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Haematological emergencies managing hypercalcaemia in adults and children with haematological disorders

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Summary

Hypercalcaemia is a common metabolic complication of malignant disease often requiring emergency intervention. Although it is more frequently associated with solid tumours, malignancy-associated hypercalcaemia (MAH) is seen in a significant number of patients with blood diseases. Its association with myeloma and adult T-cell leukaemia/lymphoma is well recognized but the incidence of hypercalcaemia in other haematological neoplasms, affecting adults and children, is less clearly defined. Haematologists need to be familiar with the clinical manifestations of, the differential diagnosis to be considered and the most effective management strategies that are currently available for MAH. The key components of management of MAH include aggressive rehydration, specific therapy to inhibit bone resorption and, crucially, treatment of the underlying malignancy. Bisphosphonates have revolutionized the management of MAH over the last 20 years, however the elucidation of molecular pathways implicated in MAH is facilitating the development of more targeted approaches to treatment.

Keywords: hypercalcaemia, haematological malignancy, paediatric haematology, therapy, bisphosphonates.

Hypercalcemia may complicate the clinical course of approximately one-third of cancer patients (Grill & Martin, 2000). The incidence of hypercalcaemia varies according to the type of cancer and, with the exceptions of multiple myeloma, and adult T-cell leukaemia/lymphoma (ATLL), is lower in haematological malignancy as compared to most solid tumours (Mundy & Martin, 1982; Vassilopoulou-Sellin *et al*, 1993). Hypercalcaemia may occur at presentation, relapse or following transformation of haematological neoplasms. Malignancy-associated hypercalcaemia (MAH) causes significant morbidity, may be life-threatening and generally requires urgent intervention. Haematologists need to be aware of the conditions most commonly associated with hypercalcaemia (Table I), the symptoms of hypercalcemia and the clinical significance of a given serum calcium level. Presenting symptoms may include; malaise, anorexia, nausea, vomiting, polyuria and polydipsia, constipation, confusion, stupor and coma. Central nervous system symptoms increase with the severity of hypercalcaemia and occur in up to 80% of patients with a serum calcium >3·5 mmol/l (14·0 mg/dl) (Ralston *et al*, 1990). Longstanding hypercalcaemia can result in nephrolithiasis and nephrocalcinosis usually in the context of primary hyperparathyroidism, although this is rarely seen in haematological MAH (Lankisch *et al*, 2004). The epidemiology, pathophysiology, diagnosis and management of hypercalcaemia in haematological disorders will be discussed.

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Epidemiology of malignancy-associated hypercalcaemia

In patients diagnosed with cancer there is wide variability in the reported incidence of hypercalcaemia in different studies (Burt & Brennan, 1980; Vassilopoulou-Sellin *et al*, 1993). This may be attributable to the study population and design, the upper limit of normal used for defining hypercalcaemia and the influence of referral bias on incidence rates in tertiary referral cancer centres. The reported incidence of MAH in haematological neoplasms is summarized in Table II. In contrast to adult malignancies, hypercalcaemia is rarely (0·4–1·3% of cases) seen in paediatric malignant disease (Leblanc *et al*, 1984; McKay & Furman, 1993; Kerdudo *et al*, 2005). This may reflect the different spectrum of blood disorders encountered in childhood as well as inherent genetic and biological differences associated with childhood haematological malignancy.

Pathophysiology

Normal calcium homeostasis

The serum calcium concentration is tightly regulated within a narrow range by the action of calciotropic hormones on bones, kidneys and gut (Clines & Guise, 2005). Parathyroid hormone

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Table I. Causes of hypercalcaemia in adults and children.

Malignancy-associated		
	Adults	Children
Solid tumours	Lung	Neuroblastoma
	Head & neck	Rhabdoid tumours
	Urological	Rhabdomyosarcoma
	Breast	Ewing Sarcoma
Haematological (% affected)	Myeloma (13%–30%)	ALL (0·3–0·6%)
	ATLL (50%–70%)	NHL (rare)
	HL* (5%)	
	NHL* (0·8%–13%)	
	AML† (rare)	
Other causes		
Parathyroid hormone (PTH)		
Primary hyperparathyroidism‡		
Tertiary Hyperparathyroidism (chronic renal disease, vitamin D deficiency)		
Rarely ectopic PTH production by malignancy		
Drug-induced		
Thiazide diuretics		
Lithium		
Milk-alkali syndrome (usually due to ingestion of antacids)		
Vitamin A derivatives (e.g. ATRA in APML)		
Theophylline		
Vitamin D-associated		
Excessive Vitamin D intake (vitamin supplements)		
Granulomatous disease (sarcoidosis, mycobacterial infection)*		
Endocrine disorders		
Thyrotoxicosis		
Adrenal insufficiency		
Phaeochromocytoma		
Factitious Hypercalcemia (Pseudohypercalcaemia)		
Calcium-binding paraproteins (e.g. Myeloma, Waldenstrom's macroglobulinaemia)		
In vitro calcium release (e.g. essential thrombocythaemia)		
Miscellaneous		
Rhabdomyolysis		
Immobilization with increased bone turnover (e.g. Paget's disease)		
Subcutaneous fat necrosis in infancy		
Congenital Hypercalcaemia (presenting in neonates and infants)		
Neonatal primary hyperparathyroidism§		
Familial Hypocalciuric hypercalcemia§		
William's Syndrome (Deletion of 7q11·23)		
Autosomal recessive hypophosphatasia (TNSALP deficiency)		
Secondary hyperparathyroidsism (due to maternal hypoparathyroidism or hypocalcaemia)		
Jansen's metaphyseal chondrodysplasia (activating mutation of the PTH receptor)		

ALL, acute lymphoblastic leukaemia; ATLL, adult T cell leukaemia/lymphoma; HL, Hodgkin Lymmphoma; NHL, Non-Hodgkin Lymphoma; AML, acute myeloid leukaemia; ATRA, *all*-trans retinoic acid; APML, acute promyelocytic leukaemia; TNSALP, tissue non-specific alkaline phosphatase.
*Associated with 1,25 $(OH)_2D_3$ (Calcitriol) production by macrophages.
†Associated with transformation from myeloproliferative neoplasms and chronic myeloid leukaemia, frequently acute megakaryoblastic sub-type.
‡Common cause in adults (may co-exist with malignancy), rare in children.
§Due to inactivating mutations in the Calcium receptor-sensing gene (CASR).

(PTH) and calcitriol [1,25-$(OH)_2D_3$], the biologically active form of Vitamin D, are the main physiological regulators of calcium homeostasis while calcitonin plays a modest role (see Table III). Although these regulators provide a useful defence against hypocalcaemia, they are less effective at controlling hypercalcaemia when it occurs.

Pathogenesis of malignancy-associated hypercalcaemia

Hypercalcaemia results primarily from enhanced bone resorption mediated by proteins and cytokines released by tumour cells or cells in the tumour microenvironment. Traditionally this has been separated into two entities, namely local

Table II. Reported incidence of hypercalcaemia in haematological malignancies.

Reference	Study design	Incidence of Hypercalcaemia		Definition of hypercalcaemia
Burt and Brennan (1980)	Retrospective (7 years)	Total	10·9% (149/1367)	≥2·75 mmol/l (≥11·0 mg/dl)
		Myeloma	28·1% (9/32)	
	Adult admissions	NHL	13% (63/484)	
		HL	5·4% (15/276)	
		Leukaemia	11·5% (57/496)	
Vassilopoulou-Sellin *et al* (1993)*	Retrospective (1 year)	*Severe Hypercalcaemia*		>3·0 mmol/l (>12·0 mg/dl)
		Myeloma	0·79% (1/126)	
	Adult/Paediatric	NHL	0·26% (1/381)	
	Newly Registered	Leukaemia	0·63% (1/473)	
		Moderate Hypercalcaemia		2·7–3·0 mmol/l (10·8–12·0 mg/dl)
		Myeloma	2·38% (3/126)	
		NHL	0·79% (3/381)	
		Leukaemia	0·63% (3/473)	
Firkin *et al* (1996)	Retrospective (17 months)	Total†	9·3% (15/162)	>2·5 mmol/l
	Clinical Haematology unit	Myeloma	32% (9/28)	
	Consecutive admissions	NHL	8·5% (5/59)	
	Untreated Adults			
Kiyokawa *et al* (1987)	Case series	ATLL	70% (9/13)	≥2·58 mol/l (≥10·3 mg/dl)
Kyle *et al* (2003)	Retrospective (13 years)	Myeloma	13% (132/1018)	≥2·75 mmol/l (≥11·0 mg/dl)
Kyle (1975)	Retrospective (11 years)	Myeloma	30% 869 patients	≥2·75 mmol/l (≥11·0 mg/dl)
Majumdar (2002)	Retrospective (5 years)	B-cell NHL	7·1% (8/112)	ND
Leblanc *et al* (1984)	Retrospective (6 year)[P]	NHL	2·5% (7/276)	ND
McKay and Furman (1993)	Retrospective (29 years)[P]	Total	0·46% (13/1286)[f]	≥2·88 mmol/l (≥11·5 mg/dl)
	ALL	0·6%		

NHL, Non-Hodgkin lymphoma; HL, Hodgkin lymphoma; ATLL, adult T cell leukaemia/lymphoma; ND, not described; ALL, acute lymphoblastic leukaemia; [P], paediatric.
*Fifty five percentage of patients had prior anti-neoplastic treatment.
†includes one case of CML blast crisis *f* includes 10 cases of ALL, 1 NHL, 1 HL and 1 acute myeloid leukaemia.

Table III. Regulation of normal calcium homeostasis.

Hormone	Target organ	Actions	Effect
PTH	Bone	Stimulates osteoclastic bone resorption	$\uparrow Ca^{2+}$
	Kidney	Stimulates renal tubule Ca^{2+} reabsorption	$\uparrow Ca^{2}$
		Inhibits renal tubule PO_4 reabsorbtion	$\downarrow PO_4$
		Stimulates renal 1α-hydroxylase conversion of 25-$(OH)D_3$ to 1,25-$(OH)_2D_3$ (Calcitriol)	
Calcitriol (1,25-$(OH)_2D_3$)	Gut	Increases Ca^{2+} and PO_4 absorption	$\uparrow Ca^{2+}/\downarrow PO_4$
	Bone	Increases bone resorption	$\uparrow Ca^{2+}$
		Enhances mineralization of bone	
	Kidney	Increases renal Ca^{2+} reabsorption	$\uparrow Ca^{2+}$
Calcitonin	Bone	Inhibits osteoclastic bone resorption	$\downarrow Ca^{2+}$
	Kidney	Promotes renal $Ca^{2+}$and PO_4 excretion	$\downarrow Ca^{2+}/\downarrow PO_4$

PTH, parathyroid hormone;↓, decreases serum level; ↑, increases serum level; Ca^{2+}, calcium; PO_4,phosphate.

osteolytic hypercalcaemia involving bone metastases, and humoural hypercalcaemia of malignancy where there is a detectable mediator in the serum. The most commonly detected humoral mediator is parathyroid hormone-related protein (PTHrP) but numerous cytokines (e.g. interleukin [IL]-1, IL-6, transforming growth factor alpha [TGF-α], tumour necrosis factor alpha [TNF-α], macrophage inflammatory protein [MIP-1α]), as well as calcitriol [1,25-$(OH)_2D_3$] and, rarely, ectopic PTH may be found (Clines & Guise, 2005). In a fetal rat bone bioassay numerous cytokines (including IL-1, IL-6, TNF-α and TGF-β) derived from haematological neoplasms have been implicated in enhanced local osteolysis *in vitro* (Firkin *et al*, 1998). This mechanistic distinction between local and humoural factors is probably an oversimplification as certain mediators may exhibit local and systemic effects and multiple factors may work co-operatively.

In addition to their effects on releasing calcium from bone certain mediators increase renal tubular calcium resorption (PTH, PTHrP) or increase absorption from the gut (calcitriol). Calcitriol has been implicated in hypercalcaemia associated with granulomatous disorders and certain lymphomas (Seymour & Gagel, 1993). Ectopic PTH production is an extremely rare cause of hypercalcaemia in haematological malignancies and an elevated PTH level should prompt investigation for a parathyroid adenoma (Lankisch *et al*, 2004).

PTHrP

In the late 1980s PTHrP, a peptide produced by tumours with N-terminal sequence homology to PTH, was identified (Suva *et al*, 1987). Its action through the common PTH/PTHrP receptor induces hypercalcaemia by increasing bone resorption and renal reabsorption of calcium (Nakayama *et al*, 1996; Syed *et al*, 2001). PTHrP has been identified as the major humoural factor linked with over 80% of cases of MAH in solid cancer irrespective of the presence of bony metastases (Nakamura *et al*, 1992; Wimalawansa, 1994).

PTHrP is less frequently implicated in hypercalcaemia of haematological malignancies than in solid tumours and its contribution to hypercalcaemia due to individual haematological disorders is not well established. In one study (Firkin *et al*, 1996) PTHrP was elevated in 3/9 myeloma patients and 2/4 non-Hodgkin lymphoma (NHL) patients with hypercalcaemia. Nakamura *et al* (1992) identified hypercalcaemia in 7/56 patients with haematological neoplasms. Of these seven patients, four (two with B cell NHL, one with adult T cell leukaemia and one with myeloma) had high serum PTHrP levels (Nakamura *et al*, 1992).

Rizzoli *et al* (1999) reported a lower prevalence of elevated PTHrP concentration in haematopoietic malignancies (21%) compared to lung/respiratory tumours (76%), and breast tumours (33%).

It has been proposed that PTHrP released by myeloma cells may act in a paracrine fashion to induce osteolytic activity and local bone resorption (Firkin *et al*, 1998).

RANK/RANKL/OPG signalling pathway

The receptor activator of nuclear factor κB (RANK) and its ligand, RANKL, are involved in physiological bone remodelling (Kearns *et al*, 2008). RANK is expressed on the surface of osteoclast (OC) precursors. RANKL is found on the surface of osteoblasts, bone marrow stromal cells, and is secreted by activated lymphocytes. RANKL expression is upregulated by PTH, PTHrP, 1,25-$(OH)_2D_3$ and prostaglandins. Binding of RANKL to RANK on OC precursors triggers survival and differentiation signal pathways and induces osteoclastic bone resorption, releasing calcium from bone (Roodman, 2009). Osteoclastic activity is blocked by osteoprotegerin (OPG), a soluble decoy receptor for RANKL that blocks the interaction between RANK and RANKL.

Various growth factors, hormones and cytokines have been found to regulate RANKL and OPG expression. This is often observed in a reciprocal manner with concomitant upregulation of RANKL and downregulation of OPG that may amplify pro-resorptive signals. Osteoclastogenesis is enhanced by agents that regulate OPG and/or RANKL including PTH, PTHrP, $1,25(OH)_2D_3$, IL-1, TNF-α (Kearns *et al*, 2008).

Hypercalcaemia in haematological disorders

Myeloma

Myeloma is characterized by markedly increased OC activity resulting in hypercalcaemia in many cases. The bone resorptive process releases growth factors that increase tumour cell growth and angiogenesis, further increasing the tumour cell burden and exacerbating the osteolysis. Multiple underlying mechanisms driving osteoclastogenesis and promoting hypercalcaemia have been described. The major factors that have been found to support osteoclastic activity in myeloma include RANKL, OPG, MIP-1α, IL-6 and IL-3 (Roodman, 2009).

RANKL is expressed as a membrane-bound protein on bone marrow stromal cells and osteoblasts and is secreted by activated T cells. RANKL expression was increased in bone marrow biopsy samples from myeloma patients whereas OPG expression was decreased (Pearse *et al*, 2001). Circulating levels of RANKL and OPG have been found to correlate with disease activity, severity of bone disease and poor prognosis (Terpos *et al*, 2003).

Studies have reported an infrequent association between elevated serum PTHrP levels and myeloma although the frequency of elevated serum PTHrP levels is higher in myeloma patients who are hypercalcaemic than those who are not (Horiuchi *et al*, 1997; Firkin *et al*, 1998). A study of myeloma bone marrow samples provided immunohistochemical evidence of PTHrP protein production by myeloma cells and evidence of *PTHLH* (*PTHrP*) mRNA expression by *in situ* hybridization techniques. Bone marrow samples had detectable *PTHLH* in 16/17 cases but PTHrP protein was only found in 5 of the 16 cases (Zeimer *et al*, 2002). Although the pathogenesis of hypercalcaemia in myeloma is likely to be multi-factorial, a role for PTHrP as a paracrine or systemic mediator in some cases is apparent and warrants further investigation. The extent of osteolytic bone disease does not correlate with the observed frequency of hypercalcaemia and this could reflect renal reabsorption of calcium mediated by PTHrP.

Cell-cell interactions between stromal cells expressing vascular cell adhesion molecule (VCAM)-1 and myeloma cells expressing $\alpha_4\beta_1$ integrin induce RANKL expression by myeloma cells (Oyajobi, 2007). MIP-1α, a chemokine that is over-expressed in 70% of myeloma patients, stimulates OC formation and differentiation. Upregulation of MIP-1α in myeloma is associated with increased bone destruction and poor prognosis (Roodman, 2009). Osteoblastic dysfunction is a hallmark of myeloma bone disease and the Wnt signalling

pathway plays an important role in osteoblast development, expansion and survival. Osteoblasts produce soluble inhibitors of Wnt signalling such as Dickkopf (DKK1) that are associated with inhibition of osteoblastogenesis and enhanced osteoclastogenesis.

Adult T cell leukaemia/lymphoma

Adult T-cell leukaemia/lymphoma (ATLL) is an aggressive disorder of post-thymic $CD4^+$ T lymphocytes, aetiologically linked to the human T-cell lymphotropic (HTLV-1) virus (Matutes, 2007). The majority of cases (50%–70%) of ATLL present with hypercalcaemia (Kiyokawa *et al*, 1987; Matutes, 2007). A pathological study of ATLL patients has indicated that hypercalcemia is due to increased proliferation of OCs and bone resorption (Kiyokawa *et al*, 1987). Gene expression studies of ATLL patients and HTLV-1 carriers have shown increased *PTHLH* mRNA expression compared to non-infected controls. The HTLV-1 *trans*-activator, *tax*, can activate the transcription of host cellular genes including *IL2*, *IL2RA* and*CSF2*. Evidence of *trans*-activation of the promoter of the *PTHLH* gene was demonstrated in a plasmid-construct transfection model (Watanabe *et al*, 1990). More recently it was demonstrated that nuclear factor kappa B (NF-κB) can upregulate *PTHLH* transcription in ATLL cells by a *tax*-independent mechanism (Nadella *et al*, 2007).

Although PTHrP is considered to have a role in the pathogenesis of hypercalcaemia in ATLL, raised serum levels and upregulated *PTHLH* expression are not always associated with hypercalcaemia suggesting that other mediators are implicated and overexpression of RANKL has been suggested as one mechanism (Nosaka *et al*, 2002).

Hodgkin lymphoma and non-hodgkin lymphoma

Hypercalcaemia has been reported in up to 13% of NHL and 5·4% of Hodgkin lymphoma cases (Burt & Brennan, 1980). In a review of hypercalcaemia in NHL, more hypercalcaemic patients had stage III/IV disease and median survival was significantly shorter at 10 months compared with 21 months ($P < 0{\cdot}05$) for other patients with advanced disease (Majumdar, 2002). Hypercalcaemia has been occasionally observed in aggressive lymphoma sub-types that have transformed from indolent forms (Beaudreuil *et al*, 1997).

Calcitriol [1,25-$(OH)_2D_3$] has been implicated as a key mediator of hypercalcaemia in almost all cases of Hodgkin lymphoma and 30%–40% of cases of NHL. (Seymour & Gagel, 1993). An immunohistochemical case study has indicated that lymphoma-associated macrophages may be the source of ectopic calcitriol (Hewison *et al*, 2003). Local osteolysis with increased expression of osteoclast-activating factors, including MIP-1α, MIP-1β and RANKL, in diffuse large B-cell lymphoma cells, has been described (Matsuhashi *et al*, 2004). PTHrP has also been implicated in some reports documenting hypercalcaemia associated with B-cell NHL including cases of Richter transformation (Nakamura *et al*, 1992; Firkin *et al*, 1996; Beaudreuil *et al*, 1997).

Chronic myeloid leukaemia

Hypercalcaemia is rarely observed in myeloid malignancy. There have been more than 30 case reports of hypercalcaemia associated with chronic myeloid leukaemia (CML) and these have been recently reviewed (Noguchi & Oshimi, 2007). Most patients were in blast crisis (BC) or accelerated phase (AP) and many had osteolytic lesions although the pathogenic mechanism was not described in most cases. The median survival was only 2 months (1–8 months) although the majority of cases pre-dated the era of tyrosine kinase inhibitors. TGF-α, TGF-β and prostaglandin E2 were elevated in one case of CML in B-cell blast crisis and the authors postulated that these mediators may have induced hypercalcaemia via upregulation of RANKL expression as well as inducing renal 1,25-$(OH)_2D_3$ production (Noguchi & Oshimi, 2007). Additional reports have found elevated serum PTHrP in a number of cases of CML in BC or AP with hypercalcaemia (Seymour *et al*, 1993; Kubonishi *et al*, 1997; Miyoshi *et al*, 2005).

Acute myeloid leukaemia

Hypercalcaemia is seldom a feature of acute myeloid leukaemia (Gerwitz *et al*, 1983) although, interestingly, it has been associated with acute megakaryoblastic leukaemia occurring *de novo* in adult (Muler *et al*, 2002) and paediatric cases (Qayed *et al*, 2009) and following transformation from polycythaemia vera (Kurosawa & Iwasaki, 2002), essential thrombocythaemia (Vinti *et al*, 1990), myelofibrosis (Kumar *et al*, 1999) and CML (Kornberg *et al*, 1988).

One might postulate that transformation of myeloid or lymphoid malignancies could be associated with activation of factors (e.g. NFκB) that trigger the transcriptional upregulation of *PTHLH* expression.

Acute promyelocytic leukaemia

In chronic vitamin A toxicity, retinoic acid, an active metabolite of vitamin A, causes increased bone resorption and periosteal bone formation (Scheven & Hamilton, 1990). This may be associated with an increased risk of bone fractures and hypercalcaemia (Lips, 2003). Vitamin A derivatives, such as all-*trans* retinoic acid (ATRA), used in adult and paediatric patients with acute promyelocytic leukaemia, and *cis*-retinoic acid, used to treat children with neuroblastoma, have been causally implicated in hypercalcaemia (Sakakibara *et al*, 1993; Sakomoto *et al*, 2001; Kerdudo *et al*, 2005). The effect of ATRA may be potentiated by an interaction with azole antifungals resulting from cytochrome P450 enzyme inhibition (Bennett *et al*, 2005; Cordoba *et al*, 2008). Hypercalcaemia resolves with discontinuation of ATRA with or without bisphosphonate therapy and recurrence may be prevented

using a reduced dosing regimen and avoiding potentiating drugs (Sakakibara *et al*, 1993).

Childhood haematological malignancies

A large case series of 22 paediatric ALL patients with hypercalcaemia in Japan between 1990 and 2005 has been published (Inukai *et al*, 2007) and a recent overview has collated data from this and several smaller series and case reports (Trehan *et al*, 2009). Inukai *et al* (2007) found 25 cases of ALL with hypercalcaemia (22 described) over a period of 15 years in Japan, where approximately 500 new cases are diagnosed annually, giving an estimated incidence of 0·3% for hypercalcaemia associated with ALL in this region. The clinical characteristics from this series of 22 ALL patients with hypercalcaemia were compared to Japanese registry data and revealed that most children were older (11/22 were ≥10 years), had a lower white blood cell (WBC) count (20/22 had WBC count $<20 \times 10^9$/l) and many (8/22) had no blasts detected in the peripheral blood. All patients had a precursor B-cell ALL immunophenotype. Five patients had a coagulopathy. Eleven of 21 patients with available serum PTHrP data were deemed to have PTHrP-mediated hypercalcaemia and in 2 cases this was detected by immunohistochemical staining of blast cells. One case appeared to be due to ectopic PTH production by leukaemia cells. This suggests an important role for PTHrP in a large number of paediatric cases of hypercalcaemia associated with ALL. Osteolytic lesions were observed in more than half the patients (14/22) consistent with other reports including 7 of 11 cases with associated elevated PTHrP levels. Osteoclastogenesis appears to be cytokine-mediated in some cases of ALL and elevated serum levels of IL-6, TNFα and IL-2 were demonstrated in two cases with hypercalcaemia, normal PTHrP levels and osteolytic lesions (Niizuma *et al*, 2007).

Five of the 22 patients in the large Japanese series had the t(17;19) translocation (2 cases at diagnosis and 3 at relapse) and all blasts expressed surface CD33. All five patients with t(17;19)-ALL relapsed early, however when this group was excluded the outcome for the other patients with ALL and hypercalcaemia was equivalent to that of all childhood ALL patients. In the series from St. Jude Children's Research hospital, two of six patients with hypercalcaemia and a precursor B ALL phenotype had the t(17;19) translocation and died within 2 years of diagnosis (McKay & Furman, 1993). Unfortunately, cytogenetic data were not described in many of the other published case reports of hypercalcaemia in paediatric ALL.

The t(17;19)(q21–23;p13) translocation is a rare karyotypic abnormality in childhood ALL. This translocation generates the E2A-HLF fusion transcription factor associated with transforming and anti-apoptotic effects and upregulated expression of the ABCB1 (MDR1, P-glycoprotein) drug-efflux pump (Baudis *et al*, 2006). Clinical manifestations include hypercalcaemia, coagulopathy and an overall poor prognosis. In the Japanese series, three out of four t(17;19) ALL cases who had PTHrP measured were deemed to have PTHrP-mediated hypercalcaemia. Whether E2A-HLF has a direct effect on upregulation of *PTHLH* transcription has yet to be determined. The t(17;19) translocation is not always associated with hypercalcaemia in ALL. Although it is usually apparent on conventional G-banding cytogenetic analysis, its presence should be confirmed or excluded by reverse transcription polymerase chain reaction (RT-PCR) or fluorescent *in situ* hybridization (FISH) in any ALL case presenting with hypercalcaemia given, not only, its prognostic significance but also the potential for minimal residual disease monitoring by RT-PCR (Devaraj *et al*, 1994; Yeung *et al*, 2006). In addition, the coagulation profile of any newly diagnosed or relapsed child with ALL and hypercalcaemia should be monitored carefully.

Childhood NHL is infrequently associated with hypercalcaemia but has been documented in atypical cases with extensive bony involvement (Leblanc *et al*, 1984) and extra-nodal renal disease (Levendoglu-Tugal *et al*, 2002).

Diagnostic approach

If hypercalcaemia is documented, it is important to assess the severity to guide the urgency of treatment. There is no formal consensus for grading severity of hypercalcaemia but a commonly used system categorizes mild hypercalcaemia as a serum calcium level = 2·6–2·9 mmol/l (10·5–11·9 mg/dl), moderate hypercalcaemia = 3·0–3·4 mmol/l (12–13·9 mg/dl) and severe hypercalcemia ≥3·5 mmol/l (≥14·0 mg/dl) with values corrected for serum albumin (Stewart, 2005). The presence of severe or symptomatic hypercalcaemia is generally an indication for treatment, however, asymptomatic patients with moderate or rapidly increasing hypercalcaemia may benefit from pre-emptive intervention.

Measurement of ionized calcium should be considered if there is a doubt over the validity of a total calcium measurement or if there is suspected primary hyperparathyroidism or pseudohypercalcaemia due to increased plasma-protein binding capacity. Pseudohypercalcemia or factitious hypercalcemia has infrequently been reported in myeloma due to calcium-binding paraproteins (Schwab *et al*, 1995). Factitious hypercalcemia may also be found in essential thrombocythaemia due to *in vitro* excretion of calcium by excessive numbers of activated platelets (Howard *et al*, 2000). If an elevated calcium level is confirmed a full assessment of the underlying cause should be undertaken.

Measurement of intact PTH should be performed to exclude concomitant hyperparathyroidism (Firkin *et al*, 1996). PTH levels are usually low normal or suppressed in MAH. Serum concentration of 1,25-$(OH)_2D_3$ should be measured when hypercalcaemia due to Hodgkin lymphoma or NHL, sarcoidosis or other granulomatous disease is suspected. PTHrP should be measured in conditions where hypercalcaemia is an uncommon association as it may help confirm a paraneoplastic aetiology and also because very high levels of PTHrP may predict resistance to bisphosponate treatment (Wimalawansa, 1994).

Management

The key components of management are: (i) rehydration to facilitate calciuresis (ii) inhibition of bone resorption and (iii) treatment of the underlying cause of hypercalcaemia. The available therapeutic strategies are summarized in Table IV. Factors that may exacerbate the degree of hypercalcaemia should be addressed. This includes discontinuation of drugs associated with hypercalcaemia including thiazide diuretics, lithium, and antacids. A careful drug history ascertaining use of calcium or vitamin D- containing products including multivitamins and shark cartilage-containing preparations should be undertaken (Lagman & Walsh, 2003). Supplementation of parenteral nutrition solutions with calcium and fat-soluble vitamin preparations should be avoided. Drugs that affect neurocognitive function or mental alertness, such as sedatives, hypnotics and certain analgesics, should be withheld as they may worsen the neurological effects of hypercalcaemia.

Rehydration

Patients with MAH become dehydrated due to hypercalcaemia-induced nephrogenic diabetes insipidus and reduced oral hydration due to anorexia, nausea and vomiting. The glomerular filtration rate decreases with dehydration, impairing renal excretion of calcium. Therefore intravenous volume expansion is a key part of the management of hypercalcaemia. Intravenous normal saline (0·9%) at a rate of 200–500 ml per h should be given in an effort increase the glomerular filtration to facilitate calcium excretion and inhibit calcium reabsorption (Stewart, 2005). The rate of infusion should be adjusted according to the level of dehydration, severity of hypercalcaemia and the patient's renal and cardiovascular status with close monitoring for clinical signs of fluid overload. Saline induces calciuresis and may be sufficient therapy for patients with mild to moderate hypercalcaemia provided that the underlying cause is addressed. Children should be treated with normal saline 2–3 l/m^2 per day (Kerdudo *et al*, 2005).

Diuretics

Forced saline diuresis using the loop diuretic furosemide to enhance calciuresis is a commonly used strategy and is recommended by many adult and paediatric textbooks. However, a recent systematic review suggests a limited evidence base for this approach (LeGrand *et al*, 2008). Furosemide is ineffective at restoring normocalcaemia in MAH, the optimal dosing regimen is unknown and treatment may cause significant electrolyte disturbances and exacerbate volume depletion. It should be reserved for the management of fluid overload following excessive saline rehydration.

Bisphosphonates in adult MAH

Intravenous bisphosphonates (BPs) are the most extensively studied and most efficacious agents for the treatment of MAH.

Table IV. Therapeutic strategies for malignancy-associated hypercalcaemia.

Treatment	Regimen	Mode of action	Side effects/Comments
Normal Saline (0·9%)	200–500 ml/h (adult) 2–3 l/m^2 (child)	Restores circulating volume Increases filtration Enhances calciuresis	Risk of fluid overload Care in elderly, known heart failure
Bisphosphonates	PAM 60–90 mg IV (adult)* PAM 0·5–2 mg/kg IV (child)* Over 2–4 h	Inhibits osteoclastic activity preventing bone resorption	Care in renal impairment Acute phase reactions common Fever,bone pain, ocular effects Causes $\downarrow Ca^{2+}/\downarrow PO_4/Mg^{2+}\downarrow$
	ZOL 4 mg/15 mins IV (adult)		Slow onset of action 48–72 h
Calcitonin	4–8 iu/kg 6–12 hourly SC/IM injection	Inhibits bone resorption Enhances calciuresis	Rapid onset within 2 h Modest reductions in Ca^{2+} level Tachphylaxis occurs Hypersensitivity, flushing, Nausea, vomiting, abdominal cramps
Steroids	Hydrocortisone IV 200–300 mg × 3–5 d	Inhibits conversion of 25-$(OH)D_3$ to calcitriol	May be useful in Hodgkin lymphoma/Calcitriol-mediated hypercalcaemia
Gallium nitrate	100–200 mg/m^2 IV for 5 d (24-h infusion)	Inhibits osteoclast activity Reduces bone solubility	Nephrotoxicity, care in myeloma Effective but continuous 5-day infusion
Plicamycin	25 μg/kg over 4–6 h	Inhibits OC RNA synthesis	Hepatotoxicity, Myelosuppression Coagulopathy, platelet dysfunction
Furosemide	No standard regimen	Diuretic	Reserve for management of fluid overload Widely used but unproven role

PAM, pamidronate; ZOL, zoledronate, IV, intravenous; IU, international units; SC, subcutaneous; IM, intramuscular; OC, osteoclast; RNA, ribonucleic acid; Ca^{2+}, calcium; PO_4, phosphate; Mg^{2+}, magnesium.
*Higher dose may be considered in cases with severe hypercalcaemia.

Their calcium-lowering effect is achieved predominantly by inhibition of osteoclast function and survival (Ross *et al*, 2004; Drake *et al*, 2008).

In Europe, five BPs are currently licenced for the MAH of malignancy: pamidronate, zoledronate, etidronate, clodronate and ibandronate. In the United States pamidronate and zoledronate have been licenced for this indication. Oral BPs have poor bioavailability and hypercalcaemic patients may not tolerate oral medications therefore intravenous administration is necessary. The maximal effect of BPs occurs at 48–72 h and the mean time to achieving normocalcaemia ranges from 2 to 6 d (Ross *et al*, 2004).

Pooled analyses of clinical studies of the various BPs indicated that normocalcaemia was achieved in over 70% of patients with overall efficacy calculated for different agents as follows: ibandronate (59%; range 53%–77%) and etidronate (58%; range 41%–92%) compared to clodronate (77%; range 75%–94%), and pamidronate (73%; range 40%–100%) and zoledronate (88%; range 30–88%) (Pecherstorfer *et al*, 2003).

Pamidronate is the most extensively studied class member and has been found to be more effective than saline alone, etidronate, low-dose clodronate (600 mg) and mithramycin (Ross *et al*, 2004). Pamidronate (90 mg) and higher dose clodronate (1500 mg) have been found to have similar efficacy (Atula *et al*, 2003). One study has shown inferior efficacy of pamidronate 60 mg (56%) *versus* gallium nitrate (69%) 200 mg/m^2 per day as a 5-day infusion (Cvitkovic *et al*, 2006).

The response to BPs will depend on the pre-treatment serum calcium level and also on the level of bone remodelling. Increasing the dose generally elicits a superior response. A dose-finding study demonstrated a significant difference between 30-, 60- and 90 mg doses of pamidronate with 40%(15), 61%(18) and 100% (17) of patients, respectively, achieving normocalcaemia (Nussbaum *et al*, 1993). The calcium-lowering effect was significantly superior in the 90-mg compared to the 30 or 60 mg group ($P < 0{\cdot}001$).

Regarding the optimal duration of infusion, similar efficacy has been demonstrated when pamidronate (60mg) was administered as an infusion over 2, 4, 8 or 24 h (Dodwell *et al*, 1992). Gucalp *et al*, 1994) found that giving pamidronate 60 mg over either 4 or 24 h was equally effective, safe and superior to saline alone. A practical approach is to administer a dose of 60–90 mg of pamidronate over 2–4 h, using the higher dose for patients with severe hypercalcaemia or those with significant clinical symptoms.

Zoledronate is 100 times more potent than pamidronate. Two parallel, randomized studies evaluated the efficacy of 4 or 8 mg zoledronate versus 90 mg of pamidronate in restoring normocalcaemia by day 10. The response rates were 88·4%, 86·7% and 69·7%, respectively, with significant superiority for zolendronate 4 mg ($P < 0{\cdot}002$) and 8 mg ($P < 0{\cdot}015$) *versus* pamidronate 90 mg (Major *et al*, 2001). The patients treated with zolendronate 4 or 8 mg had a longer median time to relapse of hypercalcaemia compared to those treated with pamidronate, with response durations of 32, 43 and 18 d, respectively. Another single arm study reported similar efficacy (84%) for zoledronate (Kawada *et al*, 2005). Despite apparent superior efficacy to pamidronate for MAH, there is limited published study data (including <250 patients) for zoledronate compared to pamidronate (>800 patients) and its safety profile does not appear to be superior. The shorter infusion duration of 15 min is not a particular advantage for a hospitalized patient on continuous intravenous fluids.

Of note, BPs inhibit bone resorption but do not affect the renal action of PTHrP that causes tubular calcium reabsorption. A number of studies have found an association between a high serum concentration of PTHrP and poor response to BPs with shorter time to relapse of hypercalcaemia (Gurney *et al*, 1993; Wimalawansa, 1994). Patients with higher PTHrP levels may benefit from higher doses and more frequent infusions of BP or adjunctive therapy with another agent.

Safety

Despite concerns about worsening renal failure with BP therapy this has been seldom reported in studies of hypercalcaemia management. Most patients will undergo aggressive rehydration to restore the circulating fluid volume and glomerular filtration rate prior to initiation of treatment. Pamidronate (60–90 mg) has been safely administered by slow intravenous infusion to patients with underlying renal impairment and hypercalcaemia (Machado & Flombaum, 1996). Increases in serum creatinine have been reported more frequently with etidronate (8%) and clodronate (5%) compared to the aminobisphosphonates pamidronate (2%), and ibandronate (1%) (Zojer *et al*, 1999). Ibandronate appears to be the least nephrotoxic BP but is less effective at achieving normocalcaemia (Pecherstorfer *et al*, 1996).

In the study comparing zolendronate and pamidronate 2, patients in the 4 mg group developed grade 3 renal toxicity, and in the 8 mg group, three patients developed grade 3 and two patients grade 4 renal toxicity (Major *et al*, 2001). In the pamidronate arm three patients developed grade 3 and 1 patient suffered grade 4 renal toxicity. These events were not felt to be attributable to BP therapy and there were no statistically significant differences in renal events between treatment groups.

Nevertheless, renal function should be closely monitored before and after treatment and the summary of product characteristics (SPC) for zoledronic acid (Zometa®, Novartis pharmaceuticals, Basel, Switzerland) recommends against its use in the management of MAH in patients with elevated serum creatinine ≥400 μmol/l. The SPC for pamidronate (Aredia®, Novartis pharmaceuticals) recommends against its use when the creatinine clearance is <30 ml/min apart from cases of life-threatening tumour-induced hypercalcaemia where the benefit is felt to outweigh the risk. In patients with cancer with a calculated creatinine clearance between 30 and

90 ml/min, dose reduction is not suggested, however, a maximum infusion schedule of 90 mg/4 h is recommended.

Ten to 30% of patients receiving their first nitrogen-containing BP infusion experience an acute phase reaction usually manifesting as a transient fever with associated myalgia, arthralgia and headaches (Drake *et al*, 2008). This occurs within 36 h of treatment and is self-limiting. It is thought to be due to the secretion of pro-inflammatory cytokines by activated γδ-T lymphocytes and may be prevented by premedication with antihistamines or antipyretics. As many haematological patients will have neutropaenia or immune dysfunction it is important to exclude sepsis if fever arises and a persistent fever should not be dismissed as bisphosphonate-related. Ocular inflammation (conjunctivitis, uveitis, iritis, episcleritis, scleritis) has been observed as part of the acute inflammatory reaction (Zojer *et al*, 1999).

Hypocalcaemia is observed in up to 50% of patients following bisphosphonate therapy for MAH but this rarely causes symptoms such as paraesthesia. Hypomagnaesemia and hypophosphataemia may also occur.

Bisphosphonates in children

There has been an increasing use of BPs for childhood disorders associated with osteoporosis and for metabolic bone disorders, particularly osteogenesis imperfecta (Srivastava & Alon, 2003). As MAH is rare in children the published experience of the use of BPs in this setting is limited to case reports and case series. Theoretical concerns regarding potential adverse effects on the developing skeleton have not been substantiated in the limited data so far.

Bisphosphonates are retained in the skeleton for many years and have been detected in urine samples for up to 8 years after administration (Papapoulos & Cremers, 2007). Transplacental transfer of radiolabelled 14C-alendronate has been demonstrated in pregnant rats and the offspring developed abnormalities in skeletal mineralization and ossification (Patlas *et al*, 1999). This has led to concerns regarding BP therapy in adolescent or young girls who may reach reproductive maturity within a decade of treatment. A recent review of 51 cases of BP exposure before or during human pregnancy failed to detect any significant skeletal abnormalities or congenital malformations in their offspring (Djokanovic *et al*, 2008).

Hypercalcaemia associated with ALL is usually present at diagnosis and/or subsequent relapse and is generally more responsive to treatment than hypercalcaemia associated with paediatric solid tumours (McKay & Furman, 1993; Inukai *et al*, 2007; Trehan *et al*, 2009). For patients with ALL the contribution of induction chemotherapy in normalizing the serum calcium cannot be under-emphasized and may be essential in refractory hypercalcaemia or, indeed, sufficient alone (Harutsumi *et al*, 1995; Unal *et al*, 2008).

Inukai *et al* (2007) reported the largest case series of patients with hypercalcaemia and ALL, which comprised 22 cases treated between 1990 and 2005. Children treated with BPs (11/22) achieved a more rapid reduction in serum calcium (<2·5 mmol/l [10 mg/dl] within 4 d) and more rapid resolution of renal impairment compared to those who did not receive BPs.

Kerdudo *et al* (2005) reported their experience of BP usage in children with MAH who had failed to respond adequately to initial hydration and other measures or who had hypercalcaemia persistently >3·5 mmol/l within 24 h. Pamidronate, with a mean dose of 1 mg/kg (range 0·5–2 mg), successfully resolved hypercalcaemia within 1–4 d in all eight cases.

Andiran *et al* (2006) reported 2 cases of ALL-associated hypercalcaemia and reviewed eight others reported in the literature, all of which were treated with pamidronate when other measures had failed. In general, a dose of 0·5–2 mg/kg (at varying infusion schedules of between 2 and 24 h) adequately restored the serum calcium level within 1 to 4 d.

Conversely, BPs do not always successfully control the hypercalcaemia. Buonuomo *et al* (2004) reported a case of a 9-year-old patient who presented with hypercalcaemia complicated by acute pancreatitis that was refractory to rehydration, forced diuresis and intravenous clodronate therapy. Once the diagnosis of ALL was established, specific chemotherapy was commenced resulting in normalization of calcium within 72 h. Hypercalcaemia that was refractory to five doses of pamidronate in a case of T-cell ALL was successfully treated with induction chemotherapy (Unal *et al*, 2008).

Other treatments

Calcitonin

Calcitonin is a naturally occurring regulator of calcium homeostasis secreted by the parafollicular C cells of the thyroid. It inhibits bone resorption and promotes renal excretion of calcium and phosphate. Salmon calcitonin (given in a dose of 4–8 units/kg subcutaneously or intramuscularly 2–4 times a day) causes a rapid reduction in serum calcium levels within 2 h with a peak response between 12 and 24 h. However, its hypocalcaemic effect is modest (reductions of 0·5 mmol/l at best) and transient, with a median duration of one (range 2–4) day (Wineski, 1990). Furthermore, repeated administration results in downregulation of calcitonin receptors on osteoclasts, causing tachyphylaxis. Its main side effects are nausea, vomiting, abdominal cramps and pain at the injection site. Overall, its efficacy is poor, inducing normocalcaemia in just one-third of patients in clinical studies (Pecherstorfer *et al*, 2003). It has been used more frequently in childhood MAH and may have a useful adjunctive role with BPs in severe symptomatic hypercalcaemia when there is a clinical urgency to reduce the calcium level rapidly (Mathur *et al*, 2003). However, there is little evidence that this approach is associated with superior efficacy compared with rehydration and bisphosphonate therapy alone (Inukai *et al*, 2007).

Corticosteroids

Corticosteroids inhibit 1α-hydroxylase-mediated conversion of 25-hydroxyvitamin D_3 to calcitriol. Patients with calcitriol-mediated hypercalcaemia associated with Hodgkin lymphoma and NHL may respond to corticosteroid therapy. Due to the anecdotal nature of reports, the optimal dosing is not known although a dose of hydrocortisone 200–300 mg intravenously for 3–5 d may be used (Bilezikian, 1992). Corticosteroids are an active component of many lymphoma treatment regimens however the calcium-lowering effect appears to reflect 1α-hydroxylase inhibition and is not merely a surrogate for cytotoxic activity (Seymour *et al*, 1993). Corticosteroids may also inhibit secretion of cytokines, such as interferon-γ, that increase calcitriol production by macrophages and also reduce intestinal calcium absorption. Although the majority of patients with Hodgkin Lymphoma will have calcitriol-mediated hypercalcaemia this mechanism only affects about 30% of NHL cases with hypercalcaemia. In practical terms, serum calcitriol levels may not be readily available in the emergency setting to inform the therapeutic pathway and standard therapy with saline rehydration and bisphosphonates should be initiated for NHL patients whereas steroid therapy should certainly be considered for Hodgkin lymphoma patients.

Gallium nitrate

Originally developed as an anti-tumour agent, gallium nitrate inhibits osteoclast activity and enhances hydroxyapatite crystallization, reducing bone mineral solubility (Leyland-Jones, 2004). It induces normocalcaemia in 70%–80% of patients and has been found to have superior efficacy compared to calcitonin, etidronate and, more recently, pamidronate in clinical studies (Warrell *et al*, 1988, 1991; Cvitkovic *et al*, 2006). Its potential utility is tempered by the need to administer it as a continuous infusion for 5 d, nephrotoxicity (urine output should be maintained >2000 ml/day) and the small numbers (<150 patients) treated in clinical trials to date. Furthermore, acute renal impairment has been observed in a patient with myeloma and caution is advised in this setting until further data are available (Warrell *et al*, 1988). There is no published paediatric experience with this agent.

Plicamycin (mithramycin)

Plicamycin is an anti-neoplastic agent originally used for testicular cancer that induces hypocalcaemia by inhibiting RNA synthesis in OCs (Ross *et al*, 2004). Given as an intravenous infusion, 25 μg/kg over 4–6 h, it causes a rapid fall in serum calcium within 12 h of administration, peaking between 48 and 72 h. In a pooled analysis, its overall efficacy in achieving normocalcaemia has been reported as 56% (Zojer *et al*, 1999). Its use has been limited by side effects including nausea, liver toxicity, bone marrow suppression, platelet dysfunction and abnormalities in multiple clotting factors, thus making it a particularly unsuitable choice for patients with haematological malignancy (Pecherstorfer *et al*, 2003).

Future directions

As our understanding of the molecular pathology of bone resorption increases, new pathways for targeted therapy have been identified. Drugs that interfere with the RANKL system, including the monoclonal anti-RANKL antibody, denosumab, and the decoy receptor OPG, show promise as novel agents against bone resorption and MAH. Denosumab has been shown to produce a rapid and sustained reduction in markers of bone resorption in patients with myeloma and breast cancer and its use in MAH is under investigation (Body *et al*, 2006). In a murine model of PTHrP-mediated MAH, OPG was found to induce a more rapid and durable reversal of hypercalcaemia compared to BPs (Morony *et al*, 2005). Anti-PTHrP antibodies have been shown to normalize calcium levels in an animal model of MAH (Sato *et al*, 2003). It remains to be seen whether these strategies will be effective and safe for the management of human MAH cases. The widespread use of bisphosphonate maintenance therapy in myeloma patients may be reducing the incidence of recurrent hypercalcaemia. Promoting osteoblastogenesis with bortezomib therapy and anti-DKK1 antibodies or blocking osteoclast formation using lenalidomide, denosumab and antagonists to CCR1 (MIP-1α receptor) are additional strategies that may counter the imbalance responsible for osteolysis and hypercalcaemia in myeloma (Roodman, 2009).

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