ORIGINAL ARTICLE

ZOLEDRONIC ACID IN METASTATIC BONE DISEASE: AN AUDIT BASED DISCUSSION

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Background: Metastatic bone disease is a common problem in patients with advanced cancer causing significant morbidity and poor quality of life. Effective and less toxic treatments, like bisphophonates, can reduce morbidity in such cases. **Objectives:** The objectives of this study were to determine whether Zoledronic acid was administered in accordance with current recommendations for its prescribing and to produce protocols for improved patient outcomes. **Methods:** The study was a retrospective audit of 39 consecutive patients with metastatic bone disease secondary to solid tumours who were treated with Zoledronic acid. The records were analysed to establish the administered dose of Zoledronic acid relative to creatinine clearance. The standards for Zoledronic acid therapy were defined from best practice guidelines. **Results:** The commonest diagnosis in patients receiving Zoledronic acid was carcinoma prostate 19/39 (49%) followed by carcinoma breast 11/39 (28%), gastrointestinal malignancies 4/39 (10%) and renal cell carcinoma 3/39 (8%). Indications for therapy were metastatic bone disease alone 31 (79%), hypercalcaemia alone 0/39 (0%), metastatic bone disease with hypercalcaemia 5/39 (13%), and prevention of chemotherapy induced bone loss 1/39 (3%). The dose of Zoledronic acid was appropriate to the creatinine clearance in 25/39 (64%), inappropriate in 5/39 (13%) and unclear from the notes in 9/39 (23%). **Conclusions:** Majority of patients received Zoledronic acid for the appropriate indications. The dose of Zoledronic acid was appropriate to serum creatinine clearance in a majority of patients. Poor documentation of data pertaining to Zoledronic acid treatment is observed which can potentially lead to major errors in prescribing. We recommend using a standard form to document each episode of therapy with Zoledronic acid.

Keywords: Zoledronic Acid, Metastatic Bone Disease, Audit

INTRODUCTION

Metastatic bone disease is a common problem in patients with advanced cancer.[1] It can cause pain, fractures, and hypercalcaemia leading to an increased need for analgesics and radiotherapy. These factors have an adverse effect on patients' quality of life. Therefore newer, effective, and potentially less toxic treatments are always welcome for these patients. In recent years, bisphosphonates have been shown to reduce skeletal morbidity from metastatic bone disease and have been adopted in various protocols for such patients. At Withybush General Hospital in Pembrokeshire (UK), we have been offering this treatment to our cancer patients for some years.

The aims and objectives of the study were to determine whether Zoledronic acid was administered in accordance with current recommendations for its prescribing. This included looking at the indications for Zoledronic acid therapy and the frequency, duration and appropriate monitoring of its use within the chemotherapy day unit at Withybush General Hospital.

MATERIAL AND METHODS

This was a retrospective audit of 39 consecutive patients with metastatic bone disease secondary to solid tumours who were treated with Zoledronic acid. Only the most recent episode of treatment was taken for the purpose of the audit. Data were gathered from patients' notes and the Hospital Information and Support System (HISS). We recorded the main diagnosis, indication for biphosphonate therapy, monitoring and documentation of serum calcium, serum creatinine, serum creatinine clearance and calcium supplementation (if indicated), the frequency and total duration of therapy. We also looked at whether the dose of Zoledronic acid given was appropriate to individual patient's creatinine clearance. The standards for Zoledronic acid therapy were defined from best practice guidelines.[2] The data were analysed by the palliative care team through tabulation and graphs.

RESULTS

Out of the total number of patients 39 (100%), the commonest diagnosis in patients receiving Zoledronic acid was carcinoma prostate 19/39 (49%) followed by carcinoma breast 11/39 (28%), gastrointestinal malignancies 4/39 (10%), and renal cell carcinoma 3/39 (8%). Indications for therapy were metastatic bone disease alone 31 (79%), hypercalcaemia alone 0/39 (0%), metastatic bone disease with hypercalcaemia 5/39 (13%), and prevention of chemotherapy induced bone loss 1/39 (3%). In two patients the indication for therapy was not clear from the notes.

Serum urea, electrolytes, creatinine and creatinine clearance were done in all patients prior to the therapy but were documented in none of the patient notes. Serum calcium was done in 37/39 (95%) patients but

documented in only 20/39 (51%). The dose of Zoledronic acid was appropriate to the creatinine clearance in 25/39 (64%), inappropriate in 5/39 (13%), and unclear from the notes in 9/39 (23%) patients. Calcium supplementation was provided in 34/39 (87%) patients. Results showed that all 5/39 (13%) patients who did not get calcium supplements, had metastatic bone disease *with* hypercalcaemia. Zoledronic acid was given 4-weekly in 32/39 (81%), 6-weekly in 4/39 (10%), 8-weekly in 1/39 (3%) and 4-monthly in 1/39 (3%). In 1/39 (3%) patients, the frequency of administration was unclear from the notes. Also, 32/39 (82%) patients received Zoledronic acid for two years or less and 7/39 (18%) for more than two years.

Table-1: Estimated Creatinine Clearance CrCl) and corresponding recommended Zoledronic acid dose

Baseline CrCl (ml/min)	Zoledronic acid dose (mg)
>60	4
50–59	3.5
40–49	3.3
30–39	3.0
<30	Omit

DISCUSSION

Bisphosphonates are analogues of pyrophosphate and act primarily by stabilising osteoclast activity in the bone. Zoledronic acid (intravenous only) and Ibandronate (intravenous and oral) are potent bisphosphonates and have been evaluated in clinical trials in patients with bone metastases secondary to various malignancies.[3] They have an established role in the treatment of malignant hypercalcaemia and have been shown to significantly reduce Skeletal Related Events (SREs)[4] in patients with metastatic bone disease. Bisphosphonates have also been used to reduce chemotherapy-induced bone loss.[5]

SRE's are a composite end point that includes bone pain, hypercalcaemia, pathological fractures and the need for radiotherapy. A recent systematic review concluded that bisphosphonates provide some relief from pain caused by cancer that has involved bone but there was not enough evidence to support its use for immediate effect or as first-line therapy for pain relief.[6] However, like any other medication, these drugs are not free from toxicity either. The reported complications with bisphosphonate use can be nausea, vomiting, hypocalcaemia, and more serious complications like renal toxicity and osteonecrosis of the jaw. Therefore, it is vital and prudent that special care must be taken in prescribing these drugs in individual patients[7] and that these adverse effects be monitored and dealt with in time to prevent further morbidity.

Zoledronic acid has been the most widely used bisphosphonate in metastatic bone disease and has shown benefit across a wide variety of tumour types.[8] Current recommendations for its use are to give it on a monthly basis as a 15-minute infusion.[9] Regarding monitoring, it is recommended to check the renal function and serum calcium levels prior to each injection and to prescribe calcium supplements in normocalcaemic patients. The guidance is to continue treatment for two years in a stable disease. Further use beyond two years is left to the discretion of the treating physician.[10]

In future, the frequency of administration of Zoledronic acid will likely be based on urinary N-telopeptide (NTX) levels, which are markers of bone resorption (and hence osteolytic activity) and are also surrogate markers for mortality in cancer patients.[11,12] A recent study of lung cancer patients with high NTX levels, Zoledronic acid was shown to have significantly reduced the relative risk of death by 35% (p=0.024).[13]

CONCLUSIONS

The vast majority of patients received Zoledronic acid for appropriate indications. Even though serum urea, electrolytes, creatinine and creatinine clearance were done in all patients prior to the administration of Zoledronic acid, they were documented in none. The dose of Zoledronic acid was appropriate to serum creatinine clearance in a majority of patients. The commonest schedule in patients receiving Zoledronic acid was every four weeks, which is in accordance with current guidance. Most patients had serum calcium levels checked but almost half of these were not documented in the notes. Calcium supplements however were prescribed appropriately in all cases. Nearly one in every five patients was on Zoledronic acid for more than two years.

RECOMMENDATIONS

Bisphosphonates are used as a primary therapy for reducing and delaying bone complications and are generally quite well tolerated. Preclinical and clinical data have also shown a possible survival benefit from biphosphonate treatment in patients with cancer.[11] In United Kingdom, various District General Hospitals (DGHs) such as Withybush General Hospital, are increasingly treating larger number of patients with cancer, with a significant proportion having associated bone metastases requiring treatment with potent biphosphonates.

The audit study highlights poor documentation of data pertaining to Zoledronic acid treatment. This can potentially lead to major errors in prescribing which is unacceptable in clinical practice. There is, therefore, a need for clear guidelines on their use to be in place in such hospitals and for developing robust mechanisms to ensure a regular audit on their prescribing. We would encourage hospitals to use a form such as the one we are piloting (Table-1, Figure-1) which would hopefully ensure safe and effective prescribing of Zoledronic acid in a similar way to the prescribing and documentation of chemotherapy for cancer patients.

PATIENT'S ID LABEL

Zoledronic Acid Administration Document

Indication(s) (circle as appropriate)
1. Hypercalcemia 2. Painful bone metastases 3. Both hypercalcemia AND metastatic bone disease
Other (please specify).....

Frequency of administration
1. 4-weekly 2. Other (please specify).....

Start date: ..... Target end date: .....
Has a dental referral been considered? .....

Estimated CrCl (ml/min) by Cockroft-Gault equation = $\frac{(140\text{-age in yrs})\times(\text{weight in kg})\times 1.23}{\text{Serum Creatinine } (\mu\text{mol/L})}$
(For women multiply the result of calculation by 0.85)

Estimated Creatinine Clearance CrCl) and corresponding recommended Zoledronic acid dose

Baseline CrCl (ml/min)	Zoledronic acid dose (mg)
>60	4
50-59	3.5
40-49	3.3
30-39	3.0
<30	Omit

Date	Serum Calcium (corrected) (mmol/L)	Serum Creatinine (µmol/L)	Estimated Creatinine Clearance (ml/min)	Dose of Zoledronic acid prescribed (mg)	Calcium supplement (if indicated)

Figure-1: Zoledronic Acid Administration Document

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