

### In this article...

- Causes and prognosis of malignant hypercalcaemia
- Relationship between calcium, bone formation and cancer
- Mechanism of action of bisphosphonates (zoledronic acid and pamidronate)

# Malignant hypercalcaemia: definition, symptoms and treatment



Nursing Times  
Self-assessment

## Key points

**Hypercalcaemia is an abnormally high level of calcium in the blood**

**The incidence of malignant hypercalcaemia varies widely between different cancers**

**Prognosis in solid tumours is generally poor once hypercalcaemia occurs**

**Treatment with bisphosphonates or denosumab is often effective but can have side-effects**

**Patients will often have advanced cancer and will, therefore, need supportive end-of-life care**

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**Abstract** Hypercalcaemia – an abnormally high level of calcium in the blood – is common in advanced cancer. It can often be successfully treated, whether with bisphosphonates or the human monoclonal antibody denosumab, and the side-effects of treatment can often be successfully managed. However, many patients face the challenges posed by other burdensome symptoms of malignant disease and a poor prognosis. This article provides an extensive overview of malignant hypercalcaemia, including its causes, symptoms, treatment and implications for nursing practice.

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**M**alignant hypercalcaemia is preventable; once diagnosed, it can often be effectively treated (Pettifer and Grant, 2013) although treatment carries risks of its own. However, the condition often occurs as a late complication of cancer and indicates widespread disease, so the effects of successful treatment are likely to be short-lived. This makes its management a combination of providing compassionate end-of-life care and the correct treatment.

## Incidence and prognosis

Hypercalcaemia is defined as a higher-than-normal corrected calcium level in the blood (NHS Scotland, 2014). Depending on the definition used, it is either  $>2.6\text{mmol/L}$  (Pettifer and Grant, 2013) or  $>2.65\text{mmol/L}$  (National Institute for Health and Care Excellence, 2014).

The incidence of malignant hypercalcaemia varies widely between different cancers. It occurs most often in breast cancer and myeloma, and is associated with squamous cancers (lymphomas and leukaemias) (Ross et al, 2004). It is uncommon in

small-cell lung cancer and adenocarcinomas (stomach, colon and prostate cancer). Prostate cancer – even with extensive bone metastases – rarely causes hypercalcaemia (Pettifer and Grant, 2013).

Although hypercalcaemia is generally associated with bone metastases, which are common in advanced cancer, the presence and extent of bone metastases do not correlate with the incidence or level of hypercalcaemia (Ross et al, 2004). Around 20% of patients with malignant hypercalcaemia do not have bone metastases (NHS Scotland, 2014).

Metastases are a major cause of death in patients with cancer but, while visceral metastases are more likely to be fatal, patients with only bone metastases can survive for 10 years or more (National Horizon Scanning Centre, 2008). However, the average life expectancy after a diagnosis of bone metastases is approximately two years (Beaumont and Leadbeater, 2011).

Prognosis in solid tumours is generally poor once hypercalcaemia occurs as it usually develops when cancer is widespread (NHS Highland, 2012). Despite treatment,

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survival is often only three or four months, or even less (Pettifer and Grant, 2013).

As well as hypercalcaemia, patients with bone metastases may experience severe pain and skeletal-related events (SREs) such as pathological fractures, caused by little or no force at all, and spinal cord or nerve root compression (Drudge-Coates and Turner, 2013). They may need radiotherapy (to treat pain or avoid fractures) or bone surgery. SREs have serious negative consequences, including reduced quality of life and increased risk of death (Gralow and Tripathy, 2007).

Skeletal pain, the most common pain in cancer, can be intermittent or constant, severe and debilitating. It is also difficult to manage, particularly if it is movement-related (Yorkshire Palliative Medicine Clinical Guidelines Group, 2008).

### Hypercalcaemia and cancer

#### Normal bone formation

Calcium is the most common mineral in the body – around 90% of it being stored in bone and teeth – and is crucial to normal functioning, particularly to muscle and nerve action and to blood clotting. Serum calcium is normally maintained by parathyroid hormone (PTH), vitamin D and calcitonin, which the body uses to balance the amounts of calcium that are:

- Released from bone;
- Needed to rebuild new bone;
- Absorbed from food;
- Excreted by the kidneys (Pettifer and Grant, 2013).

Bone is constantly being remodelled by two cell types: osteoclasts and osteoblasts. Osteoclasts destroy old bone, releasing calcium and phosphate into the blood. The formation, function and survival of osteoclasts requires the activation of a cytokine (a chemical messenger that acts on cell receptors) called RANK-L, which is produced by osteoblasts (Yee and Raje, 2012).

Calcitonin, secreted by the thyroid in response to high serum calcium, stimulates the action of osteoblasts, which reform calcium and phosphate into new bone (Pettifer and Grant, 2013). PTH, secreted by the parathyroid glands in response to low serum calcium, stimulates osteoclasts and increases the release of calcium into the blood by the kidneys (Drudge-Coates and Turner, 2013).

#### Action of cancer cells

The most common causes of hypercalcaemia are malignancy and hyperparathyroidism (Twycross et al, 2009). Many cancers, with or without bone metastases,

secrete cytokines and/or PTH-related protein/peptide (PTHrP) that mimic the action of PTH on the osteoclasts and kidneys. This mechanism is the most important cause of hypercalcaemia in cancer (Pettifer and Grant, 2013).



Cancer cells also suppress osteoblast activity and increase the activation of RANK-L. This increases osteoclast formation and activity, encouraging bone resorption – which, in turn, leads to the release of growth factors that increase PTHrP production. A vicious cycle of bone-destructive metastases and hypercalcaemia ensues, and more bone is broken down than is replaced. This is commonly seen in myeloma, breast cancer and endometrial cancers (Suva et al 2011; Fizazi et al, 2009).

#### Bone metastases

Primary tumours constantly release cells that invade surrounding normal tissue and enter the bloodstream. In breast cancer, lymph node invasion can lead to bone metastasis as tumour cells are drained into the systemic circulation. Once in the systemic circulation, cancer cells interact with normal cells, and those that survive travel to distant organs, including bone. Bone is a common site for metastasis due to the high blood flow in bone marrow and the fact that adhesive molecules on tumour cells bind to cells in the bone marrow. Tumour cells:

- Invade the bone marrow cavity;
- Stimulate their own vascular supply;
- Migrate to the bone surface, from where they may seed other organs or even re-seed the site of the original tumour, perhaps years later (Suva et al, 2011).

Bone metastases occur from almost every type of cancer. The incidence of bone involvement in advanced multiple myeloma (a primary bone tumour) is 95-100% (NHSC, 2008). Breast and prostate cancers account for more than 80% of cases of metastatic bone disease and cause the greatest morbidity (bone marrow failure, anaemia, pain and SREs). Untreated, about half of patients who have advanced prostate cancer with bone metastases will have at least one SRE in two years and, once they have had one SRE, the risk of more increases (So et al, 2012).

Pain is the most common, and usually the earliest, symptom of bone metastases.

Common sites include the base of the skull (associated with cranial nerve palsies, neuralgias and headaches). Vertebral metastases cause neck and back pain, with or without neurologic complications. Pelvic and femoral lesions cause pain in the back and legs, often leading to mechanical instability and incident pain.

Causes of pain due to bone metastases include:

- Nerve entrapment;
- Increased bone pressure or stretching of bone due to the presence of a tumour;
- Bone fracture;
- Inflammation caused by cytokines;
- Bone destruction;
- Neuropathic pain due to destruction of sensory nerves by osteoclasts.

Acute pain from injury tends to be short-lived, while chronic pain can be caused by a tumour pressing on nerves or poorly controlled acute pain (Drudge-Coates and Turner, 2013).

Many patients with advanced cancer – particularly breast cancer – live with bone pain for several years (Gralow and Tripathy, 2007). Most patients with breast cancer experience weeks of increasing pain before fractures occur (Beaumont and Leadbeater, 2011).

#### Fractures

Bone metastases weaken bones and increase the risk of fractures, which are sometimes the first sign of bone metastasis. Spinal vertebrae and the long bones of the arms and legs are the most common fracture sites. Pathological fractures can be treated but may be slow to heal and require surgery; they are linked with significantly reduced survival (So et al, 2012). Chemotherapy, antihormonal therapies – used in breast and prostate cancer – and glucocorticoids also increase bone loss and combine with factors such as age, history of fracture, low calcium intake, vitamin D deficiency, smoking and lack of exercise to further increase the risk of bone fracture (YPMCGG, 2008).

#### Symptoms of hypercalcaemia

Hypercalcaemia affects several organ systems, so symptoms vary. It is not always obvious whether symptoms are due to hypercalcaemia as many can be attributable to other features of advanced malignancy or the side-effects of chemotherapy or analgesia. Hypercalcaemia should always be considered when patients deteriorate for no obvious reason (Pettifer and Grant, 2013).

Early symptoms of hypercalcaemia include fatigue, muscle weakness, anorexia

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and constipation. If it is not treated, symptoms may worsen and widen to include confusion, nausea and vomiting, which can cause dehydration (Drudge-Coates and Turner, 2013). Hypercalcaemia decreases renal reabsorption of sodium and water, resulting in polyuria. Patients also may experience polydipsia but struggle to increase oral fluid intake, which will exacerbate the problem (Ross et al, 2004).

Hypercalcaemia can precipitate or exacerbate bone pain, and bone pain due to hypercalcaemia responding poorly to treatment (NHS Highland, 2012). Severe symptoms of hypercalcaemia include ileus, drowsiness, hypertension, visual disturbance, dizziness, agitation, muscle spasms or tremors, absent or diminished reflexes, dysarthria, dysphagia and, eventually, coma (Drudge-Coates and Turner, 2013).

### Treating hypercalcaemia

Mild hypercalcaemia is often asymptomatic; symptoms significant enough to warrant treatment usually only develop when serum calcium levels exceed 3.0mmol/L (Pettifer and Grant, 2013). It is the rapidity of onset and the increase in hypercalcaemia that appear to determine the severity of symptoms, rather than the serum calcium level itself. For example, there may be few symptoms in chronic severe hypercalcaemia until a quick moderate rise in serum calcium levels occurs, following which symptoms rapidly develop (Twycross et al, 2009).

Nevertheless, serum calcium levels of >3.0mmol/L warrant urgent treatment, whether or not the patient experiences any symptoms. Untreated severe hypercalcaemia (>4.0mmol/L) is usually fatal within a few days due to renal failure, seizures or cardiac arrhythmia (NHS Scotland, 2014).

Before starting treatment, hyperthyroidism and uncontrolled diabetes should be excluded, as their clinical features are similar to those of hypercalcaemia (Pettifer and Grant, 2013; NHS Highland, 2012).

### Initial treatment

In severe hypercalcaemia, initial treatment involves antiemetics and intravenous (IV) saline to correct dehydration and the sodium deficit caused by diuresis and reduced oral fluid intake, and to promote renal calcium excretion (Drudge-Coates and Turner, 2013).

Drugs that affect renal function (such as non-steroidal anti-inflammatory drugs, diuretics, angiotensin-converting enzyme inhibitors, angiotensin II receptor antagonists) and drugs that promote

**Table 1. Initial treatment of hypercalcaemia with intravenous bisphosphonates**

	Zoledronic acid	Pamidronate
Dose	4mg	15-90mg (see Table 2)
Onset of effect	<4 days	<3 days
Maximum effect	4-7 days	5-7 days
Duration of effect	4 weeks	2.5 weeks
Patients to regain normal calcium levels	90%	70-75%

Source: Twycross et al (2017)

**Table 2. Intravenous pamidronate infusion**

Corrected plasma calcium level	Dose	Diluent and maximum infusion time
<3.0mmol/L	15-30mg	500ml NaCl 0.9% over ≥60 minutes
3.0-3.5mmol/L	30-60mg	500ml NaCl 0.9% over ≥60 minutes
3.6-4mmol/L	60-90mg	500ml NaCl 0.9% over ≥90 minutes
>4.0mmol/L	90mg	500ml NaCl 0.9% over ≥90 minutes

Sources: Twycross et al (2017); NHS Scotland (2014)

hypercalcaemia (such as lithium, ranitidine, cimetidine, calcium, vitamin A and vitamin D) should be stopped (NHS Scotland, 2014; Drudge-Coates and Turner, 2013).

The diuretic furosemide may be used after rehydration if there are signs or risks of fluid overload – particularly in patients with renal or heart failure and in emergency treatment – as furosemide reduces renal calcium reabsorption (Bennett et al, 2012). IV fluids may be sufficient in mild hypercalcaemia and may minimise renal damage (YPMCCG, 2008), but in severe hypercalcaemia bisphosphonates are required (Pettifer and Grant, 2013).

IV bisphosphonates aim to decrease bone resorption. The most widely used are pamidronate and zoledronic acid (Bennett et al, 2012); zoledronic acid is more effective in malignant hypercalcaemia due to its speed of onset and duration of action (West Midlands Palliative Care Physicians, 2012). Its infusion time is 15 minutes, compared with 2-4 hours for pamidronate. The total pamidronate dose (maximum 90mg) can be given as one or more infusions over 2-4 days (Kent and Medway Cancer Collaborative, 2018). If required, a further dose of either bisphosphonate can be administered (WMPCP, 2012). However, doing so within five days significantly increases the risk of renal impairment (Hospice in the Weald, 2013) and doing so within seven days increases the risk of hypocalcaemia (NHS Scotland, 2014). Plasma calcium levels start falling within 24 hours of treatment with bisphosphonates. Normalisation takes up to

seven days (KMCC, 2018) and lasts for 20-30 days (Bennett et al, 2012).

Serum calcium levels should be checked:

- Between five and seven days after the bisphosphonate infusion, then weekly – as long as the risk of hypercalcaemia remains and treatment is ongoing (Hospice in the Weald, 2013);
- When patients experience symptoms or every three to four weeks (WMPCP, 2012), which is the length of time for which one infusion usually maintains normal calcium levels (NHS Highland, 2012).

Table 1 summarises the initial treatment of hypercalcaemia with IV pamidronate or zoledronic acid, while Table 2 summarises the use of IV pamidronate. Oral bisphosphonates might help maintain normal calcium levels, but they can be ineffective as they are poorly absorbed and their absorption is further impaired by food (Twycross et al, 2017), drinks, antacids and drugs containing calcium, among others (Bennett et al, 2012).

For patients with bone metastases but normal calcium levels (YPMCCG, 2008), treatment with IV bisphosphonates every three to four weeks aims to:

- Prevent progression of bone metastases;
- Increase bone mass and strength (Twycross et al, 2017);
- Reduce pain and SREs (Drudge-Coates and Turner, 2013).

Treatment with denosumab (see below) or IV zoledronic acid after a first SRE reduces bone pain and the risk of subsequent SREs (So et al, 2012).

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### Bisphosphonates: mechanism of action

Bisphosphonates rapidly bind to exposed bone surfaces, particularly at sites of bone resorption (Twycross et al, 2017). They are absorbed and accumulated, and then ingested by osteoclasts; this disrupts the cellular metabolism and maturation of osteoclasts, and eventually induces their death, while new bone production continues normally (Yee and Raje, 2012; Beaumont and Leadbeater, 2011; Suva et al, 2011; Gralow and Tripathy, 2007). Bisphosphonates can remain in bone for months, so one infusion has prolonged effects (Twycross et al, 2009).

IV bisphosphonates may:

- Stimulate bone formation by osteoblasts (Bennett et al, 2012);
- Delay the development of bone metastases;
- Delay SREs in patients with bone metastases;
- Improve the patient's quality of life (Suva et al, 2011).

Bisphosphonates need to be given for at least six months to benefit skeletal morbidity and at least 12 months to reduce the need for orthopaedic surgery; however, analgesic effects may appear much sooner (Hospice in the Weald, 2013).

### Bisphosphonates: side-effects and precautions

Bisphosphonates are generally well tolerated with a low incidence of mild side-effects (Hospice in the Weald, 2013), but side-effects can be severe enough to warrant the discontinuation of therapy. Oral bisphosphonates especially may cause gastrointestinal disturbances, while flu-like and other symptoms can occur after IV treatment.

Severe pain in affected bones can occur and stopping the bisphosphonate can bring about immediate and/or incomplete pain relief (Quinn, 2008). Osteomalacia and mid-shaft fractures of the femur due to bone demineralisation are rare and only likely with high-dose, prolonged use; they can occur with little or no trauma and patients may experience low-grade thigh/groin pain.

Vitamin D supplements should be given during treatment with bisphosphonates and any vitamin D deficiency should be corrected before treatment is started (Bennett et al, 2012).

Renal function may be affected with long-term use of bisphosphonates (Pettifer and Grant, 2013). Rebound hypocalcaemia necessitates calcium supplementation and there is a risk of osteonecrosis of the jaw (ONJ) (Gralow and Tripathy, 2007),

**Table 3. Bisphosphonate doses and infusion rates in renal impairment**

	Drug	Dose and infusion rate
eGFR >60ml/min/1.73m <sup>2</sup>	Zoledronic acid	4mg in 100ml sodium chloride 0.9% over 15 minutes
	Pamidronate	90mg in 500ml sodium chloride 0.9% over 2-4 hours
eGFR = 30-60ml/min/1.73m <sup>2</sup>	Zoledronic acid	3-3.5mg in 100ml sodium chloride over 15 minutes
	Pamidronate	90mg in 500ml sodium chloride 0.9% over 4 hours
eGFR <30ml/min/1.73m <sup>2</sup>	Avoid bisphosphonate infusion	

eGFR = estimated glomerular filtration rate.

Sources: NHS Scotland (2014); Hospice in the Weald (2013)

especially when treatment lasts for more than two years (Hospice in the Weald, 2013); adequate hydration is therefore required. Serum creatinine clearance (NHS Highland, 2012) and calcium levels should be monitored monthly, both before and during treatment, and hypocalcaemia should be corrected beforehand.

Although bisphosphonates are not contraindicated in renal impairment, an estimated glomerular filtration rate (eGFR) of <30ml/min/1.73m<sup>2</sup>, or trending downwards, increases the risk of hypocalcaemia. The incidence of hypercalcaemia in patients with renal impairment can be as high as one in 10, especially with more-potent bisphosphonates such as zoledronic acid; however, patients are rarely symptomatic. Those who develop symptoms may have tingling in the lips or tongue, paresthesia, tetany or seizures.

Bisphosphonates should be withheld if serum calcium is <2.0mmol/L, and doses and infusion rates should be reduced (or treatment discontinued altogether) in renal failure (Pettifer and Grant, 2013). Risk factors for renal toxicity include:

- Increasing age;
- Increasing number of bisphosphonate infusions;
- Multiple myeloma (YPMCGG, 2008).

Table 3 shows bisphosphonate doses and infusion rates in renal impairment.

### Treating bone pain

Radiotherapy usually relieves localised pain from bone metastases but, like high-dose opioids, it can cause significant side-effects and many patients have widespread or recurrent pain in irradiated sites. Bisphosphonates have acute and long-term analgesic effects on metastatic bone pain from a variety of tumours, as they improve skeletal integrity (Gralow and Tripathy,

2007). More than one infusion may be needed to improve pain, but a lack of response to two infusions may prompt discontinuation (YPMCGG, 2008). Initiating zoledronic acid before pain occurs, rather than waiting for it to start, provides better analgesia and fewer SREs – although patients with or without bone pain have the same risk of SREs (So et al, 2012).

### Treatment with denosumab

Denosumab is not a bisphosphonate but a human monoclonal antibody that reduces osteoclast bone destruction by binding to, and neutralising, RANK-L. In early cancer, denosumab can reduce bone loss from anti-hormonal treatments; it may also delay disease progression in breast and prostate cancers. Unlike bisphosphonates, it does not affect renal function but it is contraindicated in severe hypocalcaemia; calcium and vitamin D supplementation is required in all patients unless they are hypercalcaemic (Hospice in the Weald, 2013).

The recommended denosumab dose in cancer is 120mg given once every four weeks by subcutaneous injection – there is no need for venous access. Denosumab is generally very well tolerated; adverse reactions include diarrhoea, constipation and ONJ. There is a risk of severe, symptomatic and even fatal hypocalcaemia, mostly within the first six months of treatment but possibly at any time; that risk is greater in patients who have severe renal impairment or are having dialysis (NHSC, 2008).

### Osteonecrosis of the jaw

As explained, ONJ is a potential side-effect of treatment with bisphosphonates or denosumab. It can manifest as:

- Numbness in the jaw;
- Discharge, swelling or redness of the gums;



- Loosening of the teeth;
- Oral ulcerations (asymptomatic or painful) exposing underlying bone;
- Pathological fracture in the jaw (Hospice in the Weald, 2013; Quinn, 2008).

All patients due to receive bisphosphonates, or who have done so in the last three months therefore need good dental care and hygiene. If patients need dental treatment, bisphosphonates should not be started until that has been completed (NHS Scotland, 2014). If patients already taking bisphosphonates need significant jaw bone surgery, it may be appropriate to interrupt bisphosphonate treatment for several weeks before surgery – however, bisphosphonates have very long half-lives so bone turnover takes a long time to normalise when the drugs are stopped. Some dental procedures may be appropriate while patients are taking bisphosphonates – for example, if the alternative is tooth extraction, which greatly increases the risk of ONJ.

Jaw bones are particularly susceptible to injury and infection because of repeated minor trauma from chewing and the use of dentures (Hospice in the Weald, 2013), and the thin mucosa and bacteria-rich environment (Quinn, 2008). Sixty per cent of cases of ONJ occur after dental surgery, and 85% of patients with ONJ have multiple myeloma or metastatic breast cancer. Treatment includes surgery; antibiotics and chlorhexidine mouthwash can be used for infections (Hospice in the Weald, 2013).

### Outcomes of treatment

Treatment with IV bisphosphonates or denosumab reduces bone pain and SREs in metastatic cancer, but bisphosphonates can negatively affect renal function and both types of drugs can induce hypocalcaemia (So et al, 2012; NHSC, 2008). These treatments and their associated risks reflect the pathology of metastatic bone

disease and the complex relationships between cancer, bones and calcium.

Treating severe hypercalcaemia can markedly improve symptoms, even in patients with advanced disease and limited life expectancy, but treatment may be inappropriate when the prognosis is very poor (Pettifer and Grant, 2013). Treatment does not necessarily resolve all symptoms (NHS Scotland, 2014); refractory hypercalcaemia may occur towards the end of life (NHS Highland, 2012), when attention should focus on relieving symptoms such as pain, confusion and constipation.

Treatment is effective in 70-90% of cases (Pettifer and Grant, 2013) but cannot alter the underlying disease processes (Twycross et al, 2009). Hypercalcaemia is, therefore, likely to recur in patients with advanced cancer and subsequent episodes will be harder to treat (Pettifer and Grant, 2013). A rapid relapse may signify a poor prognosis (NHS Scotland, 2014). Prescribing higher doses or swapping for an alternative bisphosphonate may delay recurrence (Hospice in the Weald, 2013); zoledronic acid may be effective when other bisphosphonates fail (YPMCGG, 2008).

### Implications for practice

The nurse's role includes:

- Informing patients and relatives about early symptoms, and encouraging them to report these to clinicians promptly (Drudge-Coates and Turner, 2013);
- Treating patients who are symptomatic.

The benefits of treatment are likely to become more and more short-lived as patients deteriorate and their malignancy progresses (Pettifer and Grant, 2013). A diagnosis of bone metastases, a recurrence of hypercalcaemia or a progression of cancer can be more distressing for patients and families than the original cancer diagnosis (Oncology Nursing Society, 2002), as they suggest the cancer is aggressive and incurable (Drudge-Coates and Turner, 2013). The side-effects of treatment for bone pain can further erode patients' quality of life (Gralow and Tripathy, 2007).

One crucial aspect of the nurse's role is, therefore, to help patients and families face the many challenges associated with living with metastatic bone disease, including:

- Loss of health, function and independence;
- Coming to terms with a poor prognosis;
- Finding hope, if only for comfort and, ultimately, a pain-free death.

Nurses can also support patients by raising the issue of advance care planning; discussing what is most important to them

now and in future, their sources of support and their needs (emotional, psychological, social and spiritual); and helping them plan for the end of life (Drudge-Coates and Turner, 2013; ONS, 2002). **NT**

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