BISPHOSPHONATE THERAPY

Executive Summary

Bisphosphonates are powerful and specific inhibitors of osteoclasts and their use in cancer patients prevents the increased bone resorption that accompanies metastatic bone disease (1,2). Through this mechanism, bisphosphonates reduce complications or skeletal related events (SREs) such as fractures, the need for palliative radiotherapy to relieve pain, spinal cord compression and hypercalemia from bone metastases (3,4). They can also reduce bone pain and analgesic requirements (5,6) and improve quality of life (7-9).

Up to 75% of prostate cancer patients, 70% of breast cancer patients and 30-40% of other solid organ tumors will develop bone metastases (10). Additionally, almost all patients with multiple myeloma will develop bone lesions during the course of the disease (11). In the absence of a bisphosphonate, SREs occur in around one half to two thirds of patients (depending on the underlying malignancy and concomitant cancer treatments) (9,12,13), contributing significant morbidity to the clinical course of the underlying disease and increasing the health care costs of treating advanced malignancy (3, 14).

Bisphosphonates reduce the number of patients with breast cancer experiencing an SRE, extend the time to first and subsequent SREs and prevent around one third of all skeletal morbidity (8,12,13,15). Zoledronic acid is the most effective agent (16-18) with a 41% reduction in the overall risk of SREs when compared to placebo (19). Placebo controlled trials have also shown benefits for oral clodronate (20-22), (intravenous (23,25) and oral ibandronate (24,25) and pamidronate (8,9,15).

In hormone resistant prostate cancer, inhibition of bone resorption is also of clinical relevance despite the osteoblastic nature of most prostate bone metastases (26,27). However, only zoledronic acid has shown significant benefits in terms of reducing SREs (12,28), although intravenous ibandronate has similar efficacy to palliative radiotherapy for the acute relief of bone pain (6). In this disease setting, zoledronic acid decreased the
number of patients experiencing an SRE by 9% (33% vs 44%), increased the median length of time to first SREs (>420 days vs 321 days), reduced the overall risk of SRE by 36% and improved pain scores (12).

Similarly, in non-breast and non-prostate solid tumors (50% NSCLC and 50% miscellaneous other solid tumors), zoledronic acid increased the median time to the first event (230 days vs 163 days) and decreased the overall risk for SREs by 31% (12,29).

In multiple myeloma (30), bisphosphonates reduce vertebral fractures, SREs and bone pain (relative risk of 0.74, 0.80 and 0.75, respectively) with oral clodronate (31,32), pamidronate (33) and zoledronic acid (16,17) having similar effects on skeletal morbidity. However, zoledronic acid improved overall survival when compared with oral clodronate (34).

The current evidence supports the addition of bisphosphonates including zoledronic acid, pamidronate, ibandronate, and clodronate to the EML. Of these, zoledronic acid has the best efficacy and is the recommended bisphosphonate for solid tumors (3). In multiple myeloma, pamidronate and zoledronic acid were equally efficacious and both are considered as appropriate options (35,36).

The reviewers also discussed denosumab as an alternative to bisphosphonates. Denosumab is a monoclonal antibody against RANKL that reduces SREs across all solid tumors (37). However, denosumab is much more expensive than bisphosphonates which are now generic medications and, although modest benefits compared to bisphosphonates have been demonstrated, is not being recommended for inclusion in the Essential Medicines List at this time due to the adverse economic impact this agent would have on health care budgets.
Public Health Relevance

The skeleton is one of the most common locations to which cancer metastasizes. The propensity for solid tumor malignancies to metastasize to bone varies: 65-75% of patients with advanced prostate cancer and 70% of patients who die of breast cancer will develop bone metastases. The incidence of bone metastases is lower, 15-30%, in patients with lung, colon, stomach, bladder and other cancers and only 5% of patients with certain GI malignancies (10). In patients with multiple myeloma, 60% of patients will have bone lesions at the time of presentation and nearly all patients will develop bone lesions during the course of the disease (11).

Bone metastases can cause skeletal-related events (SREs) including fractures, spinal cord compression, hypercalcemia and significant pain, which can then necessitate treatment with radiation and/or chemotherapy or surgical intervention in the case of fractures or spinal complications. In patients with bone metastases treated with systemic anticancer treatments and no bisphosphonates, SREs occur in 46 to 64% of patients in two years (depending on the underlying malignancy), contributing importantly to the significant overall morbidity of advanced cancer (9,12,13).

Overview of Regimens

Solid tumor bone metastases (including breast cancer)

Zoledronic acid Intravenous infusion 4mg every 4-12 weeks (12,13,16)

Alternatives (breast cancer only)

Pamidronate Intravenous infusion 90mg every 4 weeks (8,15)
Ibandronate Oral 50mg daily (24)
Ibandronate Intravenous infusion 6mg every 4 weeks (23)
Clodronate Oral 1600mg daily (20,21,22)

Treatment should be continued throughout the course of the disease (3,4,7,38,39)
Adminstration of zoledronic acid every 12 weeks may be as effective as the approved every 4 weeks schedule (40-42).

**Multiple Myeloma**
Zoledronic acid Intravenous infusion 4mg every 4 weeks (16,17)

* Alternatives
  Pamidronate Intravenous infusion 90mg every 4 weeks (31,34)
  Clodronate Oral 1600mg daily (32,33)

Treatment should be continued throughout the course of the disease. However, to reduce the risk of treatment complications, interruption after 12-24 months should be considered in patients in remission and restarted on progression (35,36).

**Review of Benefits and Harms**
The overall benefits of bisphosphonates in metastatic bone disease clearly exceed the potential harms of treatment and are a recommended addition to standard anticancer treatments across all tumor types (3,35,36,37,39,40).

**Benefits**

*Breast cancer bone metastases*

**Zoledronic acid**
Placebo controlled trial demonstrates 41% reduction in risk of skeletal event (19)
Similar reduction in proportion of patients experiencing an SRE as pamidronate (16) but overall risk of SRE reduced by further 20% (17).

**Pamidronate**
Placebo controlled trials demonstrated significant reduction in SRE for both chemotherapy (8) and endocrine therapy (15) treated patients. Overall benefits included reduction in pain and improved quality of life (9).
Ibandronate
Placebo controlled trials with both intravenous (23) and oral formulations (24) demonstrated significant reduction in skeletal morbidity rate. Not approved in United States

Clodronate
Relatively small placebo controlled trials have demonstrated significant benefits in skeletal morbidity (20-22). Acute effects on bone pain less evident than with intravenous aminobisphosphonates. Not approved in the United States

Prostate cancer bone metastases (castration resistant)
Zoledronic acid is approved worldwide for patients with castration resistant prostate cancer on the basis of a randomized trial demonstrating significant reduction in proportion of patients experiencing an SRE, prolonged time to first SRE and overall risk reduction for SRE of 36% (12). Pamidronate ineffective in randomized trial conducted in very advanced painful bone metastases (28). Use alongside androgen deprivation therapy +/- docetaxel chemotherapy reduced SREs but did not improve survival (43).

Other solid tumor bone metastases
Randomised placebo controlled trial of zoledronic acid in a broad range of solid tumors other than breast and prostate demonstrated significant reduction in skeletal morbidity (13). Specific benefit clearly demonstrated in NSCLC and renal cancer subsets (17). No randomized trial evidence to support use of any other bisphosphonate in these disease settings

Multiple myeloma
Placebo controlled trial evidence for both pamidronate (31) and clodronate (32,33) in multiple myeloma. Comparison of pamidronate with zoledronic acid suggested similar efficacy (16,17). Zoledronic acid was more effective than oral clodronate in prevention of
skeletal morbidity and extended survival by 3 months (34). Clodronate not approved in United States.

**Harms**

*Complications of treatment*

There are several risks to treatment with bisphosphonates that require monitoring [3,44].

Intravenous bisphosphonates are commonly associated with the acute phase response (fever and flu-like symptoms), bone/joint pain. Less common side effects include kidney injury (45), ocular inflammation (46) and atrial fibrillation (47).

Osteonecrosis of the jaw (ONJ) is a significant clinical problem associated with long-term bisphosphonate use (48). The frequency of ONJ is 1-2% of patients for each year on monthly intravenous bisphosphonate therapy (49,50); the risk may be less with daily oral agents or administration of intravenous treatment on a 3 monthly schedule (51). It is recommended that patients have a dental exam and preventive dental work (such as tooth extraction) performed prior to administration of bisphosphonate therapy and invasive dental work should be avoided (51). When extraction or jaw surgery cannot be avoided, prophylactic antibiotics should be given. The bisphosphonate should be discontinued until healing is complete unless the patient has ongoing significant symptomatic bone disease.

Patients are also at risk of hypocalcemia. Vitamin D supplementation is recommended and most patients should be placed also on calcium supplementation, though this should be individualized based on the characteristics of the malignancy and renal function (52).

Atypical femoral fractures (subtrochanteric and diaphyseal regions) can also occur rarely (<1 in 1000) and may be related to long term suppression of bone remodeling induced by bisphosphonate treatments (53).
References


45. Guarneri V, Donati S, Nicolini M, Giovannelli S, D'Amico R, Conte PF. Renal safety and efficacy of i.v. bisphosphonates in patients with skeletal metastases treated for up to 10 Years. (200%) Oncologist 10(10):842-848.


