SUMMARY OF GUIDELINES ON THE USE OF BISPHOSPHONATES IN PALLIATIVE CARE

Yorkshire Palliative Medicine Clinical Guidelines' Group July 2008

HYPERCALCAEMIA OF MALIGNANCY (HCM)

- Prehydration with fluids is desirable.
- There are few comparative studies between bisphosphonates for the treatment of HCM. The results of these suggest that ibandronic acid and pamidronate (doses of at least 60mg) are of equal efficacy and that sodium clodronate 1500mg achieves the same rate of normocalcaemia as pamidronate 90mg but for a shorter duration. Zoledronic acid appears to be more effective than pamidronate in a single trial, with an 18% greater response rate after 10 days and 14 day longer median duration of normocalcaemia. However, this greater effectiveness may be off set by significantly greater cost for some centres.
- For patients with frequently relapsing hypercalcaemia, zoledronic acid may give a longer time period between treatments. A dose of 8mg could be considered as this has been reported as having a longer duration of action then 4mg (note concern with higher doses and renal impairment).
- Retreatment with a bisphosphonate has been associated with at least 50% achievement of normocalcaemia, based on small numbers in refractory and relapsing HCM. Theoretically, in refractory HCM, zoledronic acid may elicit a response where other bisphosphonates have failed due to its higher response rate.
- The nadir for sodium clodronate is day 4, ibandronic acid day 5, pamidronate approximately day 7 and zoledronic acid day 6-11. By day 4, 76% of patients will be normocalcaemic with ibandronic acid, 33-50% with pamidronate and 45% with zoledronic acid. Approximately another 40% will be normocalcaemic by day 10 with pamidronate or zoledronic acid. When rechecking corrected serum calcium in patients who remain symptomatic, these figures should be taken into account.
- The SPC recommends modifying the dose of pamidronate dependant on the uncorrected serum calcium level. Several comparative studies use pamidronate 90mg to treat HCM in all patients regardless of level of hypercalcaemia and without significant adverse effects (renal or symptomatic hypocalcaemia). Pamidronate 90mg is also standard treatment for prevention of SRE (when calcium levels prior to treatment are likely to be within normal range). Using pamidronate 90mg for any level of hypercalcaemia in patients with cancer is likely to increase the response rate and duration of response and is therefore recommended (although outside product licence). This practice is supported by a recent systematic review of bisphosphonates in the treatment of HCM [Saunders 2004].

BONE PAIN

- The Cochrane Review of bisphosphonates for the relief of pain secondary to bone metastases, published in 2002 and including articles up to 2000, concluded benefits for the treatment group. They found a NNT at 4 weeks of 11 (95% CI 6-36) and at 12 weeks of 7 (95% CI 5-12) [Wong 2002]. The NNH was 16 (95% CI 12-27) for discontinuation of therapy. The authors stated that there was insufficient evidence to recommend bisphosphonates for immediate effect, as first line therapy, or to define the most effective bisphosphonate overall and for different primary neoplasms. They concluded that bisphosphonates should be considered where analgesics and/or radiotherapy are inadequate for the management of painful bone metastases.
- We also conclude that there is little evidence to suggest the use of one bisphosphonate over another with regards to efficacy although a small study suggests clodronate to be less effective than pamidronate. Beyond this the choice of bisphosphonate should be governed by local cost in terms of both drug and time / service provision.
- The underlying type of malignancy should not affect the type of bisphosphonate used if for pain alone, except in prostate cancer see full guidelines.

- In individual studies the magnitude of pain response is small e.g. in breast cancer; 0.3 on 5 point scale (oral ibandronate), 0.5 on 5 point scale (6mg intravenous ibandronate), 1.2 on 9 point scale (90mg intravenous pamidronate).
- More than a single treatment may be required to improve pain in some patients.
- Lack of response to 2 treatments may be an indication to discontinue.

RENAL IMPAIRMENT

- Clodronate, pamidronate and zoledronic acid appear to be associated with greatest risk of renal toxicity. Studies have so far shown ibandronic acid to have a renal safety profile comparable to placebo.
- Risk factors include coexisting renal impairment, concomitant use of nephrotoxic drugs, shorter infusion time, increasing age, increasing number of bisphosphonate infusions, hypercalcaemia, prior exposure to bisphosphonates and patients with multiple myeloma.
- As the dose prescribed and infusion time of each drug should be modified according to the degree of renal impairment, we recommend that renal function is checked prior to each infusion for every bisphosphonate.

HYPOCALCAEMIA

- Asymptomatic hypocalcaemia during treatment with bisphosphonates is common but symptomatic hypocalcaemia is rare.
- Calcium and Vitamin D supplements (Calcium 500mg and Vitamin D 400IU daily) should be prescribed for all patients prescribed zoledronic acid and should be considered for any patient with risk factors for developing hypocalcaemia (hypoparathyroidism, vitamin D deficiency, hypomagnesemia and concomitant use of certain drugs) during treatment with bisphosphonates.
- Monitoring of serum calcium is suggested during treatment with bisphosphonates (e.g. prior to infusion when renal function is already being monitored). Bisphosphonate treatment should be withheld if serum calcium is below 2.0mmol/I. For asymptomatic patients with a serum calcium <2.2 but >2mmol/I treatment should continue but calcium supplements should be considered. Patients should be warned of the symptoms of hypocalcaemia and if any concern a nadir calcium level could be checked 4-11 days after infusion (dependant on drug, see hypercalcaemia section).

OSTEONECROSIS OF THE JAW (ONJ)

- ONJ is a rare condition. The risk for developing ONJ increases with dose and duration of treatment with bisphosphonates.
- Zoledronic acid appears to be associated with a higher incidence than any of the other iv bisphosphonates.
- Local trauma, including tooth extraction and infection are important predisposing factors. Therefore it is recommended that before initiating non urgent therapy patients should be referred for dental review to optimise oral hygiene. Patients receiving bisphosphonates should be informed of the need to maintain good oral hygiene during treatment, including regular dental check ups.
- There is a lack of prospective, randomised outcome studies once ONJ develops. Antimicrobial rinses, antibiotics, analgesia and surgical debridement are possible treatment options. Once ONJ is established it is advisable to discontinue bisphosphonates until the lesions resolve, even though doing so may not actually promote healing of the lesions.