Feasibility of administering zoledronic acid in palliative patients being cared for in the community: results of a pilot study

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ABSTRACT

Tumour-induced hypercalcemia (TIH) and pain from bone metastases are common complications of advanced malignancy and have a significant negative impact on quality of life. Many cancer patients in the advanced stages of their palliative illness prefer to avoid hospitalization and to receive their care in the community setting. This small open-label prospective pilot study explored the feasibility of administering zoledronic acid intravenously in the community setting (home and residential hospices). It enrolled a convenience sample of 12 patients with advanced cancer and TIH (n = 7), malignant bone pain (n = 3), or TIH and malignant bone pain (n = 2). The mean duration of infusion was 15 minutes (range: 14–30 minutes). The total nursing time required was 95 minutes, and the mean total cost, including nursing time, travel time, and drug costs was $708.97 per infusion. This cost was compared with costs for clodronate and pamidronate ($402.52 and $406.12 respectively). Calcium fell from a mean of 2.97 mmol/L on day 0 to 2.63 mmol/L on day 4 and to 2.54 mmol/L on day 10. Delirium resolved in 2 of 5 patients with TIH-associated delirium. Intravenous zoledronic acid administered in the community to palliative patients at the end of life is feasible and safe, and the short duration of infusion offers advantages to patients and nursing resources alike. The higher cost of zoledronic acid per infusion may be offset by the advantage of its short infusion time.

KEY WORDS

Palliative care, bisphosphonates, hypercalcemia, bone pain, home care, hospice care

1. INTRODUCTION

Metastatic bone pain and tumour-induced hypercalcemia (TIH) are common complications of advanced malignancy. Both have a significant adverse effect on quality of life. Parenteral bisphosphonates are currently considered the standard for treatment of TIH [1]. They have been shown to reduce skeletal events, bone pain, and need for radiotherapy in patients with bone metastases from multiple myeloma and breast and prostate cancer [1]. There is also some evidence that they lower morbidity in metastatic bone disease from other solid tumours [1,2]. Single-dose treatments usually suffice in the case of TIH; regular monthly treatments are generally required to prevent skeletal events. Although the role of bisphosphonates in the management of acute malignant bone pain is equivocal [3], some select patients may experience improved pain control after single dosing [4]. Long-term treatment appears to improve pain control, but reliance should not be placed on bisphosphonates as the primary mode of pain control.

The bisphosphonates most widely reported to be prescribed in the cancer setting are clodronate, pamidronate, and zoledronic acid. Zoledronic acid is the most potent of the three [5]. All three agents are administered intravenously, but clodronate may also be administered orally or subcutaneously [6]. Although useful in the community palliative care setting, subcutaneous clodronate requires an infusion time of 8–12 hours, compared with 2 hours for pamidronate and 15 minutes for zoledronic acid [5]. In the treatment of TIH, zoledronic acid appears superior to pamidronate in terms of the number of people who respond and the incidence of relapse [7]. The short infusion time for zoledronic acid makes it particularly appealing in settings in which nursing resources are more limited, including the community setting. Several reports have evaluated the administration of bisphosphonates, and in particular zoledronic acid, in the community [8–10]; however, with the exception of one study by Santangelo and colleagues, involving elderly Italian patients in nursing homes [11], these reports did not focus on patients with very advanced

disease or on those being cared for by palliative care services.

With this in mind, we set out to explore the feasibility and safety of using zoledronic acid in very advanced cancer patients receiving care in the community by palliative home care and hospice services. We compared the costs of using zoledronic acid with the inferred best-scenario costs of using clodronate or pamidronate. Because this was our team's first community-based drug study, we used the opportunity to explore the logistics and processes that would be required for future community-based clinical research.

2. PATIENTS AND METHODS

In this pilot open-label prospective study, which was approved by the local ethics review board, patients with symptomatic TIH or severe malignant bone pain who were referred to the community-based palliative care consult team (physicians and nurses) of the Calgary Regional Palliative Care Team were screened for eligibility to participate. Patients for whom the team felt treatment would be beneficial were approached to participate in the study. The team took various clinical factors into account when considering the appropriateness of proposing treatment, including the patient's wishes, goals of care, and life expectancy, and the potential benefit-versus-burden ratio. The goal was to recruit 15 patients to the study.

Patients were eligible for the trial if they had advanced cancer and low performance status (such that transfer to hospital for treatment would have been highly burdensome) and if they were receiving care from either the palliative home care program of the Calgary Health Region or a residential hospice. In the Calgary Health Region palliative care program, patients are eligible for residential hospice if they have less than a 3-month life expectancy and require 24-hour care. The Calgary Health Region has a mobile phlebotomy service that comes to patient homes and hospice residences for blood investigations in patients that the consult service feels warrant further investigation and treatment. The diagnosis of hypercalcemia was made by the consult service or hospice physician. In the case of patients with bone pain, the phlebotomy service was summoned for baseline blood tests (calcium, albumin, creatinine) before treatment. Blood was also drawn to assess calcium and creatinine levels on days 4 and 10 after treatment.

Patients were stratified into one of three clinical indications for intravenous bisphosphonates: TIH, malignant bone pain, or a combination of the two. Patients with TIH were considered eligible

- if they had a corrected serum calcium of 2.5 mmol/L or more, *and*
- if they were experiencing symptoms judged by their physician to be a result of hypercalcemia *or*
- if they had asymptomatic hypercalcemia, but a corrected calcium level of 3.0 mmol/L or more.

Patients with malignant bone pain were eligible if they described average pain intensity of 6 or more out of 10 on a numeric rating scale despite optimal treatments, which included a strong opioid with or without prior palliative radiotherapy. All patients had to have adequate renal function (defined as serum creatinine 140 μmol/L or lower for the purposes of this study) and adequate hydration as judged by the physician. Patients were ineligible if they had a known hypersensitivity to zoledronic acid or significant renal impairment, if they had received bisphosphonate treatment within the preceding 7 days, or if they did not provide consent. If the patient was unable to provide informed consent, informed consent from the patient's designated guardian or closest family member was obtained.

Once the physician had completed the prescription, the outpatient pharmacy was notified. A local courier delivered the medication, together with intravenous tubing, a pump, and related supplies to the patient's home, and picked up supplies after drug administration. In some cases, these items were picked up and delivered by family members. On the day of medication administration (day 0), the palliative care physician performed a physical exam, and on days 0, 4, and 10, each patient was asked to complete the Edmonton Symptom Assessment System scale if able to do so. If the patient was delirious, the physician or nurse completed the Confusion Rating Scale and the Short Blessed (Orientation–Memory–Concentration) Test as was normal practice for the team [12]. A package with assessment forms was left in the home for the patient's home care nurse to complete. A nurse from the Calgary Home Parenteral Therapy Program administered zoledronic acid 4 mg in normal saline 100 mL over 15 minutes. The distance and time required for traveling to the patient's place of residence, the duration of the infusion, and the total nursing time at the patient's residence was recorded.

Although a formal economic evaluation was not undertaken in this pilot study, costs were calculated using the local hourly rate of a nurse consultant, the costs of the medications in the community, the duration of the infusions, and the nursing time spent with the patient and traveling. Comparisons were made with the other two bisphosphonates available for use in the region, namely pamidronate (intravenous) and clodronate (subcutaneous). The nursing times and the travel times and distances that would potentially be required (best-case scenario) for administering these drugs were inferred from the data collected in the present study, assuming that nurses would administer,

monitor, and assess the patients treated the alternative bisphosphonates in the same way they did for patients treated with zoledronic acid. The infusion times for intravenous pamidronate and subcutaneous clodronate were assumed to be 2 hours and 10 hours respectively, per the standard practice of the palliative care program at the time of the study. For clodronate, 10 hours was used instead of 6 or 8 hours, because the longer time appears to result in fewer cases of irritation and inflammation at the infusion site. It was normal practice for nurses to remain in the home for the duration of a pamidronate infusion. In the case of clodronate, staying for the total duration was deemed not feasible; instead, nurses were present only for approximately the first hour and last hour of the infusion. Patients and families were instructed on complications that could occur and when to call the nurse if problems appeared. Hence, the nursing time in the case of clodronate was calculated at 2 hours (120 minutes).

For comparison purposes, the cost for treating TIH in hospital was also estimated. The assumption was made that the patient would be admitted only for the duration of the treatment, arguably a significant underestimation, because in many cases patients remain in hospital for several days. The infusion durations, including the time to set up the infusion, were assumed to be 30 minutes, 2.5 hours, and 3.5 hours for zoledronic acid, pamidronate, and clodronate (intravenously rather than subcutaneously as in the home setting) respectively. The cost of occupying an acute hospital bed was set by the institution at $154.00 per hour, and the drug costs were assumed to be the same as they were in the community.

3. RESULTS

The study enrolled 12 patients (11 treated at home, and 1 treated in a residential hospice): 7 with TIH, 3 with malignant bone pain, and 2 with both TIH and malignant bone pain. The primary cancer sites were genitourinary ($n = 3$), head and neck ($n = 3$), lung ($n = 2$), breast ($n = 2$), melanoma ($n = 1$), and unknown ($n = 1$). The median age of the patients was 66 years (range: 46–81 years). Three patients received subcutaneous hydration by hypodermoclysis in the days preceding study enrolment.

Median survival for the cohort was 22 days post treatment with zoledronic acid (range: 1–113 days). Of the 12 patients, 6 were able to remain at home until death. Of the 6 who were not able to remain at home, 4 were admitted to residential hospices and 2 to the regional acute inpatient palliative care unit, where they died. Five patients were delirious at the time of treatment as determined by a combination of physical examination, administration of the Short Blessed Test and the Confusion Rating Scale or the Folstein Mini-Mental State Examination. Of the patients who were delirious at baseline, 3 did not reverse with therapy. Survival was 1, 5, and 8 days in these patients. Within the period of observation of the study, 2 patients demonstrated resolution of delirium. They survived for 61 and 89 days after treatment with the bisphosphonate. In patients treated for TIH, the mean corrected serum calcium level dropped from 2.97 mmol/L on day 0 (range: 2.63–3.49 mmol/L) to 2.63 mmol/L on day 4 (range: 2.31–3.40 mmol/L; $p = 0.0246$; $n = 9$) and to 2.54 mmol/L on day 10 (range: 2.28–3.46 mmol/L; $p = 0.0199$; $n = 8$). Missing data precluded an evaluation of the effect of the treatment on pain levels.

No adverse drug effects were reported on the day of the infusion, and all adverse effects reported on day 4 or day 10 were mild: fatigue in 3 patients; flu-like symptoms and edema in each of 2 patients; and shortness of breath, weakness, and gait instability in 1 of the foregoing 2 patients. Given the high prevalence of these symptoms in advanced palliative patients, it was impossible to determine with confidence how many were attributable to the known adverse effects of the treatment and how many to terminal illness. Three deaths occurred during the study period on days 1, 5, and 8 after treatment. All were deemed to be the result of progressive disease. One patient opted not be assessed on day 10. No renal impairment was seen in association with the administration of zoledronic acid. Mean serum creatinine was 75.3 mmol/L on day 0 (range: 54–124 mmol/L); 61.0 mmol/L on day 4 (range: 44–79 mmol/L; $n = 10$); and 66.3 mmol/L on day 10 (range: 42–97 mmol/L; $n = 8$). No episodes of symptomatic hypocalcemia were noted.

Table I summarizes the times and travel distances required for treatment. The cost of treatment was calculated by taking into account the nursing time, the drug costs, and the costs of infusion materials (Table II). The total cost of nursing time, the drug, and the equipment was estimated to be $709 (2004 Canadian dollars).

Given the assumptions described in "Patients and Methods," and excluding the cost of ambulance transport to and from hospital, the in-hospital costs

TABLE I Required time and distances for home infusion of zoledronic acid

Drug infusion duration	14–15 min in 10 of 12 patients (range: 14–30 min)
Mean travel time to patient	17 min (range: 5–30 min)
Nursing time in the home or residence	61 min (range: 40–115 min)
Total nursing time (time in the home plus to/from travel time)	95 min
Mean travel distance	25 km

TABLE II Estimate of the costs of bisphosphonate treatments in the community setting (home or residential hospice) available to the Calgary Palliative Care Service at the time of the study[a]

Cost variables	*Cost in time and 2004 Canadian dollars for*		
	Zoledronic acid (intravenous)	*Pamidronate (intravenous)*	*Clodronate (subcutaneous)*
Cost per dose ($)[b]	620.00	230.00	160.00
Total nursing time (min)[c]	15 (infusion time) + 80 (other) = 95[d]	120 (infusion time) + 80 (other) = 200	120 (time at bedside) + 2 × 80 (other)[e] = 280
Total nursing cost ($)[f]	78.85	166.00	232.40
Travel distance (km)	25	25	25
Travel cost[g]	10.12	10.12	10.12
Total cost	708.97	406.12	402.52

[a] Data for pamidronate and clodronate are estimates based on best-case scenarios.
[b] Includes pharmacy fees and a flat $40 for infusion material such as tubing and needles.
[c] Required time at the home, including duration of infusion, assessment, set-up and discontinuation of the infusion, plus travel time to and from the home.
[d] Average duration of infusion and travel time as determined in the present study. (Comparison columns assume that each travel time would be the same as with zoledronic acid.)
[e] In the Calgary Regional Program, the nurse does not remain throughout the 8-hour infusion. Two visits are required: at least 1 hour at treatment initiation, and then time at treatment completion for reassessment and treatment discontinuation.
[f] Total nursing time × $50/hour ($0.83/min).
[g] 25 km × $0.405/km (the regional reimbursement rate).

were estimated to be $704.00, $697.00, and $615.00 for clodronate, zoledronic acid, and pamidronate respectively. The cost of patient transportation by ambulance to and from hospital is itself much greater than the total cost of home administration of any bisphosphonate.

4. DISCUSSION

The study confirmed the feasibility and safety of administering intravenous zoledronic acid to advanced palliative patients with TIH or severe malignant bone pain in our community setting. Frail patients could receive intravenous treatment at their residence, avoiding the inconveniences of a hospital admission.

The infusion time for zoledronic acid and the total time that the nurse was in the patient's house were comparable to those reported by Chern and colleagues [13], who found a mean of 78 minutes in the clinic or at home. Our time was shorter than the 98 minutes reported by Barrett-Lee *et al.* [14] in a study of patients making hospital outpatient visits for treatment with intravenous zoledronic acid.

The short infusion time observed in our study imparts an advantage for zoledronic acid over the other bisphosphonates. Although the total cost of infusing zoledronic acid was higher than that for administering pamidronate or clodronate, patients spent considerably less time receiving zoledronic acid, and nurses had more time to attend to the patient. Moreover, it could be argued that the higher cost of zoledronic acid was offset by its reported therapeutic superiority, potentially requiring fewer repeat treatments. In the pooled analysis by Major *et al.* [7] of two randomized controlled clinical trials of zoledronic acid compared with pamidronate, the complete response rates by day 10 were 88.4% for zoledronic acid (8 mg) and 69.7% for pamidronate (90 mg). Normalization of calcium levels by day 4 occurred in 50% of patients treated with zoledronic acid as compared with only 33.3% of patients treated with pamidronate. In addition, the median duration of complete response favoured zoledronic acid (43 days) over pamidronate (18 days). A lower dose of zoledronic acid (4 mg) was also superior to pamidronate in terms of duration of response and complete response rate.

Three other studies have evaluated the intravenous administration of zoledronic acid in the community [8–10]. The primary indication for treatment was malignant bone pain, and patients were maintained on monthly zoledronic acid infusions for prolonged periods. The studies involved patients with much longer survival and better performance status than the frail cohort involved in our study. Santangelo and colleagues treated advanced palliative patients with a life expectancy of less than 3 months at home [11]. The focus of their study, which involved 35 patients in Italy, was on the management of pain. Clodronate 300 mg was administered intravenously every other day for an unspecified length of time, a regimen that likely required considerably greater utilization of resources and nursing time than the regimen in our study did.

Zoledronic acid was safe and practical to administer in our study population. Overall, treatments were well tolerated, and no serious adverse effects were reported in our small group of patients.

The clinical results in our study warrant further reflection. Although calcium levels were significantly reduced from a mean of 2.97 mmol/L on day 0 of treatment to a mean of 2.54 mmol/L on day 10, the clinical impact was not clear—perhaps because of the small number of patients. Delirium appeared to have resolved in 2 of 5 patients treated because of TIH-related delirium. It must be noted that the cause of delirium in the palliative setting is often multifactorial, which may explain why the condition did not resolve in the other 3 patients. Those 3 patients were also close to death when they received treatment; they died within 1–8 days of receiving treatment. The two patients that responded lived considerably longer (61 and 89 days). The fact that 3 patients died during the study at days 1, 5, and 8 raises the question of whether they should have received treatment in the first place. Whether a patient is likely to benefit from a treatment at the end of life should always be considered, and the benefits should be weighed against the burden of treatment. Predicting when a person will die is often difficult; occasionally, a decline in a patient's condition may not necessarily indicate that the patient is close to death. Clearly, the selection of appropriate patients for treatment needs closer attention in the future. The small number of patients treated for pain control ($n = 5$) and the absence of some Edmonton Symptom Assessment System data in those patients preclude an analysis of the effect of the treatment on pain.

Recruitment to the study was slow. Our experience indicates that patient accrual can be challenged by the speed of illness advance, by the logistics of mobilizing the study team to obtain follow-up data, and by the complexity of intercurrent illness. Although the community setting is an important one in which to conduct relevant end-of-life care research, sufficient support and logistics are necessary.

Although the present study is small and incomplete, it provides useful pilot and feasibility data for a larger study, because economic data are important. A larger follow-up study would be strengthened by more rigorous assessment of pre- and post-treatment pain scores and adverse effect assessment, and a more homogenous study population.

5. CONCLUSIONS

This preliminary study suggests that, given the appropriate resources, it is feasible to administer zoledronic acid intravenously for hypercalcemia of malignancy or for bone pain to patients with advanced illness in the home or a residential hospice setting. The short duration of infusion for zoledronic acid represents an important advantage over other bisphosphonates, and the potency of the drug may offset its greater costs. However, meticulous identification of patients who could potentially benefit from treatment is required, particularly when dealing with patients with a limited life expectancy. Moreover, better indicators for predicting survival and response are needed. Further research is needed to maximize the efficiency and effectiveness of community-based clinical trials in palliative care.

6. CONFLICT OF INTEREST DISCLOSURE

This work was sponsored by an unrestricted study grant from Novartis, the pharmaceutical company that produces both zoledronic acid and the original form of pamidronate.

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