Zoledronic acid (for tumour induced hypercalcaemia and prevention of progression of bone metastases)

Indication

1. Tumour induced hypercalcaemia
2. Prevention of progression of bone metastasis

Regimen details

Zoledronic acid 4mg in 100ml 0.9% sodium chloride

Cycle frequency

Prevention

Zoledronic acid is to be given with each cycle of chemotherapy for those patients who are receiving chemotherapy; 3-4 weekly
Alternatively, every four weeks if patient is not currently receiving chemotherapy.

Hypercalcaemia

May be repeated after 5 days if unsuccessful in lowering calcium level and patient is adequately hydrated. 8mg dose may be considered (Nb no reference to this in SPC but company has some data on file) Median time to relapse after attaining normocalcaemia is 30-40 days. So retreat as clinical circumstances dictate. Calcium levels should be monitored between doses.

Number of cycles

Indefinite for prevention
Normally single dose for hypercalcaemia

In multiple myeloma patients, consider either discontinuing treatment after 2 years for stable responding patients or decreasing frequency to every three months

Administration

All patients must be adequately hydrated before treatment commences. This includes patients for prevention and treatment. Side effects and renal dysfunction have been recorded in patients receiving the infusion at the recommended rate and the risk of this is increased without adequate hydration.

Pre-medication

N/A

Emetogenicity

N/A

Additional supportive medication

Prevention only: patients must be prescribed Calcichew D3 Forte (or equivalent), 1 tablet daily for the duration of the zoledronic acid course.

Extravasation

Irritant

Investigations – pre first cycle

U&Es and calcium

Investigations –pre subsequent cycles

U&Es and calcium

Standard limits for administration to go ahead

If blood results not within range, authorisation to administer **must** be given by prescriber/ consultant.

Prevention: Creatinine ≤ 265, normocalcaemia
Treatment: Creatinine ≤ 400, corrected Ca^{2+} > 2.7mmol/L

Dose modifications

Prevention

Baseline Creatinine Clearance (ml/min)	Zoledronic acid Recommended Dose
> 60	4.0 mg
50 – 60	3.5 mg
40 – 49	3.3 mg
30 – 39	3.0 mg

Zoledronic acid is not recommended for those presenting with severe renal failure (Cl_{Cr}<30ml/min)
If creatinine increases by > 50 μmol/l from normal baseline creatinine or > 100μmol/l from abnormal baseline creatinine withhold treatment until level falls to within 10% of baseline value

Treatment
No modification required if Cr < 400
Cr >400: consultant's decision
Any possible deterioration in renal function should be reported to the consultant

Adverse effects –

for full details consult product literature/ reference texts

The most common side effects for zoledronic acid include transient flu-like symptoms, nausea/vomiting, musculoskeletal pain, diarrhea, fatigue, edema, headache, dizziness, renal impairment and cough/dyspnoea.

Deterioration of renal function has been noted with zoledronic acid. Factors that may increase the potential of deterioration include pre-existing renal impairment, concomitant use of nephrotoxic drugs, dehydration, prolonged exposure to bisphosphonates, zoledronic acid doses > 4mg, or using an infusion time shorter than the recommendations (in 100mL diluent over 15 minutes). Cases of acquired Fanconi syndrome have been reported and signs include hyperaminoaciduria, glucosuria in the presence of normal serum glucose, phosphate wasting and other clinical features. If this develops, zoledronic acid should be discontinued and the patient treated appropriately.

Hypocalcemia has been reported, and is usually asymptomatic, but may be severe (e.g. tetany, QTc changes) and has a variable onset time. It may be more common in patients with prior thyroid surgery.

An **acute phase reaction** is common, with symptoms such as fever, fatigue, bone pain and/or arthralgias, myalgias, arthritis, joint swelling and flu-like illness. These reactions usually appear within 3 days after the dose and usually resolve within a few days.

Musculoskeletal pain may occur from days to months after starting treatment and may sometimes be severe. These symptoms recurred in some patients who were re-challenged with the same or different bisphosphonates.

Osteonecrosis of the jaw (ONJ) has been reported, especially in patients also receiving steroids, radiotherapy, anti-angiogenic drugs and chemotherapy who have had invasive dental surgery. Risk may also be increased in those with co-morbid conditions (e.g. anemia, coagulopathies), periodontal and other dental diseases, poorly fitting dentures and smokers. A higher frequency has been reported in advanced breast cancer or multiple myeloma patients. The onset can occur from months to years after the start of bisphosphonate therapy. Patients should be advised to have dental examinations prior to starting therapy and to avoid invasive dental procedures while receiving zoledronic acid. The start of treatment should be delayed in patients with unhealed open soft tissue mouth lesions.

In multiple myeloma patients, consider either discontinuing treatment after 2 years for stable responding patients or decreasing frequency to every three months. Cases of osteonecrosis of other anatomical sites, including the femur, hip, humerus, external auditory canal, tibia, ribs, spine, knee, and metatarsal bones have been reported post-market in patients treated with zoledronic acid.

Atypical fractures of the femur (subtrochanteric or diaphyseal) have been reported with bisphosphonate use, primarily in patients receiving long-term treatment. These fractures are often bilateral, occur with minimal or no trauma, with symptoms including thigh or groin pain. Imaging features of stress features may be seen weeks to months before presentation with a completed femoral fracture. Poor healing of these fractures has also been reported.

Additional comments

Dental procedures

A dental examination with appropriate preventive dentistry should be considered prior to treatment with bisphosphonates in patients with concomitant risk factors.
While on treatment, these patients should avoid invasive dental procedures if possible. For patients who develop osteonecrosis of the jaw while on bisphosphonate therapy, dental surgery may exacerbate the condition. For patients requiring dental procedures, there are no data available to suggest whether discontinuation of bisphosphonate treatment reduces the risk of osteonecrosis of the jaw. Clinical judgment of the treating physician should guide the management plan of each patient based on individual benefit/risk assessment.

References

Cancer Care Ontario Drug Monograph - https://www.cancercareontario.ca/en/system/files_force/zoledronic%20acid – accessed 15/7/2020

Zoledronic acid SPC - https://www.medicines.org.uk/emc/product/7205 - accessed 15/7/2020

THIS PROTOCOL HAS BEEN DIRECTED BY DR CHARNLEY, CONSULTANT ONCOLOGIST

RESPONSIBILITY FOR THIS PROTOCOL LIES WITH THE HEAD OF SERVICE

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