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Our Lady's Hospice & Care Services
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Question: What is the evidence to support the use of denosumab to treat hypercalcaemia associated with malignancy?

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Summary:

- There is very limited evidence available to support the use of denosumab to treat hypercalcaemia associated with malignancy (HCM).
- Denosumab is not licensed for the treatment of HCM.
- Denosumab 60mg and 120mg subcutaneously have been used to treat HCM.
- It is important to monitor that patient's serum calcium levels very carefully during treatment.

Preparations

There are two licensed denosumab products available in Ireland, Prolia® 60 mg solution for injection and Xgeva® 120 mg solution for injection.

Licensed Indications

- Prolia® is licensed for the treatment osteoporosis in postmenopausal women and in men at increased risk of fractures. It is also licensed for the treatment of bone loss associated with hormone ablation in men with prostate cancer at increased risk of fractures.[1]
- Xgeva® is licensed for the prevention of skeletal related events in adults with bone metastases from solid tumours and for the treatment of adults and

skeletally mature adolescents with giant cell tumour of bone that is unresectable or where surgical resection is likely to result in severe morbidity. [2]

Mechanism of Action

Denosumab is a human monoclonal antibody that specifically targets the receptor activator of nuclear factor-kappa B ligand (RANKL), a mediator of the resorptive phase of bone remodelling.[3]

When should Denosumab be used to treat hypercalcaemia?

Denosumab has been suggested as a treatment option for patients with hypercalcaemia that is refractory to bisphosphonates,[3,4] or in whom bisphosphonates are contraindicated due to severe renal impairment.[4]

What dose of Denosumab should be used to treat hypercalcaemia?

Denosumab 60mg (SC) and denosumab 120mg (SC) have been suggested in the literature to treat hypercalcaemia.[3,5,6,7,8,9] The optimal dose of denosumab in the setting of renal impairment is uncertain, it may be prudent to begin with a lower dose of 0.3mg/kg.[4,10]

- Bech et al outlined a case report of a 50-year-old woman with multiple myeloma complicated by severe hypercalcaemia and renal failure.[5] She was treated with intravenous fluids and a single subcutaneous dose of denosumab 60 mg. Serum calcium level decreased rapidly and was associated with recovery of renal function.[5]
- Freeman et al present the case of a 66 year old man with severe hypercalcaemia that was resistant to treatment with pamidronate and calcitonin.[6] He was commenced on subcutaneous denosumab 120mg every 4 weeks, two weeks after receiving the first dose the patient's calcium level normalised and has been maintained for more than 10 months.[6]
- Hu et al conducted a single-arm, open-label, proof-of-concept study in 15 patients with hypercalcaemia of malignancy.[7] Patients received subcutaneous denosumab 120 mg on days 1, 8, 15, and 29, then every 4 weeks. Over the course of the study, 11 patients (73%) had a complete response, with a median

time to complete response of 9 days. The median duration of response was 26 days.[7]

- Dietzek et al performed a retrospective chart review of all patients who received denosumab for hypercalcaemia of malignancy.[8] Seven patients received doses of denosumab for hypercalcaemia of malignancy. The most common tumour types were breast cancer and hematologic malignancies. All patients had bone involvement. Two patients received single doses of 60 mg. The other five patients received 120 mg. The authors concluded that denosumab helped decrease calcium in patients with hypercalcaemia of malignancy. However, symptomatic hypocalcaemia may result from denosumab in hypercalcaemia of malignancy.[8]
- Hu et al conducted a single arm interventional study on 33 patients with cancer and hypercalcaemia refractory to IV bisphosphonate therapy.[9] Densoumab 120mg SC was administered on day 1, 8, 15 and 29 and then given every 4 weeks thereafter. 33 Patients received at least one dose of denosumab. By day 10, denosumab lowered serum calcium in 21 patients (64%). The estimated median duration of response was 104 days.[10]

Renal Impairment

- Denosumab, unlike bisphosphonates, is not cleared by the kidney, and as a consequence there is no restriction of its use in patients with chronic kidney disease, for whom bisphosphonates are used with caution or contraindicated. However, the optimal dose of denosumab in the setting of renal impairment is uncertain. In trials of denosumab for osteoporosis, patients with chronic kidney disease were at higher risk for hypocalcaemia following denosumab administration than patients with normal renal function.[4]
- Cicci et al outlined 4 cases of patients who presented with refractory HCM secondary to multiple myeloma in the setting of renal dysfunction.[10] The first patient received a fixed dose of denosumab 60mg which resulted in significant and prolonged hypocalcaemia. To minimise the risk of hypocalcaemia, the subsequent 3 patients received a weight-based regimen of 0.3mg/kg, the calcium levels initially corrected within a 1- to 5- day period. Two of the patients developed mild hypocalcaemia, which normalised with time. The final patient was

unresponsive to treatment. The authors conclude that given the potential for under-dosing with this strategy, the serum calcium levels should be re-evaluated 1 week later, with a second dose administered if serum calcium levels have not been achieved.[10]

How long does it take for the calcium levels to fall?

Based on the information outlined in the studies above a response can be seen within 1 day to 10 days.

- Boikos et al presented a case report of a 52-year-old man with a history of metastatic renal cell carcinoma to the lungs with hypercalcaemia.[11] Treatment with zoledronic acid and subsequently calcitonin did not control the calcium levels. After the initiation of denosumab (dose not outlined), the calcium level of the patient fell rapidly to normal levels within 2 days, which was durable for at least 1 month.[11]
- In the study outlined above by Hu et al[7] denosumab was discontinued if albumin corrected serum calcium (CSC) was greater than 12.5 mg/dL after four denosumab doses or by study day 57.[7]

How long with the effect of the denosumab on serum calcium levels last?

Information from the studies outlined above suggests that the effect can last from several days to several months.

Until further evidence is available it would be prudent to consider that denosumab can render patients substantially hypocalcaemic without substantial renal impairment.[12] Patients should therefore have their blood monitored regularly.[12]

References

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