GUIDELINE

Title: Hypercalcemia of Malignancy

Date Approved: March 17, 2005

Approved By: Palliative Care Clinical Practice Guideline Committee

A. PURPOSE:

- To provide a strategy for the management of hypercalcemia of malignancy in palliative patients, with the goal of reducing associated symptoms and improving quality of life.

B. DEVELOPMENT:

- Articles were identified through a search of MEDLINE from 1984 to 2004, using the search term "hypercalcemia", subheading "therapy", and limits "human", "English language" and "cancer". Also, the developers' article collections on this topic were perused, as well as the articles' reference lists.

  Both clinical trials and review articles were used as sources of information.

C. BACKGROUND:

- Hypercalcemia occurs in up to 40% of all cancer patients.
- It may develop either in the presence of skeletal metastases (local osteolytic hypercalcemia e.g. metastatic breast cancer, multiple myeloma) or in their absence (humoral hypercalcemia of malignancy e.g. squamous cell carcinomas, renal cell carcinoma).
- In both situations, tumour-derived parathyroid hormone-related peptide (PTHrP) is thought to play a major causative role by promoting osteoclastic bone resorption and tubular reabsorption of calcium filtered by the kidney.
- Tumour types commonly associated with hypercalcemia include squamous cell carcinoma of the lung, head and neck, and esophagus; breast carcinoma; multiple myeloma; renal cell carcinoma; transitional cell urothelial carcinoma; ovarian carcinoma; lymphoma.
- The development of hypercalcemia usually indicates limited life expectancy (weeks to months), except in multiple myeloma and breast cancer.

D. DIAGNOSIS:

- The onset of hypercalcemia may be insidious.
- Symptoms and signs include nausea, anorexia, constipation, polyuria, thirst, dehydration, lethargy, confusion, stupor, and coma.
- Serum calcium is partially protein bound and therefore needs to be corrected for serum albumin level:

  [(40 – measured albumin) x 0.02] + measured calcium = corrected calcium
- Alternatively, ionized calcium may be measured, which is more accurate.
- Hypercalcemia = corrected serum calcium > 2.60 mmol/L or ionized calcium > 1.25 mmol/L.

E. TREATMENT: GENERAL CONSIDERATIONS:

Recommendation 1: The decision to treat hypercalcemia must take into consideration the potential benefits and burdens of therapy, the patient's place in the disease trajectory, and overall goals of care. The urgency of treatment depends on the severity of hypercalcemia and associated symptoms.

- The potential benefit of improved symptoms must be weighed against the potential burdens of performing bloodwork and administering parenteral fluids and medications.
- A patient who is already extremely debilitated by the effects of advanced cancer is less likely to experience benefit from treatment of hypercalcemia.
- The patient's preferences with respect to medical interventions must be taken into consideration.
- In situations of severe hypercalcemia and associated symptoms, treatment should be implemented as soon as possible.

Recommendation 2: Normal saline hydration is the usual first step in the treatment of hypercalcemia.

- Normal saline hydration corrects volume depletion from calcium-induced diuresis and decreased fluid intake; promotes renal calcium excretion.
- This intervention reduces serum calcium by a median of 0.25 mmol/L.
- The routine use of furosemide in conjunction with hydration to promote calcium excretion is not recommended, because of the risk of volume and electrolyte depletion.

Recommendation 3: Bisphosphonates are the mainstay of treatment of hypercalcemia.

- These drugs are pyrophosphate analogues that bind to hydroxyapatite crystals in bone matrix and inhibit osteoclastic bone resorption.
- Resistance to bisphosphonates may occur due to the fact that bisphosphonates do not reduce PTHrP-induced renal calcium re-absorption.
- Bisphosphonates are appropriate to administer when serum calcium is ≥ 3.0 mmol/L, or when a serum calcium of < 3.0 mmol/l is accompanied by symptoms. It is unclear whether treatment of serum calcium of < 3.0 is of benefit in asymptomatic patients; however, symptoms of hypercalcemia may be subtle.
- Renal failure is the most serious potential adverse effect. Therefore, dehydration should be corrected and serum creatinine checked prior to administration. Depending on the degree of renal failure, bisphosphonates may be contraindicated or dose adjustments may be required (see Procedure). Also, caution is required in patients receiving other drugs that may affect renal function (e.g. NSAIDs, ACE inhibitors, aminoglycosides).
- Treatment may be repeated when hypercalcemia recurs (consider weekly blood testing to monitor serum calcium).
- The available agents for treatment of hypercalcemia are clodronate, pamidronate and zoledronate. Key features are compared in the table below. No agent has been proven to be clearly superior to the others in terms of efficacy. The option for subcutaneous administration makes clodronate the agent of choice in some settings, such as hospice or home. Other considerations include cost (check with Pharmacy) and formulary status (refer to the Capital Health Regional Formulary). When resistance to a bisphosphonate occurs (i.e. serum calcium fails to normalize within one week or duration of effect is shorter than indicated below), a more potent bisphosphonate may be tried.

	Clodronate	Pamidronate	Zoledronate
Relative potency	1	10	1000
Dose	1500 mg	90 mg	4 mg
Median duration of effect	14 days	28 days	30 days
Route and rate of administration	SC/IV over 4 hours	IV over 4 hours	IV over 15 minutes

- The parenteral route is preferred to the oral route, due to the poor oral bioavailability of bisphosphonates and the high frequency of gastrointestinal intolerance.
- Etidronate has weak inhibitory activity on bone resorption and is not recommended for the treatment of hypercalcemia. Alendronate and risedronate have not been extensively evaluated for this indication.
-

Recommendation 4: Corticosteroids may have a role in the management of hypercalcemia associated with hematological malignancies.

- Corticosteroids may lower serum calcium if they have an antineoplastic effect on the underlying malignancy, e.g. multiple myeloma, lymphoma and leukemia.
- The decision to use corticosteroids must take into consideration their potential adverse effects. In general, their use should be reserved for situations in which bisphosphonates are not easily accessible or are ineffective, or in which other indications for corticosteroids (e.g. pain, nausea) also exist.
- The optimal type and dose of corticosteroid for this indication have not been established.

Recommendation 5: Calcitonin salmon may be used as a short-term (days) adjunctive treatment of severe hypercalcemia, while awaiting onset of effect of the bisphosphonate.

- Calcitonin inhibits osteoclastic function and number, and inhibits renal tubular reabsorption of calcium.
- Onset of action is rapid (hours).
- Duration of effect is short (hours) and response decreases with repeated administration (days).
- Serum calcium usually does not normalize if calcitonin is used alone.
- A small risk of hypersensitivity reaction exists due to salmon derivation.
- In limited studies, calcitonin salmon nasal spray was less effective for the treatment of malignant hypercalcemia than when administered by the parenteral route.

Recommendation 6: Dietary calcium does not need to be restricted. However, calcium supplements should be discontinued.

- Hypercalcemia of malignancy occurs as a consequence of osteolysis and renal tubular reabsorption of calcium. The contribution of dietary calcium is negligible.

Applicability

- The ability to apply this guideline depends on access to bloodwork, the subcutaneous or intravenous route of administration, and drugs.
- The cost implications of drugs and other resources may be significant and need to be taken into consideration in each clinical setting and situation.
- Key review criteria for monitoring and audit include normalization of serum calcium and improvement of hypercalcemia-related symptoms.

F. PROCEDURE:

BIPHOSPHONATES:

Contraindications

- Renal impairment with serum creatinine > 400 mmol/L or calculated creatinine clearance < 10 mL/min
- Hypersensitivity to bisphosphonates or vial constituents

Dosage, Route and Rate of Administration

1. Clodronate (e.g. Bonefos®, Ostac®)
   - 1500 mg in NS 500 mL IV or SC as a single infusion over at least 4 hours. The rate of infusion may be decreased if necessary to improve local tolerability. (D5W in small volumes has also been used for SC administration; it is unclear which solution is better tolerated, but NS may be advantageous for hydration purposes. Smaller volumes have been used for SC infusion; however, the higher concentration may be associated with decreased local tolerability, resulting in the need to reduce the rate of infusion.)
   - Dosing in decreased renal function: If creatinine clearance is 10-50 mL/min, a dose reduction of 25-50% is recommended. (Consider decreasing the dose by increments of 300 mg, as clodronate is available in ampoules of 300 mg).
2. Pamidronate (e.g. Aredia®, Pamidronate DIS®)
   - 90 mg in NS or D5W 500 mL IV as a single infusion over at least 4 hours.
   - Dosing in decreased renal function: No dose reduction required.
3. Zoledronic Acid/Zoledronate (e.g. Zometa®)
   - 4 mg in NS or D5W 100 mL IV over at least 15 minutes.
   - Dosing in decreased renal function: No dose reduction required. (see table)

Baseline Creatinine Clearance (mL/min)	Zometa* Recommended Dose↕
> 60	4.0 mg
50 – 60	3.5 mg
40 – 49	3.3 mg
30 – 30	3.0 mg

Zometa* is a registered trademark

↕ Doses calculated assuming target AUC of 0.66 (mg-hr/L) (CrCl=75mL/min)

Dilution, Storage and Stability

- Refer to site-specific Parenteral Manual policies and procedures (e.g. CH Regional Parenteral Manual).
- Store intact bisphosphonate products at room temperature.
- Bisphosphonates should not be administered undiluted or by IV bolus injection.
- Bisphosphonates are compatible with NS or D5W. They are incompatible with calcium-containing solutions (e.g. Ringers, Ringers Lactate) and should not be mixed with other drugs.
- Clodronate is available as 5 mL ampoules of 60 mg/mL or 10 mL ampoules of 30 mg/mL. If the diluted solutions are not prepared aseptically in pharmacy, care should be taken in the handling of the glass ampoules. The solution should be prepared using filter needle technique, or the diluted solution should be infused using a filtered tubing set/needle system if available. Diluted solutions are stable for 12 or 24 hours, depending on the product. Refer to Pharmacy for preparation and stability information.

- Pamidronate (30 mg and 90 mg) and zoledronate (4 mg) are available in single-dose vials without preservative that must be reconstituted with sterile water for injection prior to dilution; diluted solutions are stable for 24 hours. Refrigerate for sterility.

Monitoring

1. Local reactions
   - SC infusions of clodronate: Refer to the Intermittent SC Injections Clinical Practice Guideline and Hypodermoclysis (HDC) Administration Protocol for Palliative Care Patients.
   - IV infusions: Refer to the Parenteral Manual.
   - Observe for local reactions, thrombophlebitis, redness and swelling.

2. Systemic adverse effects
   - "Flu-like" symptoms: Mild fever, chills, bone pain, arthralgia, and myalgia lasting up to 48 hours may occur with pamidronate and zoledronic acid. Mild fever can be prevented by prophylactic use of acetaminophen.
   - Renal dysfunction: Check serum creatinine prior to each dose.
   - Ocular complications: Uveitis, conjunctivitis, episcleritis and scleritis have been reported with bisphosphonates. Health Canada has recommended that patients on bisphosphonates who develop visual loss or ocular pain should be referred to an ophthalmologist.
   - Osteonecrosis of the jaw: This complication has been reported in cancer patients receiving pamidronate and zoledronic acid, usually for a number of months. Novartis and Health Canada have recommended consideration of a dental examination with appropriate preventive dentistry, prior to treatment with bisphosphonates, in patients with concomitant risk factors (e.g. chemotherapy, radiotherapy, corticosteroids, poor oral hygiene). While on treatment, invasive dental procedures should be avoided if possible.
   - Other: Nausea, vomiting, pruritis, hives, chest tightness, hypotension, headache, anxiety, insomnia, fatigue, somnolence, pancytopenia, allergic reactions. Hypocalcemia may occur, but is usually asymptomatic. Bronchoconstriction may develop in ASA-sensitive asthmatics.

CALCITONIN SALMON (e.g. Calcimar Salmon®, Caltine®):

Contraindications:
- Known hypersensitivity to salmon calcitonin.
- Skin testing should be considered with suspected sensitivity to salmon calcitonin and in individuals with fish allergy. Refer to Pharmacy, product monograph, or CPS for detailed instructions on the procedure and the preparation of diluted solution for the test dose.

Dosage, Route and Administration
- Initial dose: 4 IU/kg q12h SC or IM. If no response after 1-2 days, increase the dose to 8 IU/kg q12h; then after another 2 days, if no response, increase to 8 IU/kg q6h.
- Dose should not exceed 2 mL SC per injection site; if dose exceeds 2 mL, the IM route is preferable.
- IM or SC injection should use alternate sites; the SC route is preferred for self-administration.
- Do not mix with other drugs.

]

Storage and Availability

- Caltine® Injection is available as 100 IU/mL glass ampoules, which should be stored in the refrigerator.
- Calcimar® Injection is available as multi-dose 2 mL vials of 200 IU/mL with preservative, which should be stored in the refrigerator. The solution is stable for 2 weeks at room temperature.

Monitoring

- Local reaction: Observe for site irritation, pain and inflammation. Refer to the Intermittent Subcutaneous Injections Clinical Practice Guideline.
- Systemic adverse effects: Nausea, vomiting, allergic reactions, facial flushing, anorexia, diarrhea, epigastric discomfort, abdominal pain, and unusual taste.

References:

Kovacs CS, MacDonald SM, Chik CL, Bruera E. Hypercalcemia of malignancy in the palliative care patient: a treatment strategy. J Pain Symptom Manage 1995;10:224-32.

Shustik C. Tumour-induced hypercalcemia. Current Oncol 2001;7:173-9.

Stewart AF. Hypercalcemia associated with cancer. N Engl J Med 2005;352:373-9.

Roemer-Becuwe C, Vigano A, Romano F, Neumann C, Hanson J, Quan HK, Walker P. Safety of subcutaneous clodronate and efficacy in hypercalcemia of malignancy: a novel route of administration. J Pain Symptom Manage 2003;26:843-8.

Product Monographs

Health Canada. Bisphosphonates and ocular disorders. Canadian Adverse Reaction Newsletter 2003;13:1-2.

Health Canada. Health Canada Endorsed Important Safety Information on Aredia (pamidronate disodium) and/or Zometa (zoledronic acid). 2004. Available at: http://www.hc-sc.gc.ca/hpfb-dgpsa/tpd-dpt/aredia_zometa_hpc_e.html.

Chastis V, ed. Capital Health/Caritas Health Group Regional Parenteral Manual. Edmonton Regional Pharmacy Services. 2003.

Intermittent Subcutaneous Injections Clinical Practice Guideline. Capital Health Regional Palliative Care Program. 2003.

Hypodermoclysis (HDC) Administration Protocol for Palliative Care Patients. Capital Health Regional Palliative Care Program. February 2003. Available at: http://www.palliative.org.

Health Canada Endorsed Update Letter on Renal Safety for Zoledronic Acid. August 2005.