Zoledronic acid

Essential medicine status

Section: 8. Immunomodulators and antineoplastics > 8.2. Antineoplastics and supportive medicines > 8.2.5. Supportive medicines

ATC codes: M05BA08

Indication	Malignant neoplasm metastasis in bone or bone marrow ICD11 code: 2E43
INN	Zoledronic acid
Medicine type	Chemical agent
List type	Complementary
Formulations	Parenteral > General injections > IV: 4 mg per 5 mL in 5 mL vial ; 4 mg per 100 mL in 100 mL bottle
EML status history	First added in 2017 (TRS 1006)
Sex	All
Age	Adolescents and adults
Therapeutic alternatives	The recommendation is for this specific medicine
Patent information	Patents have expired in most jurisdictions Read more about patents.
Tags	Cancer
Wikipedia	Zoledronic acid
DrugBank	Zoledronic acid

Expert Committee recommendation

In relation to the application, the Expert Committee noted that it did not follow the standard template, and some important elements of the evaluation were missing or inadequately addressed. Despite these shortcomings, the Expert Committee considered that zoledronic acid has been shown to be a valid treatment option for use in patients with malignancy-related bone disease. Based on the positive evaluation, the Committee recommended zoledronic acid be added to the complementary list of the EML for this indication. The Committee did not recommend listing with a square box, as it considered the evidence presented in the application for alternative bisphosphonates was not adequate to support their inclusion on the EML. The Expert Committee recommended the establishment of an EML cancer medicines working group to coordinate comprehensive evaluation of available treatment options for different cancers. In particular, noting the role of zoledronic in the management of bone metastases associated with multiple myeloma, and that multiple myeloma was not included in the 2015 review of cancer medicines on the EML, the Committee highlighted the need for the working group to evaluate treatments for multiple myeloma as a priority for EML inclusion.

Background

Bisphosphonates have not previously been considered by the Expert Committee for addition to the EML.

Public health relevance

The skeleton is one of the most common locations to which cancer metastasizes. The propensity for solid tumour malignancies to metastasize to bone varies: bone metastases will develop in 65–75% of patients with advanced prostate cancer and 70% of patients who die of breast cancer. The incidence of bone metastases is lower in patients with lung, colon, stomach, bladder and

other cancers (15–30%), and only 5% of patients with certain gastrointestinal malignancies (1). 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 (2). Bone metastases can cause skeletal-related events (SREs) including fractures, spinal cord compression, hypercalcaemia 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 regimens and no bisphosphonates, SREs occur in 46–64% of patients within 2 years (depending on the underlying malignancy), contributing importantly to the significant overall morbidity of advanced cancer (3–5).

Benefits

Bisphosphonates are specific inhibitors of osteoclasts, and their use in cancer patients prevents the increased bone resorption that accompanies metastatic bone disease (6, 7). Through this mechanism, bisphosphonates reduce complications or SREs such as fractures, the need for palliative radiotherapy to relieve pain, spinal cord compression and hypercalcaemia from bone metastases (8, 9). They can also reduce bone pain and analgesic requirements (10, 11) and improve quality of life (3, 12, 13). 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) (3–5), contributing significant morbidity to the clinical course of the underlying disease and increasing the health care costs of treating advanced malignancy (8, 14). Bisphosphonates reduce the number of breast cancer patients experiencing an SRE, extend the time to first and subsequent SREs, and prevent around a third of all skeletal morbidity (4, 5, 13, 15). Zoledronic acid is likely to be the most effective agent (16–18), reducing by 41% the overall risk of SREs when compared with placebo (19). Placebo-controlled trials have also shown benefits for oral clodronate (20–22), IV (23, 24) and oral (24, 25) ibandronate and pamidronate (3, 13, 15) but to a lesser extent than zoledronic acid (17). 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 (4, 28), although IV ibandronate has similar efficacy to palliative radiotherapy for the acute relief of bone pain (11). In this disease setting, zoledronic acid reduced 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 SREs by 36% and improved pain scores (4). Similarly, in non-breast and non-prostate solid tumours (50% non-small cell lung cancer and 50% miscellaneous other solid tumours), zoledronic acid increased the median time to the first event (230 days vs 163 days) and reduced the overall risk for SREs by 31% (4, 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 and extended survival by 3 months (34).

Harms

Several risks are associated with treatment with bisphosphonates and require monitoring (8, 35). Intravenous bisphosphonates are commonly associated with the acute-phase response (fever and influenza-like symptoms), and bone/joint pain. Less common side-effects include kidney injury (36), ocular inflammation (37) and atrial fibrillation (38). Osteonecrosis of the jaw (ONJ) is a significant clinical problem associated with long-term bisphosphonate use (39). The frequency of ONJ is 1–2% of patients for each year on monthly IV bisphosphonate therapy (40, 41); the risk may be less with daily oral agents or with a 3-monthly schedule of IV treatment (42). It is recommended that patients have a dental examination and preventive dental work (such as tooth extraction) before administration of bisphosphonate therapy; invasive dental work should be avoided (42). 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 hypocalcaemia. Vitamin D supplementation is recommended and most patients should be placed also on calcium supplementation, which should be individualized on the basis of the characteristics of the malignancy and renal function (43). Atypical femoral fractures (subtrochanteric and diaphyseal regions) can also occur rarely (<1 in 1000) and may be related to long-term suppression of bone remodelling induced by bisphosphonate treatments (44).

Additional evidence

N/A

Cost / cost effectiveness

In 2015, the MSF International Medical Products Price Guide (45) reported a median buyer price for zoledronic acid 4 mg/5 mL vial of US$ 23.45.

WHO guidelines

The WHO Guidelines for management of cancer pain are currently under review.

Availability

Ibandronate and clodronate are not approved in USA.

Other considerations

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 (46, 47).

Administration of zoledronic acid every 12 weeks may be as effective as the approved 4-weekly schedule (48–50).

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