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Comparative Tolerability of Drug Therapies for Hypercalcaemia of Malignancy

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Abstract

The bisphosphonates are the treatment of choice in hypercalcaemia of malignancy. However, plicamycin (mithramycin) an calcitonin treatment may still be of value should bisphophonate treatment fail, and gallium nitrate has recently been introduced as an alternative therapy. We analysed the tolerability of different treatments based on articles identified in a Medline search covering the period 1979 through September 1998. Articles were included if they met two criteria: (i) quantitative assessment of adverse effects; (ii) inclusion of ≥10 patients. Although bisphosphonates are generally well tolerated, elevation of serum creatinine level, nausea/vomiting and fever have been reported following their application. Patients receiving etidronate (n = 268) or clodronate (n = 127) more frequently experienced creatinine elevation (8 and 5%, respectively) than did patients receiving pamidronate (n = 424; 2%), aledronate (n = 79; 0%), or ibandronate (n = 203; <1%). The difference in the frequency of reported creatinine level elevations reached statistical significance only for etidronate (z-test: $p < 0.001$

versus pamidronate; $p < 0.02$ versus alendronate; $p < 0.001$ versus ibandronate). With regard to the frequency of creatinine level elevations, clodronate treatment did not differ significantly from treatment with pamidronate, alendronate and ibandronate. An exception among the bisphosphonates is tiludronate, which has been reported on s a treatment of hypercalcaemia in only 1 study (n = 19) resulting in 1 case of lethal and 1 case of manageable acute renal failure. Nausea and vomiting are rare adverse effects of bisphosphonate treatment but seem to be more frequent with first generation drugs: etidronate (8%) and clodronate (7%) versus pamidronate (2%) [$p < 0.001$ and 0.009, respectively] and versus ibandronate (<1%) [$p< 0.002$ and 0.02, respectively]. Bisphosphonates containing a nitrogen atom were associated with an acute phase reaction leading to reported fever in 16% of pamidronate, 20% of aledronate, and 11% of ibandronate-treated patients.

The most frequently reported adverse effects of treatment with the cytostatic drug plicamycin were hepatotoxicity (26%), nausea/vomiting (23%), and serum creatinine level elevation (5%). Furthermore, plicamycin application was associated with bone marrow suppression and a bleeding tendency due to abnormalities in multiple clotting factors and platelet dysfunction. The use of calcitonin is limited more by the short duration of its therapeutic effect than by toxicities (most frequent: nausea/vomiting in 16% of treated cases). The few publications on gallium nitrate in the treatment of hypercalcaemia of malignancy characterise it as an efficient drug, which is, however, associated with a higher frequency of renal toxicity (10%) and of nausea and vomiting (14%) than are the bisphosphonates.

Hypercalcaemia is a serious complication in patients with solid and haematological malignancies. It is diagnosed in 20 to 40% of patients at some time during the course of their disease. According to a study by Vassilopoulou-Sellin et al.,[1] the incidence of hypercalcaemia is low at initial presentation, occurring in 4.8% of newly diagnosed patients with renal cell cancer, 3.2% of patients with myeloma, 1.9% of patients with non–small cell lung cancer and 0.9% of patients with breast cancer. Most patients with hypercalcaemia have advanced disease and a poor prognosis, with median survival from onset of hypercalcaemia ranging from 2 to 6 months.[2,3]

Cytokines and hormones released by the tumour stimulate bone resorption and renal calcium reabsorption, thus leading to an increase in serum calcium levels. Neoplastic bone involvement may or may not be present in patients with hypercalcaemia of malignancy, and the severity of hypercalcaemia does not correlate with the extent of bone metastases.[4] Symptoms of hypercalcaemia closely resemble symptoms of brain metastases and are more pronounced the higher the levels of serum calcium. Most striking among these symptoms is the progressive impairment of cerebral function: tiredness, dizziness, nausea, lethargy, somnolence and coma. Other consequences of elevated serum calcium level concern the gut (vomiting and constipation) and the kidney (polyuria).[5] Rapid institution of antihypercalcaemic treatment is essential to improving the symptoms associated with elevated levels of serum calcium and to preventing the life-threatening deterioration consequent on hypercalcaemia.

1. Bone Physiology and Neoplastic Bone Destruction

1.1 Physiological Bone Remodelling and its Regulation

Bone is a nonstatic tissue, which continuously undergoes renewal by osteoclastic bone resorption followed by formation of new bone by osteoblasts.

Early in life, bone formation exceeds bone resorption with a net increase in bone mass, while later in life, bone resorption exceeds bone formation with net loss of bone. The bone remodelling process is initiated by the recruitment and activation of osteoclasts. The exact mechanism for the recruitment and activation of osteoclasts has been elucidated only recently. Osteoprotegerin ligand [also known as tumour necrosis factor (TNF)–related activation-induced cytokine (TRANCE), receptor activator of NFκB (RANK) ligand (RANKL), and osteoclast differentiation factor (ODF)] which is a member of the TNF family, has been identified as the major osteoclast differentiation factor.[6,7] Osteoprotegerin ligand recruits haematopoietic progenitor cells to the osteoclast lineage and directly activates mature osteoclasts *in vitro*. Furthermore, mice with a disrupted osteoprotegerin ligand gene lack osteoclasts completely and show severe osteopetrosis and a defect in tooth eruption.[8] The differentiation of haematopoietic progenitor cells to osteoclasts, induced by osteoprotegerin ligand, can be interrupted by osteoprotegerin, by binding to osteoprotegerin ligand and thus interfering with the binding of osteoprotegerin ligand to its receptor RANK.[7,9,10] Increasing evidence suggests that osteoprotegerin ligand and osteopegerin are the key extracellular regulators of osteoclast development.

Several other hormones, cytokines and vitamins have been implicated in the recruitment and stimulation of osteoclast activity, including parathyroid hormone, parathyroid hormone-related protein, colecalciferol (vitamin D), macrophage colony stimulating factor, interleukin-1, interleukin-6, interleukin-11, transforming growth factor α (TGFα), TNFα and TNFβ.[11] These regulatory signals for osteoclast activity appear to come from osteoblasts, bone lining cells or from bone marrow stromal cells. A shift in the equilibrium toward the recruitment of osteoclast precursors or toward the apoptosis of osteoclasts results in an increase or decrease, respectively, of bone resorption.

1.2 Physiological Regulation of the Serum Calcium Level

In healthy humans, the total serum calcium level is maintained within the narrow range of 2.1 to 2.6 mmol/L. Parathyroid hormone is the central regulating hormone in this process. The secretion of parathyroid hormone by the parathyroid gland responds inversely to changes in the serum level of ionised calcium. When serum calcium level falls, the serum level of parathyroid hormone increases, leading to increased bone resorption and increased renal calcium reabsorption.[12] Simultaneously, parathyroid hormone stimulates the transformation of 25-hydroxy colecalciferol (vitamin D) into the more active 1,25-dihydroxy vitamin D (calcitriol) in the kidney. Calcitriol in turn contributes to the elevation of the serum calcium level by stimulating both calcium absorption in the gut and bone resorption.

Parathyroid hormone-related protein is a proteohormone which in its aminoterminal region closely resembles parathyroid hormone: 8 of the first 13 amino acids are identical to parathyroid hormone. This homology suffices to allow parathyroid hormone-related protein to interact with the parathyroid hormone receptor. Thus, most of the calcium regulatory effects of parathyroid hormone (e.g. increase in bone resorption and renal tubular calcium reabsorption) are also mediated by parathyroid hormone-related protein. Parathyroid hormone-related protein is expressed in a variety of normal tissues including brain, breast and skin. A pivotal role has been ascribed to it in skeletal development, transepithelial calcium transport, and regulation of smooth muscle tone. Parathyroid hormone-related protein is present in placenta and milk, where it is involved in the regulation of active placental calcium transport and calcium transport through the mammary gland epithelial cells, respectively.[13,14] Its levels are significantly higher in the serum of newborn children, who are usually hypercalcaemic, than in their mothers' blood.[15] The many roles of parathyroid hormone-related protein in normal developmental and adult physiology have been reviewed elsewhere in detail.[16]

1.3 Pathophysiology of Neoplastic Bone Destruction and Tumour-Associated Hypercalcaemia

Tumour cells do not resorb bone directly but recruit the host's osteoclasts by paracrine mechanisms. The osteoclasts in malignant disease seem to be stimulated by factors which are involved in normal bone resorption. It appears that solid tumours stimulate bone resorption mainly by the secretion of parathyroid hormone-related protein, whereas in haematological malignancies 1,25-dihydroxy vitamin D and cytokines such as interleukin-6 and lymphotoxin (TNFβ) may be the mediators of osseous breakdown.[17] Parathyroid hormone-related protein elevates serum calcium level by increasing bone resorption and renal tubular reabsorption of calcium. Parathyroid hormone-related protein serum levels in normocalcaemic cancer patients lie within the normal range. In patients with solid tumours, the transition from normocalcaemia to hypercalcaemia is accompanied by a constant increase in the amount of parathyroid hormone-related protein secreted and circulating in blood.[17] In hypercalcaemic patients with haematological tumours parathyroid hormone-related protein level is only rarely elevated.[18]

Although parathyroid hormone-related protein and parathyroid hormone act through the same receptor in bone and kidney, there are clear differences between the syndromes of humoral hypercalcaemia of malignancy and primary hyperparathyroidism. In contrast to primary hyperparathyroidism, serum 1,25 dihydroxy vitamin D levels[19] and calcium absorption from the gut are decreased in patients with malignant hypercalcaemia, and there is a decrease in bone formation and decrease in serum chloride level and metabolic alkalosis.[17] These differences may be due to modification of the effects of parathyroid hormone-related protein by other factors produced by the tumour, such as interleukin-1, interleukin-6, TGFα, and TNFα.

As the serum calcium level starts to rise subsequent to the bone and renal effects of parathyroid hormone-related protein and other factors, renal water reabsorption decreases progressively, resulting in polyuria. The loss of water leads to increased reuptake of sodium and calcium by the proximal tubuli of the kidney. Thus, the serum calcium level increases further, leading to a vicious cycle.

2. Therapies for Hypercalcaemia of Malignancy

At the present time, the first intervention in a patient with hypercalcaemia of malignancy is fluid repletion with isotonic saline solution. In patients with a low to moderate elevation of serum calcium level (2.6 to 2.8 mmol/L) this therapy can be sufficient to reverse hypercalcaemia.[20] However, since the effect of fluid repletion is transient, treatment needs to be supplemented in most cases with a drug directed at the increased bone resorption. Several substances which have been found to inhibit osteoclast formation and function are used to treat hypercalcaemia of malignancy. Of these substances, bisphosphonates have in the past decade become the treatment of choice in tumour-induced hypercalcaemia.[21] In the majority of patients with tumour-associated hypercalcaemia, normocalcaemia can be restored following first treatment with a bisphosphonate, although some studies have reported an association between high serum parathyroid hormone-related protein levels and reduced response to bisphosphonate treatment.[2,22-24] The level of parathyroid hormone-related protein might influence the length of time until recurrence of hypercalcaemia. Relapsing hypercalcaemia usually does not respond as well to bisphosphonate treatment as does initial hypercalcaemia. In this case, the dose of the bisphosphonate has to be increased to produce the same effect.[25,26]

Other drugs which are sometimes used (e.g. in the rare cases where treatment with bisphosphonates does not elicit the expected response) include calcitonin, gallium nitrate, plicamycin (mithramycin) and corticoids. Calcitonin leads to immobilisation and contraction of the osteoclasts away from the bone surface.[11] However, continuous exposure to calcitonin leads to downregulation of calcitonin receptors on osteoclasts and eventually to the unresponsiveness of the bone resorbing

cells to this hormone. Gallium nitrate was initially studied as an antineoplastic drug. It has been evaluated for the therapy of hypercalcaemia of malignancy because of its hypocalcaemic effect.[27,28] Gallium localises into areas of high bone turnover and renders hydroxyapatite less soluble and more resistant to cell-mediated resorption.[29,30] Furthermore, gallium nitrate may increase bone formation by stimulating bone collagen synthesis and increasing calcium accretion into bone.[31] Plicamycin (mithramycin) is an antitumour antibiotic. Plicamycin exerts its hypocalcaemic effect by directly killing osteoclasts.[32] This effect can be achieved with about one-tenth of the dose necessary for antitumour activity.

In the past, glucocorticoids were also used for treatment of tumour-associated hypercalcaemia. However, glucocorticoid treatment has been shown hardly ever to restore normocalcaemia in patients with solid tumours. In hypercalcaemia induced by haematological tumours, glucocorticoid therapy makes sense if it can be expected to exert an antineoplastic effect. For these reasons and because glucocorticoid therapy has been extensively discussed in the literature,[33] we mention it only briefly here in this review.

For the present review, we identified trials on the treatment of hypercalcaemia of malignancy by searching the Medline from 1979 through September 1998 using the MeSH terms 'hypercalcemia' together with 'bisphosphonates (or diphosphonate)', 'calcitonin', 'mithramycin (or plicamycin)' and 'gallium nitrate'. Articles were reviewed for the following criteria: (i) quantitative assessment of adverse effects; and (ii) inclusion of ≥10 patients. Studies which did not meet these criteria were not included in our analysis. Studies included in the analysis for bisphosphonates are summarised in tables I to VI. Only adverse events which the study authors attributed to administration of the respective bisphosphonate are listed. In calculating the proportion of patients who experienced a specific adverse event (e.g. elevation of serum creatinine level) we considered only those studies in which this adverse event was expressly mentioned. For example, 280 patients were treated with etidronate in 5 published studies (see table I). Four of these studies mentioned serum creatinine level elevation, if only to state that it did not occur.[34] We considered only these 4 trials for our analysis. Although reports including fewer than 10 patients were not included in our statistical analysis, we mention selected case reports of adverse events in section 3.4.

3. Tolerability of Bisphosphonates in the Treatment of Hypercalcaemia of Malignancy

Because bisphosphonates have been evaluated for treatment of hypercalcaemia of malignancy since the late 1970s, a great deal of information regarding their efficacy and safety has accumulated. Of the 92 trials on hypercalcaemia and bisphosphonates we identified in the Medline, 41 fulfilled the criteria for inclusion in our analysis. The number of patients in the included studies ranges from 12 to 173. We omitted trials of oral bisphosphonate treatment because enteral absorption of bisphosphonates is poor (1 to 2%) and most patients with tumour-induced hypercalcaemia, who are in poor general condition, do not tolerate oral medication well. It is our opinion that, as a general rule, hypercalcaemia should be treated intravenously. Nevertheless a few comments on oral bisphosphonates in the treatment of tumour-associated hypercalcaemia are in order. Nearly two decades ago, it was shown that hypercalcaemia of malignancy could be treated with high doses of oral pamidronate.[73] In a further trial, a randomised comparison of IV pamidronate (30 mg/day) and oral pamidronate (1200 mg/day) proved these treatment schedules to be equally effective.[74] The adverse effects attributed to oral pamidronate treatment – transient fever, hypocalcaemia and hypophosphataemia – were not significantly different from those in the group treated intravenously. Some patients complained of slight epigastric discomfort and nausea at the beginning of oral treatment, but this could be relieved simply by dissolving the drug in water before administration.

Oral clodronate has been used as maintenance treatment after initial IV therapy to prevent recurrence of hypercalcaemia.[41,75,76] In 2 studies[75,76] a rise in serum calcium level was noted in some patients immediately after discontinuation of long term administration of oral clodronate. The only placebo-controlled study on oral maintenance treatment[77] evaluated the efficacy of 20 mg/kg/day etidronate to prevent recurrence of hypercalcaemia after successful initial therapy. Oral etidronate was not found to be superior to placebo in terms of maintaining normal serum calcium levels (40% of etidronate treated patients and 46% of control participants had recurrence of hypercalcaemia).

We reviewed studies on all the available bisphosphonates, not limiting our analysis to the 4 currently licensed for clinical use in different countries (tables I to VI).[26,27,34,41,35-40,42-72] The 4 bisphosphonates currently licensed for treatment of tumour-associated hypercalcaemia are: etidronate (1-hydroxyethylidene-bisphosphonic acid), clodronate (dichlormethylene-bisphosphonic acid), pamidronate (3-amino-1-hydroxypropylidene-bisphosphonic acid) and ibandronate (1-hydroxy-3(methylpentylamino)-propylidene-bisphosphonic acid).

Even in studies that explicitly evaluate adverse effects, the data are often incomplete. Most studies list only serious adverse events (that, by definition, prolong hospitalisation, lead to hospitalisation, result in permanent damage, or end in death). Non serious adverse events, e.g. changes in body temperature or serum electrolyte levels, are underreported. A further problem in identifying adverse effects of different treatments of hypercalcaemia of malignancy is the fact that patients with hypercalcaemia of malignancy are severely ill, with symptoms that could equally be attributed to the neoplastic disease, to its treatment, or to the hypercalcaemia itself, rather than to a specific calcium-reducing drug. For example, nausea/vomiting is reported to be an adverse effect of clodronate treatment,[38] but it is also a frequent symptom of

Table I. Clinical studies of etidronate for hypercalcaemia of malignancy

Infusion regimen	n	Percentage of patients							Reference
		efficacy[a]	Cr elevation	nausea/ vomiting	fever	infusion site reaction	hypocalcaemia	other	
7.5 mg/kg/day on days 1-3[b]: infusion time 2.5-3h	12	92	NR	NR	NR	NR	50		35
5-25 mg/kg; 24h infusion	26	NR	0	NR	NR	NR	0		34
7.5 mg/kg/day on days 1-3; infusion time of 2h	170	63	9	9	NR	NR	15	Altered taste 3.5	36
7.5 mg/kg/day on days 1-5; infusion time 4h	37	43	11	NR	NR	NR	NR	Hyperphosphataemia 11	27
7.5 mg/kg/day on days 1-3; infusion time 2h	35	41	6	6	9	0	6	Hypophosphataemia 3, seizures 3	37
Overall[c]	280	58 (254)[d]	8 (268)[d]	8 (205)[d]	9 (35)[d]	0 (35)[d]	14 (243)[d]		

a Efficacy = percentage of patients achieving normocalcaemia.

b A few selected patients received therapy for up to 5 days.

c The last line of the table summarises the efficacy data and the reported frequencies for each adverse effect. Studies not reporting efficacy or frequency of the respective adverse effect were excluded from the analysis.

d The number in brackets indicates the number of patients who could be included in the analysis.

Cr elevation = elevation of serum creatinine level (usually defined as an increase of >0.5 mg/dl); **n** = number of patients enrolled in the study; **NR** = not reported.

Table II. Clinical studies of clodronate for hypercalcaemia of malignancy

Infusion regimen	n	Percentage of patients							Reference
		efficacy[a]	Cr elevation	nausea/ vomiting	fever	infusion site reaction	hypo-calcaemia	other	
4-20 mg/kg; infusion time 1h	14	NR	NR	14	NR	NR	0		38
2.5 mg/kg on day 1; 5 mg/kg on days 2-6; infusion time 2h	12	92	0	NR	NR	NR	17		39
100-300 mg/day on days 1-3[b]; infusion time 3h	26	89	NR	NR	NR	NR	0		40
300 mg/day on days 1-NS; infusion time 2h	34	94	0	NR	NR	NR	NR		41
300mg (single dose); infusion time 2h	15	93	7	20	0	NR	NR	Obstipation 53	42
300 mg/day for up to 7 days; infusion time 3h	25	81	NR	0	NR	NR	16	Paraesthesia 4, diarrhoea 4	43
300 mg/day on days 1-5; infusion time 4h or 1500mg day 1; 24h infusion	45	75	0	NR	NR	NR	7		44
1500mg (single dose); infusion time 4h	21	80	24	0	0	0	NR		45
Overall[c]	192	77 (178)[d]	5 (127)[d]	7 (75)[d]	0 (36)[d]	0 (21)[d]	7 (122)[d]		

a Efficacy = percentage of patients achieving normocalcaemia.

b A few selected patients received therapy for up to 10 days.

c The last line of the table summarises the efficacy data and the reported frequencies for each adverse effect. Studies not reporting efficacy or frequency of the respective adverse effect were excluded from the analysis.

d The number in brackets indicates the number of patients who could be included in the analysis.

Cr elevation = elevation of serum creatinine level (usually defined as an increase of > 0.5 mg/dl); **n** = number of patients enrolled in the study; **NR** = not reported; **NS** = exact number of days not stated.

hypercalcaemia. Nonetheless, it is possible to discern a consistent pattern of adverse effects for the different bisphosphonates. The reported frequencies of the most common adverse effects are summarised at the end of tables I-V.

3.1 Creatinine Level Elevation Following Bisphosphonate Treatment

At the beginning of the bisphosphonate era, intravenously injected etidronate and clodronate were reported to cause acute renal failure.[78] This renal failure was attributed to the precipitation of insoluble calcium-bisphosphonate complexes in the renal tubuli. Since these early reports, renal failure following bisphosphonate therapy for hypercalcaemia has hardly ever been reported, because care has been taken to administer bisphosphonates by slow IV infusion over several hours in sufficient solution (500ml). Restoration of normocalcaemia by fluid repletion and bisphosphonate therapy usually improves renal function (as indicated by falling serum creatinine levels) by normalising circulating fluid volume and the glomerular filtration rate. Even in patients with markedly increased serum creatinine levels (up to 6.4 mg/dl), IV bisphosphonate treatment was shown to be well tolerated and effective when the drug was administered by slow IV infusion combined with adequate rehydration.[79]

According to our analysis, an increase in serum creatinine levels was more often seen following treatment with etidronate (8% of cases) and clodronate (5%) than with the more potent aminobisphosphonates pamidronate (2%), alendronate (0%) or ibandronate (1%). The difference in the frequency of reported creatinine level elevations reached statistical significance only for etidronate

Table III. Clinical studies of pamidronate for hypercalcaemia of malignancy

Infusion regimen	n	Percentage of patients							Reference
		efficacy[a]	Cr elevation	nausea/ vomiting	fever	infusion site reaction	hypo-calcaemia	other	
15 mg/day on days 1-NS; infusion time not stated	13	NR	NR	NR	31	15	NR		46
30 or 60mg (single dose); 24h infusion	20	85	NR	0	10	NR	15		47
0.01-3 mg/kg/day on days 1-3; infusion time 2h	18	78	0	NR	11	NR	NR	Fever + hypotension + dysgeusia 5, lymphopenia 28	48
30mg (single dose); 24h infusion	16	75	0	NR	19	NR	12		49
5-15mg (sometimes repeated); infusion time 2h	25	78	0	0	8	0	NR		50
15-25 mg/day for up to 6 days or 15-30mg on day 1; infusion time 0.5-3h	27	74	NR	NR	22	NR	NR	Grand mal seizures 7, paraesthesia and mild tetany 3.5	51
60mg on day 1 or 30mg on days 1-2 or 15mg on days 1-4; infusion time 2-8h	30	93	0	NR	17	0	13	Xanthopsia 3	52
30-90mg (single dose); 24h infusion	52	83	0	0	11	0	15		26
0.5 mg/kg/day on days 1-3; infusion time 2h or 1.5 mg/kg on day 1 or 0.5 mg/kg on day 1; 24h infusion	33	97	0	NR	9	NR	NR	Reduction of lymphocyte and platelet counts NR	53
30-60mg on day 1 or 30mg on days 1-2; infusion time 4 + 8h	27	46	NR	NR	7.5	0	7.5	Confusional state, hypernatraemia, pyrexia 3.5	54
15-45mg (single dose); infusion time 4h	29	NR	NR	NR	37	NR	NR	Rigors 3	55
45mg (single dose); infusion time 3h	25	72	NR	NR	NR	NR	20	Dyspnoea 4	56
1 mg/kg; infusion time 4-24h	15	NR	0	0	0	0	NR		57
1 mg/kg; infusion time 4-24h	25	NR	0	12	0	NR	NR		58
30-60mg (single dose); infusion time 4h	28	100	NR	NR	14	NR	32		59
30 or 90mg; infusion time 4 or 24h	32	56	NR	NR	12	NR	0		60
60mg (single dose); infusion time 2-24h	50	94	0	NR	8	0	8		61
60mg (single dose); infusion time 24h	30	70	13	0	17	7	17	Hypophosphataemia 37	7
30-90mg (single dose); infusion time 12h	14	100	0	NR	NR	NR	NR		62

Table III. Contd

Infusion regimen	n	Percentage of patients							Reference
		efficacy[a]	Cr elevation	nausea/ vomiting	fever	infusion site reaction	hypo-calcaemia	other	
60mg (single dose); infusion time 24h	25	90	NR	0	40	53	32	Severe hypophosphataemia 4	63
30-90mg (single dose); infusion time 24h	50	40-100	0	NR	20	6	6	Hypophosphataemia 22	64
60mg (single dose); infusion time 4 or 24h	46	80	13	NR	22	4	4	Hypophosphataemia 33	65
90mg (single dose); infusion time 4h	20	100	0	0	15	0	NR	Reduction of lymphocyte count NR	45
Overall[b]	650	80 (568)[c]	2 (424)[c]	1 (212)[c]	16 (611)[c]	5 (383)[c]	13 (431)[c]		

a Efficacy = percentage of patients achieving normocalcaemia.

b The last line of the table summarises the efficacy data and the reported frequencies for each adverse effect. Studies not reporting efficacy or frequency of the respective adverse effect were excluded from the analysis.

c The number in brackets indicates the number of patients who could be included in the analysis.

Cr elevation = elevation of serum creatinine level (usually defined as an increase of >0.5 mg/dl); **n** = number of patients enrolled in the study; **NR** = not reported; **NS** = exact number of days not stated.

(z-test: $p < 0.001$ in comparison with pamidronate; $p < 0.02$ versus alendronate; $p < 0.001$ versus ibandronate). Treatment with clodronate was not significantly different from treatment with pamidronate, alendronate and ibandronate with regard to the relative frequency of creatinine level elevations. It has not been established why the newer, more potent (amino-) bisphosphonates are associated with lower renal toxicity. However, because a lower molar amount of the drug is required to inhibit bone resorption, it is less likely that the kidney will sustain damage from the bisphosphonate.[80] Tiludronate, a bisphosphonate containing a chlorophenyl-thiomethylene side chain, has been reported on as a treatment for tumour-associated hypercalcaemia in only 1 published study.[78] Further evaluation of this drug in hypercalcaemic patients was stopped since 1 case of lethal and 1 case of manageable acute renal failure occurred among the 19 patients treated.

Recently, we demonstrated that in normocalcaemic breast cancer patients the newly developed bisphosphonate ibandronate can be safely administered by rapid IV injection.[80] However, in hypercalcaemic patients we cannot recommend the IV bolus injection of any bisphosphonate at present, since there are as yet no data available on this form of administration. It cannot be excluded that the brief high molar concentration of the bisphosphonate (resulting from the rapid IV injection) together with the high serum calcium level is sufficient to generate bisphosphonate-calcium complexes such as known from the inadequate administration of older bisphosphonates.

3.2 Nausea/Vomiting

Nausea or vomiting are rare adverse effects of bisphosphonate treatment but seem to be more frequent with first generation drugs: etidronate and clodronate *vs* pamidronate (z-test: $p < 0.001$ and 0.009, respectively) and *vs* ibandronate ($p < 0.002$ and $p < 0.02$). Assessment of adverse effects related to the gastrointestinal tract may be especially difficult, because hypercalcaemia itself frequently manifests with nausea/vomiting, for which bisphosphonates can, in fact, generally provide symptomatic relief.

3.3 Acute Phase Reaction

Substitution of the side chain of bisphosphonates with an amino group is responsible for enhanced clinical effectiveness. However, it also leads, by unknown mechanisms, to an acute-phase response. Application of the aminobisphosphonates alendronate and pamidronate has been associated with transient, usually mild fever, lymphocytopenia, malaise, and myalgias. It occurs within 36 hours following the first application of an aminobisphosphonate and is self-limiting. Usually, it does not require specific medication and does not recur in subsequent treatments, except in patients with myeloma, where fever has been observed even with repeated treatments (unpublished observation). Secretion of TNFα by T lymphocytes expressing the activation marker CD69 may be responsible for the acute-phase response following aminobisphosphonate therapy. The basis for this hypothesis is that whereas elevated levels of CD69 T lymphocytes are detectable 10 hours after pamidronate treatment, an increase in TNFα serum levels and a decrease in the total number of circulating lymphocytes are not detectable until 24 hours following administration of this bisphosphonate.[81-83] Interleukin-6 has also been implicated as a mediator of the acute phase response.[83,84] Ocular adverse reactions (iritis, episcleritis, scleritis and conjunctivitis) may be part of the acute-phase reaction and have been reported in association with administration of pamidronate.[85-87]

An acute-phase reaction somewhat different from that seen with the aminobisphosphonates pamidronate and alendronate has been observed upon administration of ibandronate. Muscle pain is usually prominent. Furthermore, ibandronate treatment elevates rather than decreases circulating lymphocyte counts.[81]

3.4 Other Adverse Events

When all the reviewed studies are summarised, it is seen that serious complications were rarely encountered with bisphosphonate therapy. These rare cases include a patient in whom seizures developed after treatment with etidronate,[37] followed by respiratory failure and death. The presence of cerebral metastases could not be ruled out in this case. Similarly, 2 patients developed grand mal seizures 3 to 4 days after pamidronate therapy.[51] Serum calcium level decreased to the lower level of normal range in these patients. Cerebral metastases were evident using computerised tomography in 1 patient and could not be excluded in the other. It may be speculated that electrolyte changes induced by bisphosphonate treatment contributed to the development of seizures in these patients. Indeed, hypocalcaemia is observed in up to 50% of patients treated with bisphosphonates for

Table IV. Clinical studies of alendronate for hypercalcaemia of malignancy

Infusion regimen	n	Percentage of patients							Reference
		efficacy[a]	Cr elevation	nausea/ vomiting	fever	infusion site reaction	hypo-calcaemia	other	
10mg (single dose); infusion time 2h or 24h	20	80	0	NR	10	NR	NR		66
2.5-15mg (single dose); infusion time 2h or 24h	59	59	0	NR	24	3	0-15	Transaminase level elevation 14	67
Overall[b]	79	65 (79)[c]	0	NR	20 (79)[c]	3 (59)[c]	0-15 (59)[c]		

a Efficacy = percentage of patients achieving normocalcaemia.

b The last line of the table summarises the efficacy data and the reported frequencies for each adverse effect. Studies not reporting efficacy or frequency of the respective adverse effect were excluded from the analysis.

c The number in brackets indicates the number of patients who could be included in the analysis.

Cr elevation = elevation of serum creatinine level (usually defined as an increase of >0.5 mg/dl); **n** = number of patients enrolled in the study; **NR** = not reported.

Table V. Clinical studies of ibandronate for hypercalcaemia of malignancy

Infusion regimen	n	Percentage of patients							Reference
		efficacy[a]	Cr elevation	nausea/ vomiting	fever	infusion site reaction	hypo-calcaemia	other	
0.2-2mg (single dose); infusion time 4h	30	53	3	0	27	NR	NR	Transaminase level elevation 3, reduction of lymphocyte count 3	68
0.6-2mg (single dose); infusion time 2h	173	44-67	0	0.5	6	NR	2	Thrombopenia 2; oesophagitis 0.5; transaminase level elevation 0.5	69
2-6mg (single dose); infusion time 2h	131	50-77	NR	NR	13	0	5	Asymptomatic hypophosphataemia 70	70
Overall[b]	334	59 (334)[c]	<1 (203)[c]	<1 (334)[c]	11 (334)[c]	0 (131)[c]	3 (304)[c]		

a Efficacy = percentage of patients achieving normocalcaemia.

b The last line of the table summarises the efficacy data and the reported frequencies for each adverse effect. Studies not reporting efficacy or frequency of the respective adverse effect were excluded from the analysis.

c The number in brackets indicates the number of patients who could be included in the analysis.

Cr elevation = elevation of serum creatinine level (usually defined as an increase of >0.5 mg/dl); **n** = number of patients enrolled in the study; **NR** = not reported.

hypercalcaemia of malignancy, although symptomatic hypocalcaemia (paraesthesia) is rare. Severe hypocalcaemia associated with grand mal seizures followed sequential administration of clodronate and an aminoglycoside, possibly the result of the additive effect of these 2 drugs on the serum calcium level.[88] Following the administration of pamidronate, 1 patient experienced rigors[55] and another experienced dyspnoea.[56] The latter adverse effect was again observed when the patient was re-exposed to the drug. Bronchoconstriction was observed in a patient treated with clodronate and in another treated with etidronate, both with a history of aspirin (acetylsalicylic acid)–sensitive asthma.[89] A serious cutaneous reaction was observed in a patient with atopy after tiludronate treatment.[90] The histology of the lesions resembled epidermal necrolysis. These 2 reports suggest that various bisphosphonates can elicit allergic reactions in predisposed patients.

Table VI. Clinical studies of tiludronate and neridronate for hypercalcaemia of malignancy

Drug/infusion regimen	n	Percentage of patients							Reference
		efficacy[a]	Cr elevation	nausea/ vomiting	fever	infusion site reaction	hypo-calcaemia	other	
Tiludronate 3-6 mg/kg/day on days 1-3; infusion time not stated	19	72	10.5	0	NR	NR	NR	Acute renal insufficiency + death 5; reduction in lymphocyte count NR	71
Neridronate 125mg single dose; infusion time 4h	20	65	NR	10	10	NR	0	Loose bowel motions 10	72

a Efficacy = percentage of patients achieving normocalcaemia.

Cr elevation = elevation of serum creatinine level (usually defined as an increase of >0.5 mg/dl); **n** = number of patients enrolled in the study; **NR** = not reported.

Table VII. Clinical studies of plicamycin (mithramycin) for hypercalcaemia of malignancy

Administration regimen	n	Percentage of patients							Reference
		efficacy[a]	Cr elevation	nausea/ vomiting	fever	hepato-toxicity	hypo-calcaemia	other	
25 μg/kg IV, repeated for up to 5 days in 11 pts: the other 58 pts recieved a single dose only	69	61	0	NR	NR	9 (1/11): 0 (0/58)	18 (2/11): 0 (0/58)	Bleeding 9 (1/11)	91
25 μg/kg IV, repeated for up to 5 days	11	82	NR	NR	NR	36	45		92
25 μg/kg IV	14	NR	14	NR	NR	30	NR		93
25 μg/kg IV	8	NR	38	0	0	NR	NR	Oedema of eyelids 13	94
25 μg/kg IV, sometimes repeated	67	NR	NR	NR	NR	38	NR		95
25 μg/kg IV, sometimes repeated	13	NR	NR	15	NR	85	NR	Thrombocytopenia 8	46
1.25mg IV, sometimes repeated	11	27	0	NR	NR	NR	0		62
25 μg/kg IV	23	45	NR	36	9	NR	4	Thrombocytopenia 4; bleeding 4; phlebitis 11	63
Overall[b]	216	56 (114)[c]	5 (102)[c]	23 (44)[c]	6 (31)[c]	26 (174)[c]	7 (114)[c]		

a Efficacy = percentage of patients achieving normocalcaemia.

b The last line of the table summarises the efficacy data and the reported frequencies for each adverse effect. Studies not reporting efficacy or frequency of the respective adverse effect were excluded from the analysis.

c The number in brackets indicates the number of patients who could be included in the analysis.

Cr elevation = elevation of serum creatinine level (usually defined as an increase of >0.5 mg/dl); **IV** = intravenous; **n** = number of patients enrolled in the study; **NR** = not reported; **pts** = patients.

In a patient treated with high dose pamidronate (>250 mg/day, fever, hypotension and dysgeusia was observed after the first infusion.[48] Davis and Heath[54] reported confusion in a patient starting 2 to 3 days after the administration of pamidronate, associated with hypernatraemia, severe pyrexia, and evidence of pulmonary infiltrations on chest x-ray. This condition responded to antibacterial and corticosteroid treatment. The authors did not attribute this complication to pamidronate treatment.

In the only report referring to thrombocytopenia in patients treated with ibandronate[69], the frequency was low (0.5% of 173 patients).

4. Tolerability of Other Treatments for Hypercalcaemia of Malignancy

Since the antihypercalcaemic effect of bisphosphonates has been established, plicamycin and calcitonin have been used less and less frequently to treat hypercalcaemia of malignancy. Tables VII and VIII summarise the adverse effects reported by published studies.[28,46,62,63,91-97] The criteria for inclusion in our analysis were the same as those for the studies on bisphosphonates, as described in section 2. Gallium nitrate entered clinical trials a decade ago, and published data are limited so far[27,28] (see table IX).

4.1 Plicamycin (Mithramycin)

Plicamycin was first introduced as an antineoplastic drug for the therapy of testicular cancer. At the dosage used (25 μg/kg/day for up to 10 days), nausea/vomiting, bone marrow suppression and liver toxicity were frequently observed. Furthermore, plicamycin application was associated with a bleeding tendency due to abnormalities in multiple clotting factors and platelet dysfunction.[98] Ac-

cording to the manufacturer, the incidence of bleeding episodes has been 5.4% with a drug related mortality rate of 1.6% at doses of 30 μg/kg/day or less for 10 days. When hypercalcaemia is treated with plicamycin, lower doses of this drug (25 μg/kg as a single infusion or repeated once after 24 hours) are employed, and the frequency and severity of the adverse effects were lower in those studies (table VII). There is 1 reported case of fatal arterial bleeding from a duodenal ulcer following a single administration of 25 μg/kg plicamycin for treatment of hypercalcaemia.[63]

The most frequent adverse effect at the dosage used to treat hypercalcaemia is a transient elevation of liver enzyme levels. The increases occur within 2 days of drug administration and the levels return to baseline within 2 weeks in most cases.[95] Prior liver damage (e.g. hepatic metastases) does not seem to predispose to hepatic toxicity of plicamycin. Severe hepatic toxicity is unusual in the dosage applied for hypercalcaemia of malignancy, although a case of acute hepatic necrosis after plicamycin therapy has been reported.[99] Other rare complications of plicamycin therapy are acute renal insufficiency and toxic epidermal necrolysis.[100,101]

In randomised studies comparing plicamycin to pamidronate,[46,62,64] the latter was demonstrated to be more effective in normalising serum calcium levels and in improving WHO performance status.[62]

4.2 Calcitonin

In a recent evaluation of the long and short term adverse effects of calcitonin for nonmalignant bone disease (mainly Paget's disease and osteoporosis),[102] acute adverse effects were noted in 64 of 83 patients (77%) treated with subcutaneous injections of synthetic human calcitonin and 14 of 22 patients (64%) treated with synthetic salmon calcitonin. Fewer patients (32%) noted adverse effects when calcitonin was administered as a nasal spray. With subcutaneous administration the most frequent adverse effects were flushing, occurring in 69 and 41% of patients treated with human calcitonin and salmon calcitonin, respectively. This was followed by local irritation at the injection sites (65 and 32%, respectively) and nausea (22 and 14%, respectively). Following administration of salmon calcitonin as a nasal spray, 5 out of 25

Table VIII. Clinical studies of calcitonin for hypercalcaemia of malignancy

Administration regimen	n	Percentage of patients							Reference
		efficacy[a]	Cr elevation	nausea/ vomiting	fever	hepato-toxicity	hypo-calcaemia	other	
Up to 32 IU/kg IM	16	38	0	6	NR	0	0		96
4 IU/kg SC every 12h on days 1-2[b]; 8 IU/kg SC every 12h on days 3-4[b]; 8 IU/kg SC every 6h on days 5-NS	19	NR	0	12	NR	0	5		97
400IU SC every 8h for 9 days + corticosteroids	13	NR	NR	0	NR	NR	NR		46
8 IU/kg SC every 6h for 5 days ± corticosteroids	26	31	4	35	NR	NR	NR	Hypophosphataemia 45	28
Overall[c]	74	33 (42)[d]	1.5 (61)[d]	16 (74)[d]	NR	0 (35)[d]	3 (35)[d]		

a Efficacy = percentage of patients achieving normocalcaemia.

b Additional treatment not received by all patients.

c The last line of the table summarises the efficacy data and the reported frequencies for each adverse effect. Studies not reporting efficacy or frequency of the respective adverse effect were excluded from the analysis.

d The number in brackets indicates the number of patients who could be included in the analysis.

Cr elevation = elevation of serum creatinine level (usually defined as an increase of >0.5 mg/dl); **IM** = intramuscular; **n** = number of patients enrolled in the study; **NR** = not reported; **NS** = exact number of days not stated; **SC** = subcutaneous.

Table IX. Clinical studies of gallium nitrate for hypercalcaemia of malignancy

Administration regimen	n	Percentage of patients							Reference
		efficacy[a]	Cr elevation	nausea/ vomiting	fever	hepato-toxicity	hypo-calcaemia	other	
200 mg/m^2/day IV for 5 days	24	75	4	14	NR	NR	NR	Hypophosphataemia 91	28
200 mg/m^2/day IV for 5 days	34	82	15	NR	NR	NR	NR	Hypophosphataemia 97	27
Overall[b]	58	79	10 (58)[c]	14 (24)[c]	NR	NR	NR		

a Efficacy = percentage of patients achieving normocalcaemia.

b The last line of the table summarises the efficacy data and the reported frequencies for each adverse effect. Studies not reporting efficacy or frequency of the respective adverse effect were excluded from the analysis.

c The number in brackets indicates the number of patients who could be included in the analysis.

Cr elevation = elevation of serum creatinine level (usually defined as an increase of >0.5 mg/dl); **IV** = intravenous; **n** = number of patients enrolled in the study; **NR** = not reported.

patients developed flushing (20%), 4 experienced nasal irritation and/or sneezing (16%), and 2 developed rhinitis (8%).

For the treatment of hypercalcaemia of malignancy calcitonin is administered subcutaneously or intramuscularly 3 to 4 times a day for several days, which is judged uncomfortable by most patients. However, apart from pain at the site of administration, other adverse effects are rare; notably, flushing has not been reported in studies of hypercalcaemia of malignancy. The most frequent adverse effect is nausea/vomiting, which occurs in 16% of patients (see table VIII).

Therapy of hypercalcaemia with calcitonin is hampered by its low activity and an escape phenomenon, which is characterised by loss of activity as treatment continues, resulting from downregulation of calcitonin receptors on osteoclasts.[103] In a randomised comparison with pamidronate and plicamycin, calcitonin had a less pronounced effect on serum calcium level, although onset of action was most rapid in this group.[46] Indeed, the calcium lowering activity of calcitonin can be demonstrated as early as 2 hours from subcutaneous injection. The rapid effect of calcitonin is of value in combined treatment strategies (e.g. pamidronate and calcitonin).[104] Nasal calcitonin spray demonstrated low efficacy in a series of 14 patients with hypercalcaemia of malignancy, with normalisation of serum calcium level achieved in only 1 patient.[105]

4.3 Gallium Nitrate

Gallium nitrate was originally evaluated as an anticancer agent and only as a consequence of these studies has its potential in treatment of hypercalcaemia of malignancy been recognised.[106] Approximately 900 patients have been treated in clinical trials sponsored by the US National Cancer Institute since 1976, and no significant antitumour activity has been observed in any cancer with the possible exception of malignant lymphoma. Nephrotoxicity was dose limiting in these trials. The toxic effect of gallium nitrate on the kidney can be reduced if a urine output of more than 2000 ml/day is maintained throughout treatment. In the dosage applied for hypercalcaemia of malignancy (200 mg/m^2/day, days 1 to 5), an elevation of serum creatinine level is noted in 10% of patients (see table IX). One case of acute renal failure has been described in a patient with multiple myeloma after start of therapy.[28]

The effectiveness of gallium nitrate compares favourably with calcitonin and etidronate, but more data are needed to accurately define the role of this drug in malignancy-associated hypercalcaemia.

5. Conclusions

Today, IV bisphosphonates are the standard therapy for hypercalcaemia of malignancy. Newer bisphosphonates (pamidronate, alendronate and

ibandronate) are associated with a significantly lower occurrence of renal toxicity, nausea and vomiting as compared with etidronate and significantly lower occurrence of nausea and vomiting as compared with clodronate. All these newer bisphosphonates contain a nitrogen atom, which is responsible not only for their stronger osteoclast inhibiting effects but also for a transient, self limiting acute phase reaction characterised by an increase in body temperature, malaise and muscle pain. Plicamycin treatment should be restricted to patients whose condition does not respond to IV bisphosphonates. The toxicity and low efficacy of plicamycin restricts its clinical use. Calcitonin is characterised by good tolerability but poor efficacy in normalising the serum calcium level. However, a major advantage of calcitonin is the acute onset of the hypocalcaemic effect (as early as 2 hours from subcutaneous injection), which contrasts with the delayed but more pronounced effect of bisphosphonates. The combination of calcitonin and bisphosphonate treatment may therefore be of value when a rapid lowering of serum calcium level is warranted.

Gallium nitrate seems a valuable treatment for hypercalcaemia of malignancy, considering the data published to date. It is characterised by high efficacy and few adverse events apart from renal toxicity (10% of cases). However, data are as yet very limited and further trials are necessary to define exactly the role of this drug in the treatment of hypercalcaemia of malignancy.

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References

1. Vassilopoulou-Sellin R, Newman BM, Taylor SH, et al. Incidence of hypercalcemia in patients with malignancy referred to a comprehensive cancer center. Cancer 1993; 71 (4): 1309-12
2. Pecherstorfer M, Schilling T, Blind E, et al. Parathyroid hormone related protein and life expectancy in hypercalcemic cancer patients. J Clin Endocrinol Metab 1994; 78 (5): 1268-70
3. Ralston SH, Gallacher SJ, Patel U, et al. Cancer-associated hypercalcemia: morbidity and mortality. Clinical experience in 126 treated patients. Ann Intern Med 1990; 112: 499-504
4. Pecherstorfer M, Zimmer-Roth I, Schilling T, et al. The diagnostic value of urinary pyridinium cross-links of collagen, serum total alkaline phosphatase, and urinary calcium excretion in neoplastic bone disease. J Clin Endocrinol Metab 1995; 80 (1): 97-103
5. Mundy GR. Calcium homeostasis: hypercalcemia and hypocalcemia. 2nd ed. London, New York: Martin Dunitz, 1990
6. Lacey DL, Timms E, Tan HL, et al. Osteoprotegerin ligand is a cytokine that regulates osteoclast differentiation and activation. Cell 1998; 93 (2): 165-76
7. Yasuda H, Shima N, Nakagawa N, et al. Osteoclast differentiation factor is a ligand for osteoprotegerin/osteoclastogenesis-inhibitory factor and is identical to TRANCE/RANKL. Proc Natl Acad Sci U S A 1998; 95 (7): 3597-602
8. Kong YY, Yoshida H, Sarosi I, et al. OPGL is a key regulator of osteoclastogenesis, lymphocyte development and lymph-node organogenesis. Nature 1999; 397 (6717): 315-23
9. Hsu H, Lacey DL, Dunstan CR, et al. Tumor necrosis factor receptor family member RANK mediates osteoclast differentiation and activation induced by osteoprotegerin ligand. Proc Natl Acad Sci U S A 1999; 96 (7): 3540-5
10. Simonet WS, Lacey DL, Dunstan CR, et al. Osteoprotegerin: a novel secreted protein involved in the regulation of bone density. Cell 1997; 89 (2): 309-19
11. Roodman DG. Advances in bone biology: the osteoclast. Endocrinol Rev 1996; 17 (4): 308-32
12. Parfitt AM, Mundy GR, Roodman GD, et al. A new model for the regulation of bone resorption, with particular reference to the effects of bisphosphonates. J Bone Miner Res 1996; 11 (2): 150-9
13. Kovacs CS, Lanske B, Hunzelman JL, et al. Parathyroid hormone-related peptide (PTHrP) regulates fetal-placental calcium transport through a receptor distinct from the PTH/PTHrP receptor. Proc Natl Acad Sci U S A 1996; 93 (26): 15233-8
14. Uemura H, Yasui T, Yoneda N, et al. Measurement of N- and C-terminal-region fragments of parathyroid hormone-related peptide in milk from lactating women and investigation of the relationship of their concentrations to calcium in milk. J Endocrinol 1997; 153 (3): 445-51
15. Thiebaud D, Janisch S, Koelbl, et al. Direct evidence of a parathyroid related protein gradient between the mother and the newborn in humans. Bone Miner 1993; 23 (3): 213-21
16. Wysolmerski JJ, Stewart AF. The physiology of parathyroid hormone-related protein: an emerging role as a developmental factor. Annu Rev Physiol 1998; 60: 431-60
17. Mundy GR, Guise TA. Hypercalcemia of malignancy. Am J Med 1997; 103: 134-45
18. Kremer R, Shustik C, Tabak T, et al. Parathyroid hormone-related peptide in hematologic malignancies. Am J Med 1996; 100 (4): 406-11
19. Schilling T, Pecherstorfer M, Blind E, et al. Parathyroid hormone-related protein (PTHrP) does not regulate 1,25 Dihydroxyvitamin D levels in hypercalcemia of malignancy. J Clin Endocrinol Metab 1993; 76: 801-3
20. Sleeboom HP, Bijvoet OLM, Van Oosterom AT, et al. Comparison of intravenous (3-amino-1-hydroxypropylidene)-1-1-bisphosphonate and volume repletion in tumour-induced hypercalcemia. Lancet 1983; II: 239-43

21. Fleisch H. Bisphosphonates. Pharmacology and use in the treatment of tumour-induced hypercalcemia and metastatic bone loss. Drugs 1991; 42 (6): 919-44
22. Walls J, Ratcliffe WA, Howell A, et al. Response to intravenous bisphosphonate therapy in hypercalcaemic patients with and without bone metastases: the role of parathyroid hormone-related protein. Br J Cancer 1994; 70: 169-72
23. Gurney H, Grill V, Martin TJ. Parathyroid hormone-related protein and response to pamidronate in tumour-induced hypercalcemia. Lancet 1993; 341: 1611-3
24. Body JJ, Dumon JC, Thirion M, et al. Circulating PTHrP concentrations in tumor-induced hypercalcemia: influence on the response to bisphosphonate and changes after therapy. J Bone Miner Res 1993; 8: 701-6
25. Pecherstorfer M, Thiebaud D. Treatment of tumor-induced hypercalcemia with escalating doses of pamidronate (APD). Ann Oncol 1992; 3 (8): 661-3
26. Thiebaud D, Jaeger P, Jacquet AF, et al. Dose-response in the treatment of hypercalcemia of malignancy by a single infusion of the bisphosphonate AHPrBP. J Clin Oncol 1988; 6 (5): 762-8
27. Warrell RP, Murphy WK, Schulman P, et al. A randomized double-blind study of gallium nitrate compared with etidronate for acute control of cancer-related hypercalcemia. J Clin Oncol 1991; 9 (8): 1467-75
28. Warrell RP, Israel R, Frisone M, et al. Gallium nitrate for acute treatment of cancer-related hypercalcemia: a randomized, double-blind comparison to calcitonin. Ann Intern Med 1988; 108: 669-74
29. Bockman RS, Repo MA, Warrell RP, et al. Distribution of trace levels of therapeutic gallium in bone as mapped by synchroton x-ray microscopy. Proc Natl Acad Sci U S A 1990; 87 (11): 4149-53
30. Bockman RS, Boskey AL, Blumenthal NC, et al. Gallium increases bone calcium and crystallite perfection of hydroxyapatite. Calcif Tissue Int 1986; 39 (6): 376-81
31. Bockman RS, Guidon Jr PT, Pan LC, et al. Gallium nitrate increases type I collagen and fibronectin mRNA and collagen protein levels in bone and fibroblast cells. J Cell Biochem 1993; 52 (4): 396-403
32. Kiang DT, Loken MK, Kennedy BJ. Mechanism of the hypocalcemic effect of mithramycin. J Clin Endocrinol Metab 1979; 48 (2): 341-4
33. Geley S, Fiegl M, Hartmann BL, et al. Genes mediating glucocorticoid effects and mechanisms of their regulation. Rev Physiol Biochem Pharmacol 1996; 128: 1-97
34. Flores JF, Singer FR, Rude RK. Effectiveness of a 24-hour infusion of etidronate disodium in the treatment of hypercalcemia of malignant disease. Miner Electrolyte Metab 1991; 17: 390-5
35. Hasling C, Charles P, Mosekilde L. Etidronate disodium in the management of malignancy related hypercalcemia. Am J Med 1987; 82 Suppl. 2A: 51-4
36. Singer FR, Ritch PS, Lad TE, et al. Treatment of hypercalcemia of malignancy with intravenous etidronate: a controlled multicenter study. Arch Intern Med 1991; 151: 471-6
37. Gucalp R, Ritch P, Wiernik PH, et a. Comparative study of pamidronate disodium and etidronate disodium in the treatment of cancer-related hypercalcemia. J Clin Oncol 1992; 10 (1): 134-42
38. Cohen AI, Koeller J, Davis TE, et al. IV dichloromethylene diphosphonate in cancer associated hypercalcemia: a phase I-II evaluation. Cancer Treat Rep 1981; 65 (7-8): 651-3
39. Jacobs TP, Siris ES, Bilezikian JP, et al. Hypercalcemia of malignancy: treatment with intravenous dichloromethylene diphosphonate. Ann Intern Med 1981; 94: 312-6
40. Urwin GH, Yates AJP, Gray RES, et al. Treatment of hypercalcemia of malignancy with intravenous clodronate. Bone 1987; 8 Suppl. 1: S43-S51
41. Ziegler R, Scharla SH. Treatment of tumor hypercalcemia with clodronate. Recent Results Cancer Res 1989; 116: 47-53
42. Harjung H, Fritze D. Results of treating tumour-induced hypercalcemia with clodronate alone. Dtsch Med Wochenschr 1990; 115: 48-52
43. Rotstein S, Glas U, Eriksson M, et al. Intravenous clodronate for the treatment of hypercalcemia in breast cancer patients with bone metastases – a prospective randomised placebo-controlled study. Eur J Cancer 1992; 28A (4/5): 890-3
44. O'Rourke NP, McCloskey EV, Vasikaran S, et al. Effective treatment of malignant hypercalcemia with a single intravenous infusion of clodronate. Br J Cancer 1993; 67 (3): 560-3
45. Purohit OP, Radstone CR, Anthony C, et al. A randomised double-blind comparison of intravenous pamidronate and clodronate in the hypercalcemia of malignancy. Br J Cancer 1995; 72: 1289-93
46. Ralston SH, Dryburgh FJ, Cowan RA, et al. Comparison of aminohydroxypropylidene diphosphonate, mithramycin, and corticosteroids/calcitonin in the treatment of cancer-associated hypercalcemia. Lancet 1985; II: 907-10
47. Thiebaud D, Jaeger P, Jacquet AF, et al. A single day treatment of tumor-induced hypercalcemia by intravenous aminohydroxypropylidene bisphosphonate. J Bone Miner Res 1986; 1 (6): 555-62
48. Body JJ, Pot M, Borkowski A, et al. Dose/response study of aminohydroxypropylidene bisphosphonate in tumor-associated hypercalcemia. Am J Med 1987; 82: 957-63
49. Cantwell BM, Harris AL. Effect of single high dose infusions of aminohydroxypropylidene diphosphonate on hypercalcemia caused by cancer. BMJ 1987; 294: 467-9
50. Coleman RE, Rubens RD. 3(amino-1,1-hydroxypropylidene) bisphosphonate (APD) for hypercalcemia of breast cancer. Br J Cancer 1987; 56: 465-9
51. Yates AJP, Murray RML, Jerums GJ, et al. A comparison of single and multiple intravenous infusions of 3-amino-1-hydroxypropylidene-1, 1-bisphosphonate (APD) in the treatment of hypercalcemia of malignancy. Aust N Z J Med 1987; 17: 387-91
52. Morton AR, Cantrill JA, Craig AE, et al. Single dose versus daily intravenous aminohydroxypropylidene bisphosphonate (APD) for the hypercalcemia of malignancy. BMJ 1988; 296: 811-4
53. Body JJ, Magritte A, Seraj F, et al. Aminohydroxypropylidene bisphosphonate (APD) treatment for tumor-associated hypercalcemia: a randomized comparison between a 3-day treatment and single 24-hour infusions. J Bone Miner Res 1989; 4 (6): 923-8
54. Davis JRE, Heath DA. Comparison of different dose regimens of aminohydroxypropylidene-1, 1-bisphosphonate (APD) in hypercalcemia of malignancy. Br J Clin Pharmacol 1989; 28: 269-74

55. Gallacher SJ, Ralston SH, Patel U, et al. Side-effects of pamidronate. Lancet 1989; II: 42-3
56. Mannix KA, Carmichael J, Harris AL, et al. Single high-dose (45mg) infusions of aminohydroxypropylidene diphosphonate for severe malignant hypercalcemia. Cancer 1989; 64: 1358-61
57. Sawyer N, Newstead C, Drummond A, et al. One-shot high-dose pamidronate disodium (APD): effective, simple treatment for hypercalcemia in haematological malignancy. Clin Lab Haematol 1989; 11: 179-84
58. Sawyer N, Newstead C, Drummond A, et al. Fast (4-h) or slow (24-h) infusions of pamidronate disodium (aminohydroxypropylidene diphosphonate (APD)) as single shot treatment for hypercalcemia. Bone Miner 1990; 9: 122-8
59. Pecherstorfer M, Janisch S, Marosi C, et al. Treatment of cancer-associated hypercalcemia with pamidronate. Klin Wochenschr 1991; 69: 690-5
60. Gallacher SJ, Ralston SH, Fraser WD, et al. A comparison of low versus high dose pamidronate in cancer-associated hypercalcemia. Bone Miner 1991; 15 (3): 249-56
61. Dodwell DJ, Howell A, Morton AR, et al. Infusion rate and pharmacokinetics of intravenous pamidronate in the treatment of tumour-induced hypercalcemia. Postgrad Med J 1992; 68: 434-9
62. Ostenstad B, Andersen OK. Disodium pamidronate versus mithramycin in the management of tumour-associated hypercalcemia. Acta Oncol 1992; 31 (8): 861-4
63. Thürlimann B, Waldburger R, Senn HJ, et al. Plicamycin and pamidronate in symptomatic tumor-related hypercalcemia: a prospective randomized crossover trial. Ann Oncol 1992; 3: 619-23
64. Nussbaum SR, Younger J, Vandepol CJ, et al. Single-dose intravenous therapy with pamidronate for the treatment of hypercalcemia of malignancy: Comparison of 30-, 60-, and 90-mg dosages. Am J Med 1993; 95: 297-304
65. Gucalp R, Theriault R, Gill I, et al. Treatment of cancer-associated hypercalcemia: double blind comparison of rapid and slow intravenous infusion regimens of pamidronate disodium and saline alone. Arch Intern Med 1994; 154: 1935-44
66. Zysset E, Ammann P, Jenzer A, et al. Comparison of a rapid (2-h) versus a slow (24-h) infusion of alendronate in the treatment of hypercalcemia of malignancy. Bone Miner 1992; 18: 237-49
67. Nussbaum SR, Warrell RP, Rude R, et al. Dose-response study of alendronate sodium for the treatment of cancer-associated hypercalcemia. J Clin Oncol 1993; 11 (8): 1618-23
68. Wüster C, Schöter KH, Thiebaud D, et al. Methylpentylaminopropylidenebisphosphonate (BM 21.0955): a new potent and safe bisphosphonate for the treatment of cancer-associated hypercalcemia. Bone Miner 1993; 22: 77-85
69. Pecherstorfer M, Herrmann Z, Body JJ, et al. Randomized phase II trial comparing different doses of the bisphosphonate ibandronate in the treatment of hypercalcemia of malignancy. J Clin Oncol 1996; 14 (1): 268-76
70. Ralston SH, Thiebaud D, Herrmann Z, et al. Dose-response study of ibandronate in the treatment of cancer-associated hypercalcemia. Br J Cancer 1997; 75 (2): 295-300
71. Dumon JC, Magritte A, Body JJ. Efficacy and safety of the bisphosphonate tiludronate for the treatment of tumor-associated hypercalcemia. Bone Miner 1991; 15: 257-66
72. O'Rourke NP, McCloskey EV, Rosini S, et al. Treatment of malignant hypercalcemia with aminohexane bisphosphonate (neridronate). Br J Cancer 1994; 69: 914-7
73. Van Breukelen FJM, Bijovoet OLM, Frijlink WB, et al. Efficacy of amino-hydroxypropylidene bisphosphonate in hypercalcemia: observations on regulation of serum calcium. Calcif Tissue Int 1982; 34: 321-7
74. Thiebaud D, Portmann L, Jaeger P, et al. Oral versus intravenous AHPrBP (APD) in the treatment of hypercalcemia of malignancy. Bone 1986; 247-53
75. Rastad J, Benson L, Johansson H, et al. Clodronate treatment in patients with malignancy-associated hypercalcemia. Acta Med Scand 1987; 221: 489-94
76. Percival RC, Paterson AD, Yates AJP, et al. Treatment of malignant hypercalcemia with clodronate. Br J Cancer 1985; 51: 665-9
77. Schiller JH, Rasmussen P, Benson AB, et al. Maintenance etidronate in the prevention of malignancy-associated hypercalcemia. Arch Intern Med 1987; 147: 963-6
78. Bounameaux HM, Schifferli J, Montani JP, et al. Renal failure associated with intravenous bisphosphonates [letter]. Lancet 1983; I: 471
79. Machado CE, Flombaum CD. Safety of pamidronate in patients with renal failure and hypercalcemia. Clin Nephrol 1996; 45 (3): 175-9
80. Pecherstorfer M, Ludwig H, Schlosser K, et al. Administration of the bisphosphonate ibandronate (BM 21.0955) by intravenous bolus injection. J Bone Miner Res 1996; 11 (5): 587-93
81. Pecherstorfer M, Jilch R, Horn E, et al. Effect of first treatment with the aminobisphosphonates pamidronate and ibandronate on circulating lymphocyte subpopulations. J Bone Mineral Res. In press
82. Kunzmann V, Bauer E, Wilhelm M. γ/δ T-cell stimulation by pamidronate. N Engl J Med 1999; 340: 737-8
83. Sauty A, Pecherstorfer M, Zimmer-Roth I, et al. Interleukin-6 and tumor necrosis factor α levels after bisphosphonates treatment in vitro and in patients with malignancy. Bone 1996; 18 (2): 133-9
84. Schweitzer DH, Oostendorp-Van de Ruit M, Van der Pluijm G, et al. Interleukin-6 and the acute phase response during treatment of patients with Paget's disease with the nitrogen-containing bisphosphonate dimethylaminohydroxypropylidene bisphosphonate. J Bone Miner Res 1995; 10 (6): 956-62
85. Stewart GO, Stuckey BG, Ward LC, et al. Iritis following intravenous pamidronate. Aust N Z J Med 1996; 26 (3): 414-5
86. Macarol V, Fraunfelder F. Pamidronate disodium and possible ocular adverse drug reactions. Am J Ophtalmol 1994; 118: 220-4
87. Adami S, Zamberlan N. Adverse effects of bisphosphonates. Drug Saf 1996; 14 (3): 158-70
88. Pedersen-Bjergaard U, Myhre J. Severe hypocalcemia after treatment with diphosphonate and aminoglycoside [letter]. BMJ 1991; 302: 295
89. Rolla G, Bucca C, Brussino L. Bisphosphonate-induced bronchoconstriction in aspirin-sensitive asthma [letter]. Lancet 1994; 343: 426-7
90. Roux C, Listrat V, Villette B, et al. Long-lasting dermatological lesions after tiludronate therapy. Calcif Tissue Int 1992; 50: 378-80

91. Slayton RE, Shnider BI, Elias E, et al. New approach to the treatment of hypercalcemia: the effect of short-term treatment with mithramycin. Clin Pharmacol Ther 1971; 12 (5): 833-7
92. Elias EG, Evans JT. Hypercalcemic crisis in neoplastic disease: management with mithramycin. Surgery 1972; 71 (4): 631-5
93. Gasser AB, Flury R, Senn HJ. Therapie des Hyperkalziämiesyndroms mit Mithramyzin. Schweiz Med Wochenschr 1974; 104: 1792-4
94. Fillastre JP, Maitrot J, Canonne MA, et al. Renal function and alterations in plasma electrolyte levels in normocalcemic and hypercalcemic patients with malignant diseases, given an intravenous infusion of mithramycin. Chemotherapy 1974; 20: 280-95
95. Green L, Donehower RC. Hepatic toxicity of low doses of mithramycin in hypercalcemia. Cancer Treat Rep 1984; 68 (11): 1379-81
96. Silva OL, Becker KL. Salmon calcitonin in the treatment of hypercalcemia. Arch Intern Med 1973; 132: 337-9
97. Wisneski LA, Croom WP, Silva OL, et al. Salmon calcitonin in hypercalcemia. Clin Pharmacol Ther 1978; 24 (2): 219-22
98. Ahr DJ, Scialla SJ, Kimball DB. Acquired platelet dysfunction following mithramycin therapy. Cancer 1978; 41: 448-54
99. Fraisse F, Marche C, Gibert C, et al. Acute hepatic necrosis and hemorrhagic syndrome leading to a fatal outcome during treatment of hypercalcaemia with mithramycin. Ann Med Interne 1980; 131 (5): 281-4
100. Benedetti RG, Heilman KJ, Gabow PA. Nephrotoxicity following single dose mithramycin therapy. Am J Nephrol 1983; 3 (5): 277-8
101. Purpora D, Ahern MJ, Silverman N. Toxic epidermal necrolysis after mithramycin [letter]. N Engl J Med 1978; 299 (25): 1412
102. Wimalawansa SJ. Long- and short-term side effects and safety of calcitonin in man: a prospective study. Calcif Tissue Int 1993; 52: 90-3
103. Takahashi S, Goldring S, Katz M, et al. Downregulation of calcitonin receptor mRNA expression by calcitonin during human osteoclast-like differentiation. J Clin Invest 1995; 95 (1): 167-71
104. Ralston SH, Alzaid AA, Gardner MD, et al. Treatment of cancer-associated hypercalcemia with combined aminohydroxypropylidene diphosphonate and calcitonin. BMJ 1986; 292: 1549-50
105. Bower M, Stein RC, Hedley A, et al. The use of nasal calcitonin spray in the treatment of hypercalcemia of malignancy. Cancer Chemother Pharmacol 1991; 28: 311-2
106. Leyland-Jones B. Pharmacokinetics and therapeutic index of gallium nitrate. Semin Oncol 1991; 18 (4 Suppl. 5): 16-20

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