Guidelines for the use of Zoledronic Acid for the treatment of Tumor Induced Hypercalcemia
QEII Health Sciences Centre/Cancer Care Nova Scotia

Guideline Questions

≥ Does zoledronic acid provide a clinical and/or practical advantage over standard agents used in tumor induced hypercalcemia (TIH)?
≥ Which patients would benefit from the initial use of zoledronic acid as opposed to another bisphosphonate agent?
≥ Is there a role for the use of zoledronic acid in patients who have failed other bisphosphonate agents?

Objectives

≥ To make recommendations regarding the use of zoledronic acid in patients with malignancy related hypercalcemia or TIH.

Outcome Measures

≥ To review efficacy in terms of response rates, duration of response and safety profile of zoledronic acid.

Quality of Evidence

≥ Phase I, Phase II and Phase III trial included:

Phase I dose ranging trials in hypercalcemic cancer patients as well as normocalcemic patients with osteolytic bone metastases; Phase II trials of zoledronic acid for the treatment of osteolytic lesions associated with advanced multiple myeloma and breast carcinoma; Phase III trial in hypercalcemia of malignancy.

≥ Phase I dose finding study of zoledronic acid determined two effective dose levels in patients with TIH (Body et al 1999) (Level V Evidence) (Published).

≥ Two Phase III (US/Canada and Europe/Australia) identical, concurrent, parallel, multicentre, randomized, double blind, double dummy trials were conducted to compare efficacy and safety of zoledronic acid versus pamidronate for the treatment of TIH. These studies were reported in a combined analysis (Major et al 2001)(Level II Evidence)(Published).

Benefit

≥ The end points of efficacy, normalization of calcium, and duration of response was reported in the combined Phase III trials. Patients with a corrected serum calcium ≥ 3.00 mmol/L were randomized to single doses of zoledronic acid 4 mg or 8 mg (5 minute infusion) or pamidronate 90 mg (2 hour infusions). Approximately 50% of zoledronic acid patients and 33.3% of pamidronate patients treated, demonstrated onset of normalization of the corrected serum calcium by Day 4. The rate of complete response (CR) (defined as corrected serum calcium ≤ 2.7 mmol/L) (assessed at Day 10) demonstrated a statistically significant benefit of zoledronic acid 4 mg (88.4%) and 8 mg (86.7%) over pamidronate 90 mg (69.7%). There was no significant difference in the proportion of patients with CR between the zoledronic acid 4 mg and 8 mg dose groups. The median duration of CR in those patients who achieved normal serum calcium values favored zoledronic acid 4 mg and 8 mg over pamidronate 90 mg with response durations of 32, 43, and 18 days, respectively.

≥ Approximately 25% of all patients (excluding those who discontinued or died) (total of 69 patients retreated; zoledronic acid 4 mg – 19 pts, 8 mg – 12 pts and pamidronate 90 mg – 38 pts) who relapsed or were non-complete responders (defined by corrected calcium ≥ 2.9 mmol/L) were retreated with a single dose of zoledronic acid 8 mg. Fifty two percent of retreated patients achieved a CR (responses

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seen in each group; zoledronic acid 4 mg – 52.6%, 8 mg – 41.7% and pamidronate 90 mg – 55.3%) by Day 10 with median duration of response of 15 days and median time to relapse of 8 days.

Adverse Effects

- The most common drug related toxicities included fever, hypophosphatemia and symptomatic hypocalcemia. Other side effects included nausea, constipation, dyspnea, insomnia, confusion and anemia.

- Renal toxicities appeared more frequently in the zoledronic acid group. Two patients in the zoledronic acid 4 mg group demonstrated grade 3 serum creatinine toxicity. Five patients in the original treatment group and 2 patients in the re-treatment arm of zoledronic acid 8 mg exhibited grade 3/4 renal toxicity. Four patients in the pamidronate arm demonstrated grade 3/4 serum creatinine changes.

Evidence Based Recommendation

Zoledronic acid represents a new addition to the existing agents used in the treatment of TIH. This agent has been described as a more “potent” bisphosphonate compared to other marketed bisphosphonates. How does this affect clinical practice? In the randomized study of a commonly used bisphosphonate, pamidronate, zoledronic acid demonstrated superiority in terms of response rate, normalization of calcium and duration of response. Interestingly, the response rate of 69.7% with pamidronate in this trial is much lower than documented in previous studies (approx 90%) of treatment of TIH. The comparison demonstrated in the two zoledronic acid treatment arms did not show significant differences between the 4 mg and 8 mg doses therefore the 4 mg dose was selected for approval in Canada. Unfortunately, the re-treatment arm utilized the 8 mg dose and no data is available on the 4 mg dose.

In situations where patients are not presently on bisphosphonate therapy and TIH occurs, a single IV dose of a zoledronic acid 4 mg over a convenient time frame of 15 minutes after adequate hydration would be a reasonable treatment option. As many patients are already receiving bisphosphonate therapy for approved indications in bone metastases (eg. multiple myeloma and breast cancer), data is available only for retreatment of TIH with a single IV dose of 8 mg of zoledronic acid after pamidronate failure. Trials are underway to evaluate the activity of zoledronic acid in the treatment of cancer patients with bone metastases.
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Background

Hypercalcemia is a serious complication in patients with solid and hematological malignancies. An estimated 10-20% of patients with cancer will develop hypercalcemia during the course of their disease most notably in the advanced disease setting. The most common tumors associated with hypercalcemia are carcinomas of the breast, lung, renal cell, colon, head/neck and multiple myeloma.

The early signs and symptoms of hypercalcemia include fatigue, anorexia, nausea, constipation, polyuria and polydipsia, muscle weakness, lethargy and apathy. When hypercalcemia becomes severe, alteration in mental status, seizures and coma can occur. Renal and cardiac dysfunction may also occur as the hypercalcemia progresses.

Tumor induced hypercalcemia (TIH) occurs as a result of stimulation of osteoclast – mediated bone resorption. Cytokines and hormones, including the major protein parathyroid hormone related protein (PTHrP), released by tumor cells lead to increased bone resorption and renal calcium reabsorption leading to a rise in serum calcium levels. Levels of PTHrP are elevated in most patients with humoral hypercalcemia and in approximately 2/3 of patients with bone metastases. Neoplastic bone involvement may or may not be present in patients with hypercalcemia of malignancy.

Standard Therapy

Initial management of acute TIH still requires adequate hydration to restore intravascular volume and enhancing renal calcium excretion. The most effective method of treatment for TIH is control of the associated cancer. In some circumstances control of disease can not be done quickly or is not possible. In some instances normalization of calcium may occur but only briefly. Treatment of TIH often requires an additional intervention with drug therapy. Bisphosphonates are part of the standard therapy for TIH.

Bisphosphonate agents are inhibitors of osteoclastic bone resorption. They are adsorbed to hydroxapatite crystals in the bone and their ability to produce a phosphorous-carbon phosphorous bond renders them resistant to hydrolysis by phosphatases. The bisphosphonate agents presently available include etidronate, clodronate and pamidronate. These agents have demonstrated efficacy in TIH with very few toxicities.

Other agents that may be used in circumstances where a bisphosphonate does not produce a desired response include calcitonin, gallium nitrate (not available in Canada) and corticosteroids. Calcitonin works rapidly however tachyphylaxis occurs after about 48 hours. Steroids are only appropriate in steroid responsive tumors.

In most situations, bisphosphonates should given intravenously. Oral bisphosphonates are available but due to their poor absorption and gastrointestinal toxicity profile tend not to be option of choice. Patients may be maintained on oral therapy if adequate response is obtained from intravenous therapy.

Sodium etidronate was the first bisphosphonate available for TIH. Infusions are administered over a period of days and normalize calcium in approximately 15-40% of patients.

Initially, clodronate was administered as an intravenous infusion for 5 days. A single day 1500 mg infusion was determined to be equally effective and achieved normocalcemia in approximately 80-90% of patients. An oral preparation is available which may be of benefit in some situations of maintaining normocalcemia in some patients. There have been no randomized trials looking at the efficacy of oral clodronate in preventing relapse of hypercalcemia after intravenous clodronate.
Pamidronate was introduced as an agent with the advantage of a single daily infusion. Current data supports the administration of pamidronate over a period of 1-2 hours. Normocalcemia is achieved in more than 90% of patients. A comparison of trials with these agents is described in Figure 1.

Bisphosphonate use also reduces the frequency of morbid skeletal events in patients with metastatic breast carcinoma or multiple myeloma. This area of supportive care is evolving with trials ongoing in many other disease sites to attempt to reduce the complications of metastatic disease. With positive results from trials indicating a reduction in the skeletal mortality rate, more patients are exposed to regular infusions of bisphosphonates (ie. breast cancer and multiple myeloma). A decrease in the number of patients presenting with TIH has decreased over time particularly in these sites.

An association between high PTHrP levels and reduced response to bisphosphonate treatment has been reported in clinical trials. The PTHrP level may also influence the length of time to recurrence of TIH. Initial occurrences of TIH appear to be more responsive to bisphosphonate therapy compared to relapsing episodes.

The development of more potent bisphosphonates with easier schedules and improved efficacy has been ongoing. Zoledronic acid (Zometa®), a third generation heterocyclic imidazole bisphosphonate, that is chemically more active than pamidronate, received approval by the Therapeutics Products Program (TPP) (Health Canada) in 2000. It is indicated for the treatment of TIH following adequate saline rehydration.

**Figure 1**

*Comparison of randomized trials (not all inclusive) describing the progress of bisphosphonate therapy over the last decade*

<table>
<thead>
<tr>
<th>Authors</th>
<th>Drugs</th>
<th>Doses</th>
<th>Duration and Frequency of Administration</th>
<th>Response Rate % (Normalization of corrected calcium)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Purokit et al 1995</td>
<td>Pamidronate IV vs Clodronate IV</td>
<td>90 mg vs 1500 mg</td>
<td>Single 4 HR infusion vs Single 4 HR infusion</td>
<td>100 % vs 80%</td>
</tr>
<tr>
<td>Gucalp et al 1994</td>
<td>Pamidronate IV vs Saline</td>
<td>60 mg vs NA</td>
<td>Single 4 HR infusion vs Single 24 HR infusion vs Continued infusion</td>
<td>78% vs 61% vs 22%</td>
</tr>
<tr>
<td>Ralston et al 1989</td>
<td>Pamidronate IV vs Clodronate vs Etidronate</td>
<td>30 mg vs 600 mg vs 7.5 mg/kg/day</td>
<td>Single 4 HR infusion vs Single 6 HR infusion vs 2 hour infusion daily x 3 days (7 pts given oral after)</td>
<td>87.5% vs 37.5% vs 31%</td>
</tr>
<tr>
<td>Singer et al 1991</td>
<td>Etidronate vs Saline</td>
<td>7.5 mg/kg/day vs NA</td>
<td>2 hour infusion daily x 3 days plus saline up to 3 L/day</td>
<td>24% vs 7%</td>
</tr>
<tr>
<td>Gucalp et al 1992</td>
<td>Pamidronate vs Etidronate</td>
<td>60 mg vs 7.5 mg/kg/day</td>
<td>Single 24 HR infusion vs 2 hour infusion daily x3 days</td>
<td>70% vs 41%</td>
</tr>
<tr>
<td>Nussbaum et al 1993</td>
<td>Pamidronate vs Pamidronate vs Pamidronate</td>
<td>30 mg vs 60 mg vs 90 mg</td>
<td>Single 24 HR infusion vs Single 24 HR infusion vs Single 24 HR infusion</td>
<td>40% RR vs 61% RR vs 100% RR</td>
</tr>
</tbody>
</table>
Clinical Trials

An open label, single dose, phase I trial (Body et al 1999) was conducted in TIH patients to determine the appropriate dose of zoledronic acid. Thirty three patients were treated with a dose escalation schedule, to produce normocalcemia in at least 80% of TIH patients. Thirty evaluable patients demonstrated that very low doses of zoledronic acid (1.2 mg and 2.4 mg for a 60 kg individual) administered as a short infusion effectively treated TIH. The response rate of the 2.4 mg dose was 93%. The fall in serum calcium was rapid (2-3 days) and maintained for several weeks.

A Phase I study of zoledronic acid (Berenson et al 1996) was reported in patients with osteolytic bone metastases. This study demonstrated that doses of zoledronic acid up to 8 mg were safe, inhibit bone resorption and decreased bone pain.

A Phase II trial reported by Lipton et al 1999, randomized patients with osteolytic metastases to either zoledronate or pamidronate. It was concluded that a 5 minute infusion zoledronate 4 mg was at least as effective as 90 mg of pamidronate in preventing the skeletal complications of osteolytic disease. This trial was used as the basis of a larger Phase III study comparing doses of 4 mg and 8 mg of zoledronate to pamidronate 90 mg. (final analysis not completed)

Pooled analysis of two identical Phase III trials were reported in a recent publication by Major et al 2001. Two hundred eighty seven patients were randomized to one of three possible treatment arms. (Arm 1 (86 patients) -4 mg zoledronic acid; Arm 2 (90 patients) - 8 mg zoledronic acid; Arm 3 (99 patients) – 90 mg pamidronate). Patients were eligible with a defined corrected calcium level ≥ 3.00 mmol/L. Patients who were refractory to initial therapy or who relapsed up to 56 days after initial treatment with either zoledronic acid or pamidronate were re-treated with a single dose of 8 mg of zoledronic acid via a 5 minute infusion and were followed for 28 days. Mean corrected calcium levels were significantly lower in patients treated with zoledronic acid 4 mg or 8 mg than in patients treated with 90 mg pamidronate at days 4, 7, and 10. The CR rates by day 10 were 88.4% (P=.002), 86.7% (P=.015) and 69.7% for zoledronic acid 4 mg, 8 mg and pamidronate 90 mg, respectively. Normalization of corrected calcium occurred by day 4 in approximately 50% of patients treated with zoledronic acid and in only 33.3% of the pamidronate treated patients. The median time to relapse in patients treated with 4 mg or 8 mg of zoledronic acid was 30 days (P=.001) and 40 days (P=.007) compared with 17 days in the pamidronate group. The median duration of CR was zoledronic acid 4 mg – 32 days, zoledronic acid 8 mg – 43 days, compared with 18 days for the pamidronate group. There was no significant difference in the proportion of patients with CR between the zoledronic acid 4 mg and 8 mg dose groups. Approximately 25% of patients who relapsed after having achieved a CR or were refractory to initial treatments on any of the three arms, retreatment with 8 mg zoledronic acid was evaluated. Fifty two percent of patients achieved a CR by day 10 with a median duration of response of 15 days and median time to relapse of 8 days.

In an unpublished trial in patients with osteolytic bone metastases, the schedule of the zoledronic acid was extended from a 5 minute to a 15 minute infusion due to increased renal toxicity. It is felt that a 15 minute infusion will be safe.
Zoledronic Acid (TIH)

**Approved Use**

- As a single first line agent (zoledronic acid 4 mg IV) in symptomatic or asymptomatic patients with documented evidence of TIH.

Or

- As a single agent in symptomatic or asymptomatic patients with documented evidence of TIH who are refractory, partial responders or non-complete responders following treatment with another bisphosphonate such as IV pamidronate or IV or oral clodronate. Current data recommends a single 8 mg IV dose of zoledronic acid but a single 4 mg IV dose may be used as it is felt to be equivalent however has not been studied.

**Note:** Special approval of zoledronic acid as a single agent for patients outside the approved use can be sought through the Request for Non-Formulary or Restricted Drug Process. Requests should be submitted in writing with specific reference included. Guidelines will be updated and modifications made on the basis of published studies only.

**Side Effects**

The side effect profile is based on adverse effects reported from TIH trials.

<table>
<thead>
<tr>
<th>Side Effects (selected side effects with elevated values)</th>
<th>Zoledronic Acid 4 mg</th>
<th>Zoledronic Acid 8 mg</th>
<th>Pamidronate 90mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>7%</td>
<td>10.2%</td>
<td>9.7%</td>
</tr>
<tr>
<td>Hypocalcemia</td>
<td>5.8%</td>
<td>6.1%</td>
<td>1.9%</td>
</tr>
<tr>
<td>Hypophosphatemia</td>
<td>3.5%</td>
<td>3.1%</td>
<td>1.0%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>1.2%</td>
<td>1.0%</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>1.2%</td>
<td>3.1%</td>
<td>1.0%</td>
</tr>
</tbody>
</table>

**Dosing:**

**Renal Impairment:** Monitor renal function. Zoledronic acid has not been tested in patients with severe impairment (serum creatinine > 400 uM/L). Serum creatinine should be evaluated prior to each dose.

**Hepatic Impairment:** No dosage recommendations can be made in liver dysfunction.
Cost Estimates and Expected Patient Numbers

Cost
Estimated cost/dose for the treatment of TIH with zoledronic acid 4 mg is approximately $519.75.

Zoledronic Acid (for TIH only) 8 patients / year will be treated.

Drug  Estimated number of doses/patient  3 doses  Average cost/patient $1560.00

Assumptions:

- Median survival after a diagnosis of TIH approximately 2 – 6 months (Zojer et al 1999)
- Median duration of response for zoledronic acid 4 mg is approximately 32 days vs 18 days for pamidronate 90 mg (Major et al 2001)
- Median time to relapse for zoledronic acid 4 mg is approximately 30 days vs 17 days for pamidronate 90 mg (Major et al 2001)
- Based on response and duration rates for every 3 doses of zoledronic acid administered 5 doses of pamidronate would be required. (Dranitsaris 2000)
- This patient population is already treated with bisphosphonate therapy (ie. pamidronate 90 mg = 472.50/dose.)

Conclusions:

- For newly diagnosed and treated TIH patients with zoledronic acid 4 mg ($519.75) compared to standard pamidronate 90 mg ($472.50), it appears there may be a 10% increase in drug cost. However, this incremental cost may disappear with the improvements in response rate and duration.
- Incremental drug costs may become apparent if retreatment with zoledronic acid 8 mg is used after pamidronate failure.

No additional funding for the QEII HSC is currently required for the use of zoledronic acid for TIH.
Summary

In the area of supportive care, zoledronic acid provides an alternate option in the treatment of TIH. The pooled analysis of the Phase III trial demonstrates a superior response rate, time to normalization of calcium and duration of response.

A few noteworthy points with respect to the Phase III study should be mentioned. A larger number of patients enrolled in the pamidronate arm – 99 patients compared to 86 patients – 4 mg zoledronic acid dose group and 90 patients – 8 mg zoledronic acid dose group is noted. The proportion of patients with breast or hematologic malignancies was greater in zoledronic acid 4 mg group than in the zoledronic 8 mg or pamidronate 90 mg group. There appeared to be less patients in the pamidronate group with bone metastases. The choice of baseline hypercalcemia (corrected value \( \geq \) 3.00 mmol/l) may be difficult to use in clinical practice as some patients may exhibit signs and symptoms of TIH with levels lower than described in this trial. One final item is the poor response rate documented (69.7%) in the pamidronate arm that is much lower than described in previous trials.

Despite some of the items described above, zoledronic acid does seem to provide a clinical advantage over the standard bisphosphonates used. From a practical point of view, a single IV infusion of 15 minutes would provide an advantage for administration in an inpatient, outpatient or treatment at home setting. There appears to be a definite role for the use of zoledronic acid after the failure of another bisphosphonate in those patients requiring additional therapy.

Restrictions for Use

Restricted for treatment of TIH in newly diagnosed or refractory, partial responsive or non-complete responsive patients.

Treatment Location

Patients will be treated as an inpatient, outpatient or at home with adequate administration equipment, and appropriately supervised.

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Bibliography