GUIDELINES FOR THE TREATMENT OF CANCER ASSOCIATED HYPERCALCAEMIA

22.1 GENERAL PRINCIPLES

- The normal range for the serum corrected calcium or albumin-adjusted calcium is 2.2-2.6 mmol/l.
- Most laboratories now give corrected calcium results. An uncorrected calcium level may be adjusted for the serum albumin using the following formula:

  \[
  \text{Adjusted calcium (mmol/l)} = \text{Total calcium} + 0.02(\frac{40-\text{serum albumin}}{3})
  \]

- Hypercalcaemia is the commonest life-threatening metabolic disorder associated with malignancy, occurring in approximately 10-20% of patients with cancer. It occurs primarily in those with more advanced disease and is generally indicative of a poor prognosis. The incidence of cancer-associated hypercalcaemia is now falling because of earlier and prolonged use of bisphosphonates in cancer patients with metastatic bone disease.

- Symptoms of hypercalcaemia include: fatigue, weakness, constipation, nausea, vomiting, polyuria, polydipsia, cardiac arrhythmias, delirium, drowsiness and coma. The severity of symptoms correlates more closely with the rate of increase in calcium rather than the actual level. Other influencing factors include age and the overall medical condition of the patient.

- Treatment of hypercalcaemia includes rehydration and the use of bisphosphonates.

- Hypercalcaemic patients are dehydrated and sodium depleted. Rehydration with parenteral sodium chloride 0.9% should always be first line management. This may improve some of the symptoms and may reduce calcium levels by 0.4-0.6 mmol/l. It has three main effects:
  - Replace lost sodium.
  - Increase the glomerular filtration rate and circulating volume.
  - Promote urinary calcium excretion.

- Sodium chloride 0.9% should be used in preference to dextrose as the reabsorption of calcium in the proximal convoluted tubule is linked with that of sodium, hence saline produces a more effective calcium diuresis.

- Bisphosphonates are analogues of pyrophosphate and may be highly effective in the treatment of hypercalcaemia of malignancy.

- Until recently disodium pamidronate was standard treatment for cancer-associated hypercalcaemia. Zoledronic acid is a new aminobisphosphonate which is also licensed for the treatment of cancer-associated hypercalcaemia. Studies have shown it to be superior to pamidronate in terms of a more rapid onset and a longer duration of action. Ibandronic acid is a third generation bisphosphonate which appears to have a better renal profile. Clodronate is less effective than pamidronate but can be given subcutaneously so may be useful for patients in whom venous access is a problem. Local policies may govern which bisphosphonate is available for clinical use. The side effects of bisphosphonates include a transient rise in body temperature, a flu-like syndrome and asymptomatic hypocalcaemia.

- Patients who have undergone thyroid or parathyroid surgery may be particularly susceptible to developing hypocalcaemia due to relative hypoparathyroidism.
If symptomatic or severe hypocalcaemia occurs post bisphosphonate therapy, then short term supplemental therapy may be required. Although uncommon, renal toxicity has also been associated with bisphosphonate treatment and monitoring of renal function is recommended. 8,10,11,15,16

Osteonecrosis of the jaw has been reported in patients receiving bisphosphonates. 15 (see Guidelines on the Use of Bisphosphonates in Bone Pain)

22.2 GUIDELINES

Clinical assessment of the patient is crucial in determining whether treatment of hypercalcaemia is appropriate. Generally a decision to treat should be motivated by the patient’s symptomatology rather than absolute calcium level. The most important goal of treatment is to improve clinical symptoms. 3,4,5,17 [Level 4]

22.2.1 Rehydration and discontinuation of other drugs

The patient should be rehydrated with 1-3 litres of parenteral sodium chloride 0.9% before the administration of bisphosphonates. The volume and rate of fluid replacement should be adjusted in each patient according to their age, the severity of hypercalcaemia, the degree of dehydration and the ability of the cardiovascular system to tolerate rehydration. 2–3, 5 [Level 4]

Drugs which reduce renal blood flow or renal calcium excretion should be discontinued/avoided where appropriate e.g. non-steroidal anti-inflammatory agents and thiazide diuretics. 3, 7 If a diuretic is needed, a loop diuretic such as furosemide, which inhibits the reabsorption of calcium and sodium in the ascending limb of the loop of Henle, is the drug of choice. 2–3, 5 [Level 4]

22.2.2 Bisphosphonates

Please see Table 22.1 and Table 22.2 for details of the bisphosphonates available. Local policies will govern which bisphosphonate is used.

22.2.3 Monitoring of hypercalcaemia

Corrected calcium levels should be rechecked at 5-7 days after the bisphosphonate infusion. Checking calcium levels prior to this is not appropriate, as the bisphosphonate will not have achieved its maximal effect. 10, 16

Calcium levels should be rechecked every 3-4 weeks or when symptoms of hypercalcaemia occur. 1 [Level 4]

22.2.4 Management of treatment resistant hypercalcaemia

If at 5-7 days post bisphosphonate infusion, the corrected calcium level is greater than 3.0mmol/l or the patients' symptoms of hypercalcaemia persist, it may be appropriate to consider further infusions of bisphosphonates. At least 7 days should elapse before a further treatment is given, to allow maximal response to the initial dose. Options for treatment include: the same dose of bisphosphonate; an increased dose or changing to an alternative bisphosphonate. 10,16 [Level 4]

22.2.5 Management of recurrent hypercalcaemia

If the patient experiences subsequent episodes of symptomatic hypercalcaemia, a further infusion of bisphosphonate may be given. Depending on how close the recurrence is to the
original episode, it may be appropriate to give the same dose of bisphosphonate, an increased
dose or change to an alternative bisphosphonate. 10, 11, 18 [Level 4]

<table>
<thead>
<tr>
<th>Serum corrected calcium (mmol/l)</th>
<th>Dose of pamidronate sodium (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 3.0</td>
<td>30-60*</td>
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<tr>
<td>3.0-3.5</td>
<td>60</td>
</tr>
<tr>
<td>&gt;3.5</td>
<td>90</td>
</tr>
</tbody>
</table>

* According to clinical judgement

22.3 **STANDARDS**

1. Patients with proven hypercalcaemia should receive treatment within 24 hours if treatment is
   appropriate. 2, 3 [Grade D]

2. All patients with cancer-associated hypercalcaemia should be rehydrated with parenteral
   sodium chloride 0.9% prior to treatment with bisphosphonates. 2, 3, 4, 10, 11 [Grade D]

3. Serum calcium should be checked at 5-7 days. 10 [Grade D]

4. Calcium levels should be rechecked every 3-4 weeks or when symptoms of hypercalcaemia
   occur. 1 [Grade D]
<table>
<thead>
<tr>
<th>Table 22.2. Bisphosphonates available for clinical use</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Name of drug</strong></td>
</tr>
<tr>
<td>Disodium Pamidronate</td>
</tr>
<tr>
<td>Zoledronic acid</td>
</tr>
<tr>
<td>Ibandronic acid</td>
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<tr>
<td>Clodronate</td>
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<td>Calcitonin</td>
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22.4 REFERENCES


22.5 CONTRIBUTORS

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