors (CQ-G, AEH) reported no conflicts of interest.

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Appendix 1. Literature search strategies.

Ovid MEDLINE

1. diphosphonates/
2. zoledronic acid:.mp.
3. zoledronate:.mp.
4. zometa:.mp.
5. zomera:.mp.
6. or/1-5
7. exp carcinoma, renal cell/
8. renal cell cancer:.mp.
9. renal cell carcinoma:.mp.
10. or/7-9
11. 6 and 10
12. limit 11 to (human and English language)

EMBASE

1. bisphosphonic acid derivative/
2. exp zoledronic acid/
3. zoledronic acid:.mp.
4. zoledronate:.mp.
5. zometa:.mp.
6. zomera:.mp.
7. or/1-6
8. exp kidney carcinoma/
9. renal cell carcinoma:.mp.
10. renal cell cancer:.mp.
11. or/8-10
12. 7 and 11
13. limit 12 to (human and English language)