VRAAG 2: WAT IS HET EFFECT VAN HYPERHYDRATIE EN MEDICAMENTEUZE BEHANDELING OP SERUM CALCIUM BIJ PATIËNTEN MET KANKER EN HYPERCALCIËMIE IN DE PALLIATIEVE FASE?

Systematische reviews

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
Ross 2004 Saunders 2004	• Design: systematic review + meta-analysis • Funding: funded by a Health and Technology Assessment, NHS Research and Development Grant; CoI: not reported • Search date: June 2001 • Databases: MEDLINE, CANCERLIT, EMBASE, Science Citation Index Expanded, pre-MEDLINE, CENTRAL and DARE, Health Economic Evaluations Database, National Health Service Economic Evaluations Database • Study designs: RCTs • N included studies: N=26 RCTs	• Eligibility criteria: patients with confirmed malignancy and hypercalcaemia postrehydration	Oral or intravenous bisphosphonate in the experimental arm, compared to another bisphosphonate, another recognized treatment for hypercalcaemia, placebo or control group	• See below for individual relevant studies	• Review process performed by independent researchers • No language restriction
Seisa 2022	• Design: systematic review + meta-analysis • Funding: funded by the Endocrine Society; CoI: none • Search date: April 2022 • Databases: Ovid MEDLINE, Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, Daily; Ovid EMBASE; Ovid Cochrane Central Register of Controlled Trials; Ovid Cochrane Database of Systematic Reviews; and Scopus	• Eligibility criteria: patients with hypercalcemia of malignancy	Treatment in general	• See below for individual relevant studies	• Review process performed by independent researchers • No language restriction

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
	• Study designs: all • N included studies: N=21				

Primaire studies

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
Atula 2003	• Design: pooled analysis of 3 RCTs • Funding: not reported; CoI: not reported • Setting: multicenter studies, Europe and US • Sample size: N=67 • Duration: follow-up 5 days	• Eligibility criteria: patients with a clinical diagnosis of malignant hypercalcemia, aged at least 18 years, life-expectancy >4 weeks at the time of enrollment • Exclusion criteria: patients with hypercalcemia from any cause other than malignancy, or who had received systemic cancer treatment within 4 weeks prior to entry into the study, or who had received treatment for hypercalcemia within 1 week prior to entry into the study or who had received bisphosphonates within 4 weeks prior to entry into the study • *A priori* patient characteristics: ○ M/F: 24/43 ○ Mean age: 53.3 vs. 52.4 vs. 57.5y ○ Cancer type (N=51): breast N=17, lung N=11, lymphoma N=6	All patients in the studies were initially rehydrated with IV saline infusion for at least 24 hours, to obtain a urine output of at least 50 ml/h Pamidronate 90 mg IV (N=24) vs. Clodronate 1500 mg IV (N=32) vs. Clodronate 900 mg IV (N=11)	CRITICAL OUTCOMES • Serum calcium: ○ Proportion of patients achieving normocalcemia by day 5: 85% vs. 76.2% vs. 60%; p>0.15 ○ Mean corrected serum calcium at day 5: 2.44 vs. 2.52 vs. 2.57 mmol/l ○ % change in corrected serum calcium by day 5: -26% vs. -25% vs. -20%, p>0.15 • Duration of effect: not reported • Adverse events: ○ Mild or moderate hypocalcemia: N=1 vs. 2 vs. 0 ○ No other serious adverse events related to the study drugs IMPORTANT OUTCOMES • Quality of life: not reported • Symptoms of hypercalcemia: not reported	Level of evidence: high risk of bias • Unclear randomisation method and allocation concealment • Double-blind studies, but unclear if outcome assessors were blinded • Efficacy data: N=51 • All 3 RCTs were prematurely terminated because of slow recruitment rate
Chapuy 1980	• Design: cross-over RCT • Funding: grants from the Faculté Alexis Carrel, Lyon, and the Procter and Gamble Co. Ltd., Cincinnati, Ohio; CoI: not reported • Setting: single center, France • Sample size: N=5 • Duration: follow-up 8 weeks	• Eligibility criteria: patients with clinical, radiological, and bone scan evidence of skeletal metastases, hypercalcemia >2.75 mmol/liter and <3.75 mmol/l, prognosis for survival of >2 months • Exclusion criteria: treatment with mithramycin, calcitonin, phosphorus, indomethacin, or corticosteroids at a dose>15 mg/d were excluded during the week preceding the initiation of Clodronate • *A priori* patient characteristics:	Clodronate 3200 mg po for 4 weeks (N=5) vs. Placebo (N=5)	CRITICAL OUTCOMES • Serum calcium: ○ 4 patients began to show a rapid significant decrease in serum calcium, the lowest value being reached within 7-10d; 2 patients had a rapid relapse after withdrawal of Clodronate ○ 1 patient had to discontinue placebo because of worsening serum calcium ○ 1 patient had a sudden paraplegia 2d after the start of Clodronate, followed by a marked increase of serum calcium; Clodronate was not interrupted, and the	Level of evidence: high risk of bias • Unclear randomisation method and allocation concealment • Double-blind study, but unclear if outcome assessors were blinded • Results are reported by patient, not by treatment group

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		○ M/F: 2/3 ○ Age: range 42-74y ○ Cancer type: breast N=4, kidney N=1		decrease in serum calcium was rapid and acute (normal levels at week 4) • Duration of effect: not reported • Adverse events: no adverse clinical side effects, such as gastrointestinal intolerance or fever, were observed IMPORTANT OUTCOMES • Quality of life: not reported • Symptoms of hypercalcemia: not reported	
Cvitkovic 2006	• Design: RCT • Funding: supported in part by a grant from Fujisawa harmaceuticals, Inc; CoI: dr. Warrell is CEO of Genta Incorporated • Setting: multicenter study, France and US • Sample size: N=64 • Duration: follow-up max 30 days	• Eligibility criteria: histologic diagnosis of cancer; parenteral hydration of at least 2000 ml for at least 24 hours preceding study entry; total corrected serum calcium adjusted for serum albumin at least 12.0 mg/dl after hydration; serum creatinine max 2.5 mg/dl • Exclusion criteria: cytotoxic chemotherapy, mithramycin or radiation therapy within the preceding 7 days; aminoglycoside therapy; other hypocalcemic drugs; hypercalcemia due to parathyroid carcinoma; malignant lymphoma • *A priori* patient characteristics: ○ Median age: 54 vs. 55y ○ M/F: 16/16 vs. 17/15 ○ Cancer type: breast N=17, head/neck N=12, lung N=7, kidney N=5	All patients received hydration with or without diuretics for at least 24 hours preceding study entry Gallium nitrate 200 mg/m² IV daily for 5 days (N=32) vs. Pamidronate 60 mg IV; patients with serum calcium of at least 13.5 mg/dl received 90 mg IV (N=32); followed by placebo for 4 days	CRITICAL OUTCOMES • Serum calcium: ○ Mean corrected serum calcium only reported in figure ○ Normocalcemic response: 69% vs. 56% • Duration of effect: median duration 7 days vs. 1 day, no p-value reported • Adverse events: ○ No patient in either treatment group developed acute renal failure during the trial ○ Hypophosphatemia: 88% vs. 82% IMPORTANT OUTCOMES • Quality of life: not reported • Symptoms of hypercalcemia: not reported	Level of evidence: low risk of bias • Randomization codes were established separately for each site using the method of random permuted blocks • During the study, only the pharmacist who prepared the drugs and the central statistician were not blinded with respect to treatment allocation • ITT analysis • Industry-sponsored
Gucalp 1992	• Design: RCT • Funding: Supported in part by Ciba-Geigy Pharmaceuticals Division, Summit, NJ; CoI: not reported • Setting: multicenter study, US • Sample size: N=65 • Duration: follow-up max 30 days	• Eligibility criteria: histologic diagnosis of malignancy and a corrected serum calcium level of at least 12.0 mg/dl after adequate hydration; no other treatment for hypercalcemia or cancer was permitted in the 7 days (72 hours for calcitonin) before initiation of pamidronate or etidronate treatment or during the study • Exclusion criteria: creatinine level of 5.0 mg/dl or higher, congestive heart failure, other	Patients were to receive a minimum of 3l of 0.9% sodium chloride and were to have a urine output of at least 2l in the 24 hours preceding baseline calcium determination and initiation of study drug treatment	CRITICAL OUTCOMES • Serum corrected calcium: ○ Decrease: Pamidronate from 14.6 +/- 2.2 mg/dl to 10.5 +/- 1.8 mg/dl by end point, Etidronate from 13.8 +/- 1.3 mg/dl to 11.6 +/- 2.0 mg/dl; mean corrected serum calcium decreases from baseline were statistically greater in the Pamidronate than in the Etidronate group at days 4 to 7 after treatment ○ Normocalcemia by day 7: 70% vs. 41%, p=0.026	Level of evidence: unclear risk of bias • Unclear randomisation method and allocation concealment • Double-blind study, but unclear if outcome assessors were blinded

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		causes of hypercalcemia, or history of previous treatment with bisphosphonate • *A priori* patient characteristics: ○ Mean age: 56.9 vs. 53.3y ○ M/F: 15/15 vs. 22/13 ○ Cancer type: breast N=16, head/neck N=13, kidney N=10, lung N=9 ○ Bone metastases: 53% vs. 29%	Pamidronate 60 mg IV as a single 24h infusion (N=30) vs. Etidronate 7.5 mg/kg as a 2h infusion daily for 3 days (N=35) Each patient received sham infusion(s) to maintain the study's double-blind status	• Duration of effect: duration of complete response was longer for the Pamidronate than for the Etidronate group; no p-value reported • Adverse events: ○ Fever: 17/30 vs. 9/35 ○ Nausea: 0/30 vs. 6/35 ○ Infusion-site reaction: 7/30 vs. 0/35 ○ Abnormal liver function tests: 0/30 vs. 3/35 ○ Ulcerative stomatitis: 0/30 vs. 3/35 ○ Convulsions: 0/30 vs. 3/35 ○ Altered taste: 0/30 vs. 3/35 ○ Constipation: 0/30 vs. 3/35 ○ Renal failure: 13/30 vs. 6/35 ○ Hypophosphatemia: 7/30 vs. 3/35 ○ Hypomagnesemia: 7/30 vs. 3/35 IMPORTANT OUTCOMES • Quality of life: not reported • Symptoms of hypercalcemia: ○ Nausea: decreased from between 27% and 29**%** to 0% in the Pamidronate group and to 18% in the Etidronate group; vomiting decreased from between 20% and 23% in both treatment groups to very few reports of vomiting at any time during the trial ○ Mental status: mental status showed little change during the trial; very few patients had significantly impaired mental status at baseline or during the trial ○ Obstipation: not reported	
Hasling 1987	• Design: RCT • Funding: supported by grants from Norwich Eaton Pharmaceuticals, Inc., and the Procter and Gamble Co., US; CoI: not reported • Setting: single center, Denmark • Sample size: N=20 • Duration: follow-up 7 days	• Eligibility criteria: patients with malignancy and serum calcium > 2.85 mmol/l • Exclusion criteria: not reported • *A priori* patient characteristics: ○ Mean age 54.6y ○ M/F: 4/16 ○ Cancer type: breast N=15 ○ Bone metastases: 100% vs. 83%	All patients were rehydrated with 3000 ml of IV administered saline per day and received 40 mg of furosemide each day Etidronate 7.5 mg/kg IV for 3-5 days (N=12) vs. Placebo (N=6)	CRITICAL OUTCOMES • Serum calcium: ○ Both groups showed a significant decrease in the serum calcium level ($p<0.01$) during the treatment period; the observed decrease in serum calcium was significantly greater in the group treated with etidronate than in the placebo group after 3 days of treatment ($p<0.02$) and remained so throughout the study; levels only reported in figure ○ Normocalcemic response: 92% vs. 33%, $p=0.05$ • Duration of effect: not reported • Adverse events: ○ Hypocalcemia: Etidronate N=6	Level of evidence: unclear risk of bias • Unclear randomisation method and allocation concealment • Double-blind study, but unclear if outcome assessors were blinded • Two patients in the Etidronate group died before treatment completion, and were excluded

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				○ No significant changes in serum phosphate levels IMPORTANT OUTCOMES • Quality of life: not reported • Symptoms of hypercalcemia: not reported	
Kristensen 1992	• Design: RCT • Funding: not reported; CoI: not reported • Setting: single center, Denmark • Sample size: N=30 • Duration: follow-up of 8 days	• Eligibility criteria: women with histologically confirmed adenocarcinoma of the breast and hypercalcemia of malignancy • Exclusion criteria: other known disorders of calcium homeostasis, contraindications against glucocorticoids, use of glucocorticoid and change of systemic antineoplastic treatment less than 4 weeks previously, antihypercalcemic treatment less than 2 weeks previously, suspected metastases in the adrenal glands, other malignant disease, or previous inclusion in the study • *A priori* patient characteristics: ○ Age range: 44-73y vs. 42-72y ○ Bone metastases: 100% vs. 87%	Rehydration was standardized and consisted of 4l of isotonic saline supplemented with intravenous furosemide 80 mg, three times daily on days 1 and 2, subsequently reduced to 3 1 of isotonic saline and 80 mg furosemide, twice daily from day 3 to day 8 Prednisolone 25 mg po 3 times daily for 2 days (N=15) vs. No prednisolone (N=15)	CRITICAL OUTCOMES • Serum calcium: ○ Median at day 4: 1.48 vs. 1.79 mmol/l ○ Median at day 8: 1.35 vs. 1.60 mmol/l ○ Rate of decrease was higher in the prednisolone group (p=0.021) ○ Normocalcemic response: 7/15 vs. 0/15, p=0.028 • Duration of effect: not reported • Adverse events: ○ None of the patients treated with prednisolone experienced any of the well-known side-effects caused by glucocorticoids ○ In the control group a significant decrease in serum potassium was found on day 4 (p=0.0034) ○ In three patients in each group rehydration caused oedemata IMPORTANT OUTCOMES • Quality of life: not reported • Symptoms of hypercalcemia: not reported	Level of evidence: high risk of bias • Randomisation by table of random numbers • Unclear allocation concealment • Unclear blinding • No ITT-analysis for all outcomes
Major 2001	• Design: pooled analysis of 2 RCTs • Funding: Supported by Novartis Pharma; CoI: not reported • Setting: multicenter, US, Canada, Europe, Australia • Sample size: N=287 • Duration: follow-up for 56 days or until relapse	• Eligibility criteria: patients aged at least 18y with histologic or cytologic confirmation of cancer and severe hypercalcemia of malignancy, defined as baseline corrected serum calcium at least 12.0 mg/dl • Exclusion criteria: patients who had a history of allergic reaction or sensitivity to bisphosphonates or who were treated with bisphosphonates for hypercalcemia within 90 days or for other complications within 30 days of study entry; patients who exhibited serum	Patients received 250 ml of IV fluids before infusion of study drug Zoledronate single IV infusion of 4 mg (N=86) or 8 mg (N=98) vs. Pamidronate 90 mg IV (N=103)	CRITICAL OUTCOMES • Serum calcium: ○ Normocalcemic response at day 10: 88.4% vs. 86.7% vs. 69.7%; Zole 4 mg vs. Pami p=0.002, Zole 8 mg vs. Pami p=0.015 ○ Mean corrected serum calcium levels at days 4, 7, and 10 were significantly lower (p<0.05) in patients treated with 4 or 8 mg of Zoledronate than in patients treated with Pamidronate; only reported in figure • Duration of effect: median time to relapse, Zoledronate 4 or 8 mg 30 (p=0.001) and 40 days (p=0.007), respectively, compared with 17 days in the Pamidronate group • Adverse events: drug-related ○ Fever: 44.2% vs. 34.7% vs. 33.0%	Level of evidence: unclear risk of bias • Unclear randomisation method and allocation concealment • Double-blind study, but unclear if outcome assessors were blinded • 275/287 included in efficacy analysis • Industry-sponsored

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		creatinine more than 4.5 mg/dl or who were treated with calcitonin within 72 hours, with mithramycin or with a newly initiated antineoplastic cytotoxic chemotherapy or hormone therapy within 7 days, with gallium nitrate within 14 days, or with any investigational drug within 30 days of study entry; patients who were severely dehydrated, could not tolerate IV hydration, or suffered from hyperparathyroidism, adrenal insufficiency, vitamin D intoxication, milk alkali syndrome, sarcoidosis or other granulomatous disease, or multiple endocrine neoplasia syndromes • *A priori* patient characteristics: ○ Mean age: 60.0 vs. 58.7 vs. 59.0y ○ M/F: 46/40 vs. 60/30 vs. 56/43 ○ Cancer type: lung N=63, breast N=51, head/neck N=30, kidney N=30 ○ Bone metastases: 57% vs. 56% vs. 46%		○ Anemia: 22.1% vs. 27.6% vs. 17.5% ○ Nausea: 29.1% vs. 21.4% vs. 27.2% ○ Constipation: 26.7% vs. 19.4% vs. 12.6% ○ Dyspnea: 22.1% vs. 18.4% vs. 19.4% ○ Confusion: 12.8% vs. 15.3% vs. 12.6% ○ Insomnia: 15.1% vs. 15.3% vs. 9.7% ○ Vomiting: 14.0% vs. 15.3% vs. 16.5% ○ Hypokalemia: 11.6% vs. 12.2% vs. 15.5% ○ Diarrhea: 17.4% vs. 10.2% vs. 16.5% ○ Abdominal pain: 16.3% vs. 7.1% vs. 12.6% ○ Grade 3/4 serum creatinine increases: 2.3% vs. 5.2% vs. 4.0% IMPORTANT OUTCOMES • Quality of life: not reported • Symptoms of hypercalcemia: not reported	
Matsumoto 2002	• Design: RCT • Funding: not reported; CoI: not reported • Setting: multicenter study, Japan • Sample size: N=26 • Duration: follow-up 6 days	• Eligibility criteria: inpatients with hypercalcemia of malignancy, aged 16-79 years, who showed corrected serum calcium levels of 11.0 mg/dl or more after achieving correction of dehydration by at least a 2-day IV infusion of physiological saline • Exclusion criteria: patients with renal dysfunction and serum creatinine levels ≥ 5.0 mg/dl; patients with serious hepatic or cardiac disorders; pregnant women; nursing mothers; patients with a history of hypersensitivity to bisphosphonates; patients with	At least a 2-day IV infusion of physiological saline Incadronate 10 mg IV as a single infusion (N=11) vs. Elcatonin 40 IU IM twice daily for 7 days (N=10)	CRITICAL OUTCOMES • Serum calcium: ○ AUC to delineate the time-course of the decreases in corrected serum calcium level (mean +/- SD): -10.26 +/- 3.61 mg/dl per day vs. -5.05 +/- 5.31 mg/dl, p=0.04 ○ Normocalcemic response: 9/11 vs. 2/10, p=0.009 • Duration of effect: Incadronate: progressive decreases from day 2 to day 6; Elcatonin: rapid decrease on day 1, effect lasted only until day 2 • Adverse events: ○ Serum phosphate: significant differences between the treatment groups were observed in the time-courses of serum phosphate concentrations, with a transient	Level of evidence: high risk of bias • Central randomisation using the minimization method, adjusted by corrected serum calcium level at the time of enrolment (< 14.0 mg/dl versus ≥ 14.0 mg/dl), underlying tumour (parathyroid carcinoma versus other carcinomas) and study centre • Open-label study • No ITT analysis: efficacy data 21/26, safety data 24/26

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		a positive intracutaneous reaction to elcatonin; patients with a predisposition to hypersensitivity (such as a history of erythema, eczema or asthma); and patients who had received calcitonin within 1 week of the start of the study • *A priori* patient characteristics: ○ Mean age: 57.0 vs. 54.3y ○ M/F: 6/5 vs. 5/5 ○ Cancer type: lung N=4, breast N=2, oesophagus N=2, gallbladder N=2, blood system N=2, parathyroid N=2 ○ Bone metastases: 4/11 vs. 3/10		decrease observed in the Incadronate group on day 4 ○ Adverse events that may have been caused by treatment were observed in 3 patients in the incadronate group (25.0%, 3 events): mild fever in 2 patients, which developed on the day of infusion and disappeared by day 4, and exacerbation of disturbance of consciousness in one patient, which was noted from 5 days before the study and worsened after infusion IMPORTANT OUTCOMES • Quality of life: not reported • Symptoms of hypercalcemia: not reported by symptom; moderate or better improvements in subjective symptoms and objective findings were observed in 7/10 patients in the incadronate group and 1/7 patients in the elcatonin group (p=0.026)	
Ostenstad 1992	• Design: RCT • Funding: not reported; CoI: not reported • Setting: single center, Norway • Sample size: N=28 • Duration: follow-up 12 days	• Eligibility criteria: patients with persistent symptomatic tumour-associated hypercalcemia despite treatment with saline infusion and furosemide • Exclusion criteria: not reported • *A priori* patient characteristics: ○ Cancer type: lung 28%, breast 18%	Pamidronate 30-90 mg IV over 12h (N=14) vs. Mithramycin 1.25 mg IV over 4h (N=11)	CRITICAL OUTCOMES • Serum calcium: ○ Normocalcemic response by day 6: 14/14 vs. 3/11, p=0.0001 • Duration of effect: the 3 responders in the Mithramycin group recurred by day 6, 2 patients in the Pamidronate group recurred by day 12 • Adverse events: no serious side effects in any of the groups; none of the patients developed chronic renal failure IMPORTANT OUTCOMES • Quality of life: not reported • Symptoms of hypercalcemia: not reported	Level of evidence: unclear risk of bias • Unclear randomisation method and allocation concealment • Unclear blinding • 3 patients were excluded due to rapid deterioration and death
Pecherstorfer 2003	• Design: RCT • Funding: not reported; CoI: not reported • Setting: multicenter study, Europe • Sample size: N=72 • Duration: follow-up 28 days	• Eligibility criteria: patients aged ≥18 years, suffering from malignancy and presenting with an albumin-corrected serum calcium >2.7 mmol/l (10.8 mg/dl) • Exclusion criteria: nonmalignant causes of hypercalcemia, pregnancy, lactation, bisphosphonate treatment within 1 month,	Rehydration therapy was given to all patients Ibandronate 2 or 4 mg IV (N=37) vs. Pamidronate 15, 30, 60 or 90 mg IV (N=34)	CRITICAL OUTCOMES • Corrected serum calcium: ○ Mean change from day 0 to day 4: Ibandronate 0.73 +/- 0.48 mmol/l vs. Pamidronate 0.57 +/- 0.33 mmol/l; MD = 0.09 mmol/l ○ Normocalcemic response: 76.5% vs. 75.8% • Duration of effect: median 14 days vs. 4 days, p=0.0303 • Adverse events: related to study medication	Level of evidence: high risk of bias • Central stratified randomisation using minimisation procedure • Open-label study • No ITT analysis: 71/72 included in safety analysis (1 patient did not receive study medication), 67/72 in

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		calcitonin treatment within 1 week, or therapy with any investigational drug 30 days prior to or during the study • *A priori* patient characteristics: ○ Mean age: 59.4 vs. 58.9y ○ M/F: 15/22 vs. 18/16 ○ Cancer type: breast N=16, head/neck N=12, lung N=12, hematologic N=10	Doses were dependent on the severity of hypercalcemia	○ Flu-like syndrome: 2 vs. 6 ○ Respiratory: 1 vs. 2 ○ Hypocalcemia: 2 vs. 0 ○ Hypophosphatemia: 0 vs. 2 ○ Hypokalemia: 1 vs. 0 ○ Thrombocytopenia: 0 vs. 1 ○ Confusion: 0 vs. 1 ○ Diarrhea: 1 vs. 0 IMPORTANT OUTCOMES • Quality of life: not reported • Symptoms of hypercalcemia: not reported	ITT analysis, 58/72 in per protocol analysis • Not all 95%CI are reported
Purohit 1995 Vinholes 1997	• Design: RCT • Funding: not reported; CoI: not reported • Setting: single center, UK • Sample size: N=41 • Duration: follow-up of 28 days	• Eligibility criteria: patients with hypercalcemia of malignancy, who remained hypercalcemic after 48h of rehydration with 3l normal saline per day • Exclusion criteria: not reported • *A priori* patient characteristics: ○ Cancer types: breast N=15, squamous carcinoma N=12	48h of rehydration with 3l of normal saline per day Pamidronate 90 mg IV over 4h (N=20) vs. Clodronate 1500 mg IV over 4h (N=21)	CRITICAL OUTCOMES • Serum calcium: ○ Normocalcemic response: 19/19 vs. 16/20, NS ○ Serum calcium only reported in figure • Duration of effect: median duration 28 days (range 10-28) vs. 14 days (range 7-21), p=0.01 • Adverse events: ○ Fever during the first 24-48h in 3 patients after administration of Pamidronate ○ No other adverse events of treatment IMPORTANT OUTCOMES • Quality of life: Rotterdam Symptom Checklist, N=14 vs. N=16, data reported in figure ○ Significant improvement in QOL following treatment of hypercalcemia ○ Effect not maintained in the Clodronate group principally owing to recurrence of hypercalcemia • Symptoms of hypercalcemia: not reported	Level of evidence: unclear risk of bias • Unclear randomisation method and allocation concealment • Double-blind study (incl. investigators) • 1 patient in each group died within the first 48h and was not included in the efficacy analysis
Ralston 1985	• Design: RCT • Funding: not reported; CoI: not reported • Setting: single center, UK • Sample size: N=39 • Duration: follow-up of 9 days	• Eligibility criteria: patients with cancer-associated hypercalcemia • Exclusion criteria: not reported • *A priori* patient characteristics: ○ Cancer types: lung 48%, breast 17% ○ Bone metastases: 7/13 vs. 9/13 vs. 9/13	Patients were rehydrated with intravenous saline (0.9%) 500 ml every 4h for a minimum of 48h, then 500 ml every 6h for 12h Pamidronate 15 mg IV daily until normal serum calcium or nadir (N=13)	CRITICAL OUTCOMES • Serum calcium: ○ Serum calcium levels were significantly lower in Pamidronate-treated than in corticosteroids/calcitonin-treated patients at both 6 and 9 days and Mithramycin-treated patients at 9 days • Duration of effect: not reported • Adverse events: side-effects of mithramycin were nausea, vomiting, and malaise in two patients, mild thrombocytopenia in one	Level of evidence: high risk of bias • Randomisation by sealed envelopes • Unclear allocation concealment • No blinding

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			vs. Mithramycin 0.025 mg/kg IV (repeated after 2d if serum calcium remained > 2.90 mmol/l) (N=13) vs. Prednisolone 40 mg/d po + salmon calcitonin 400 IU SC every 8h for 9 days (N=13)	patient, and rises in serum aminotransferases and y-glutamyl transpeptidase in eleven; transient pyrexia occurred in four of the Pamidronate group and local thrombophlebitis at the infusion site in two; none of the corticosteroids/calcitonin group complained of nausea or vasomotor symptoms, but many found the frequent injections of calcitonin uncomfortable IMPORTANT OUTCOMES • Quality of life: not reported • Symptoms of hypercalcemia: response ○ Specific symptoms: 58% vs. 42% vs. 50% ○ Non-specific symptoms: 31% vs. 8% vs. 7%	
Rizzoli 1992	• Design: RCT • Funding: supported by the Swiss National Science Foundation (grant 3200.025.535) and by the League against Cancer of Geneva, Switzerland; CoI: not reported • Setting: single university center, Switzerland • Sample size: N=70 • Duration: follow-up 8 days	• Eligibility criteria: patients with hypercalcemia of tumoral origin • Exclusion criteria: patients who had received bisphosphonates therapy during the previous 3 weeks, and those receiving anti-cancer chemo- or radiotherapy, or specific treatment for hypercalcemia, such as calcitonin or mithramycin during the preceding week • *A priori* patient characteristics: ○ Mean age: 61.2 vs. 61.0y ○ M/F: 14/16 vs. 16/18 ○ Cancer type: epidermoid N=20, breast N=17, multiple myeloma N=9 ○ Bone metastases: 21/30 vs. 25/34	Rehydration regimen comprised 2 to 3l per day of 0.15 M sodium chloride solution Alendronate 7.5 mg IV over 4-6h (N=30) vs. Clodronate 600 mg IV over 4-6h (N=34)	CRITICAL OUTCOMES • Serum calcium: ○ % decrease: 18.9 +/- 1.5% vs. 16.0 +/- 2.0% ○ Normocalcemic response on day 3 (serum calcium < 2.70 mmol/l): 40% vs. 41% • Duration of effect: not reported • Adverse events: “the administration of alendronate or clodronate to patients with malignant hypercalcaemia was not associated with any significant alteration in plasma creatinine levels” IMPORTANT OUTCOMES • Quality of life: not reported • Symptoms of hypercalcemia: not reported	Level of evidence: high risk of bias • Two RCTs were reported, but only study 1 is included here; study 2 is a comparison of different doses of Alendronate • Unclear randomisation method and allocation concealment • Unclear blinding • 6 patients excluded after randomisation
Rotstein 1992	• Design: RCT • Funding: not reported; CoI: not reported • Setting: multicenter study, Sweden/Denmark • Sample size: N=44 • Duration: follow-up 8 days	• Eligibility criteria: female patients with bone metastases due to histologically confirmed breast cancer and hypercalcemia, persisting after adequate hydration • Exclusion criteria: patients with any other disease known to cause hypercalcemia or a serum creatinine >250 µmol/l; any previous treatment with any bisphosphonate or any treatment within 14 days	Rehydration with 2-4l 0.9% NaCl for 12-24h Clodronate 300 mg IV over 3h, daily for 7 days or until serum calcium <1.40 mmol/l (N=25) vs. Placebo (N=19)	CRITICAL OUTCOMES • Serum calcium: ○ Normocalcemic response within 7 days: 17/21 vs. 4/19, p=0.0003 ○ Mean serum calcium at end of study: 1.26 vs. 1.66 mmol/l • Duration of effect: not reported • Adverse events: ○ Adverse events were reported for 5 patients on clodronate and one on placebo: 1 patient died during treatment with clodronate due to progressive malignant	Level of evidence: high risk of bias • Unclear randomisation method and allocation concealment • Double-blind study, but unclear if outcome assessors were blinded • 4 dropouts in Clodronate group because of insufficient serum calcium values

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
		before inclusion in the study with steroids, thiazides, calcitonin or mithramycin; patients with a history of malignant neoplasms other than breast cancer • *A priori* patient characteristics: ○ Age: range 36-82y, median 51 vs. 55y ○ Bone metastases: 43/44		disease with liver failure, progressive bone metastases and hypercalcemia; 1 patient had diarrhoea for 24 h, 1 day after end of treatment; fluid retention was reported in 2 patients probably due to excess of daily rehydration and 1 patient developed mild paraesthesia; 1 patient on placebo was withdrawn because of pulmonary oedema, somnolence and severe deterioration due to progressive disease ○ Hypocalcemia: Clodronate N=4 IMPORTANT OUTCOMES • Quality of life: not reported • Symptoms of hypercalcemia: not reported	
Singer 1991	• Design: RCT • Funding: supported by a clinical grant from Norwich Eaton Pharmaceuticals Inc, a Procter & Gamble Co, Norwich, NY, and by National Institutes of Health (Bethesda, Md) General Clinical Research grant MO-1 RR-43; CoI: not reported • Setting: multicenter study, US, Canada & Europe • Sample size: N=202 • Duration: follow-up 7 days	• Eligibility criteria: patients with a histologically confirmed diagnosis of malignant disease and a total serum calcium level of at least 0.25 mmol/L above the normal upper limit; on their current chemotherapy regimen for at least 3 weeks before entry into the study without a significant change in dosage for 1 week; life expectancy of at least 6 weeks • Exclusion criteria: patients with hyperparathyroidism, active peptic ulcer in the preceding 6 months, and clinical evidence or a history of significant renal impairment (ie, serum creatinine level >221 µmol/L); patients were ineligible if, during the week before enrollment in the study, they had undergone therapy for hypercalcemia with steroids, plicamycin, indomethacin, calcitonin, or phosphate; also excluded were patients who had undergone diphosphonate therapy during the 3 months before enrollment • *A priori* patient characteristics: ○ Mean age: 58 vs. 61y ○ M/F: 64/50 vs. 27/16	Etidronate 7.5 mg/kg per day for 3 days (N=136) vs. Saline alone for 3 days (N=66) Concurrent hydration with up to 3l of saline per day	CRITICAL OUTCOMES • Serum calcium: ○ Normocalcemic response: total serum calcium (N=157) 63% vs. 33%, p=0.0006; corrected serum calcium (N=147) 24% vs. 7%, p=0.02 ○ Mean change from baseline in unadjusted total serum calcium on day 4: -0.52 +/- 0.02 mmol/l vs. -0.30 +/- 0.05 mmol/l, p<0.001 • Duration of effect: not reported • Adverse events: ○ Transient taste perversion: 3.5% vs. 0% ○ Nausea: 8.8% vs. 4.5% ○ Increases in serum creatinin: 12% vs. 5% ○ Hypocalcemia: 15% vs. 0% ○ No deaths attributable to treatment IMPORTANT OUTCOMES • Quality of life: not reported • Symptoms of hypercalcemia: not reported	Level of evidence: high risk of bias • Unclear randomisation method and allocation concealment • Double-blind study, but unclear if outcome assessors were blinded • 45 patients excluded from efficacy evaluation, but proportionally more in placebo group (22 vs. 23)

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
		○ Cancer types: respiratory and intrathoracic organs N=61, breast N=37, genitourinary tract N=26			
Thurlimann 1992	• Design: RCT • Funding: not reported; CoI: not reported • Setting: two centers, Switzerland • Sample size: N=48 • Duration: follow-up 90 days	• Eligibility criteria: patients with histologically or cytologically proven malignancy and a first occurrence of symptomatic hypercalcemia • Exclusion criteria: patients considered terminally ill and those with a serum creatinine level above 350 umol/L • *A priori* patient characteristics: ○ Mean age: 61.2 vs. 62.9y ○ M/F: 10/15 vs. 10/13 ○ Cancer type: breast N=13, lung N=11, multiple myeloma N=8, genitourinary N=5 ○ Bone metastases: 88% vs. 65%	Pamidronate 60 mg IV over 24h (N=25) vs. Plicamycin 25 µg/kg IV over 1-5' (N=23) Concurrent hydration with at least 2l 0.9% NaCl/day	CRITICAL OUTCOMES • Serum calcium: ○ Normocalcemic response between day 1 and 7: 22/25 vs. 10/22, p<0.01 ○ Normocalcemic response on day 7: 19/22 vs. 10/21, p<0.01 ○ Mean reduction on day 7: 1.09 +/- 0.37 vs. 0.67 +/- 0.57 mmol/l, p<0.01 • Duration of effect: normocalcemic response on day 90 or death 14/22 vs. 8/21, p<0.05 • Adverse events: ○ Vomiting: 0 vs. 37%, p<0.01 ○ Phlebitis at infusion site: 53% vs. 11%, p<0.05 ○ T° increase with at least 1°C within 36h of treatment: 40% vs. 9%, p<0.01 ○ Hypocalcemia: 32% vs. 5%, p<0.01 IMPORTANT OUTCOMES • Quality of life: not reported • Symptoms of hypercalcemia: not reported	Level of evidence: unclear risk of bias • Randomisation with pre-prepared envelopes • Unclear allocation concealment and blinding • One patient was not evaluable because of insufficient documentation
Warrell 1991	• Design: RCT • Funding: supported in part by grants no. CA-44538 and CA-06927 from the National Cancer Institute, Department of Health and Human Services, and by a grant from Fujisawa Pharmaceutical Co.; CoI: not reported • Setting: multicenter study, US • Sample size: N=71 • Duration: follow-up 7 days	• Eligibility criteria: patients who had been hospitalized with moderate-to-severe hypercalcemia (total serum calcium > 12.0 mg/dL) histologic diagnosis of cancer; serum creatinine < 2.5 mg/dL; no cytotoxic chemotherapy, mithramycin (plicamycin), or radiation within the preceding 7 days; no concomitant aminoglycoside therapy; a life expectancy of more than 4 weeks, or reasonable expectation of benefit • Exclusion criteria: other hypocalcemic medications, hypercalcemia due to parathyroid carcinoma, malignant lymphoma • *A priori* patient characteristics: ○ Median age: 58 vs. 59y	2 days of hydration Gallium nitrate 200 mg/m²/day IV for 5 days (N=34) vs. Etidronate 7.5 mg/kg IV daily over 4h for 5 days (N=37)	CRITICAL OUTCOMES • Serum calcium: ○ Normocalcemic response: 82% vs. 43%, p<0.001 • Duration of effect: median duration 8 days (range 0-54) vs. 0 days (range 0-23), p=0.0005 • Adverse events: ○ Renal insufficiency: 5 vs. 4 ○ Hypophosphatemia: 97% vs. 43%, p<0.001 ○ Hyperphosphatemia: 0% vs. 11% IMPORTANT OUTCOMES • Quality of life: not reported • Symptoms of hypercalcemia: ○ Nausea: not reported ○ Mental status: improvement 33% vs. 38%, NS ○ Obstipation: not reported	Level of evidence: low risk of bias • Permuted blocks randomisation • Central allocation • During the study, only the pharmacist who prepared the drugs and the central statistician were not blinded with respect to treatment allocation

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
		○ M/F: 17/17 vs. 22/15 ○ Cancer types: lung N=19, breast N=10, head/neck N=10, kidney N=9 ○ Bone metastases: 21/34 vs. 18/37			
Warrell 1988	• Design: RCT • Funding: in part by PHS grants CA-37768, CA-42445, CA-38645, and CA-29502 from the National Cancer Institute, DHHS, and by BC-553 from the American Cancer Society; CoI: not reported • Setting: single center, US • Sample size: N=50 • Duration: follow-up 7 days	• Eligibility criteria: hospitalization and intravenous hydration for at least 2 days before entry; persistent elevation of serum calcium levels to 2.99 mmol/L or greater; histologic diagnosis of cancer; serum creatinine level of 221 µmol/L (2.5 mg/dL) or less; no cytotoxic chemotherapy, mithramycin, or radiation within the preceding 7 days; no concomitant aminoglycoside therapy; life expectancy greater than 4 weeks or reasonable expectation of benefit; consent by the patient's attending physician; and signed informed consent by the patient • Exclusion criteria: other hypocalcemic medications, hypercalcemia due to parathyroid carcinoma; malignant lymphoma • *A priori* patient characteristics: ○ Median age: 56 vs. 54y ○ M/F: 14/10 vs. 13/13 ○ Cancer type: breast N=11, lung N=8, kidney N=7, head/neck N=7 ○ Bone metastases: 22/24 vs. 22/26	2 days of hydration Gallium nitrate 200 mg/m²/day IV for 5 days (N=24) + sham IM injection vs. Salmon calcitonin 8 IU/kg IM every 6h daily for 5 days (N=26) + sham IV infusion	CRITICAL OUTCOMES • Serum calcium: ○ Normocalcemic response: 75% vs. 31%, p=0.002 • Duration of effect: median duration 11 days (range 1-41) vs. 2 days (1-7), p<0.01 • Adverse events ○ Hypophosphatemia: 91% vs. 45%, p=0.001 ○ Nausea: 14% vs. 35%, p=0.094 ○ Pain at injection site: 9/22 vs. 16/26, p=0.15 IMPORTANT OUTCOMES • Quality of life: not reported • Symptoms of hypercalcemia: ○ Nausea: not reported ○ Mental status: improvement 46% vs. 27%, p=0.16 ○ Obstipation: not reported	Level of evidence: low risk of bias • Permuted blocks randomisation • Central allocation • During the study, only the pharmacist who prepared the drugs and the central statistician were not blinded with respect to treatment allocation
Wimalawansa 1997 Study 1	• Design: RCT • Funding: not reported; CoI: not reported • Setting: single university centre, US • Sample size: N=10 • Duration: follow-up 8 days	• Eligibility criteria: patients with solid tumors and cancer-associated hypercalcemia who did not have gross renal impairment (serum creatinine <90 µmol/l) • *A priori* patient characteristics: reported for study 1, 2 and 3 together ○ Median age 65y	Full rehydration with normal saline Salmon calcitonin 200 IU SC every 8h for 7 days (N=5) vs.	CRITICAL OUTCOMES • Serum calcium: ○ No statistical differences at any of the time points between groups (reported in figure) • Duration of effect: calcium-lowering effect lasted for only 3-4 days despite continued administration of calcitonin; the addition of prednisolone did not significantly prolong the effect	Level of evidence: unclear risk of bias • Unclear randomisation method and allocation concealment • Unclear blinding, but unlikely

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
		○ Solid tumors: breast N=9, head/neck N=7, lung N=7, kidney N=1	Salmon calcitonin 200 IU SC every 8h for 7 days + oral prednisolone 40 mg/day (N=5)	• Adverse events: not reported IMPORTANT OUTCOMES • Quality of life: not reported • Symptoms of hypercalcemia: not reported	
Wimalawansa 1997 Study 2	• Design: RCT • Funding: not reported; CoI: not reported • Setting: single university centre, US • Sample size: N=10 • Duration: follow-up 8 days	• Eligibility criteria: patients with multiple myeloma and cancer-associated hypercalcemia who did not have gross renal impairment (serum creatinine <90 µmol/l) • *A priori* patient characteristics: reported for study 1, 2 and 3 together ○ Median age 65y ○ Solid tumors: breast N=9, head/neck N=7, lung N=7, kidney N=1	Full rehydration with normal saline Salmon calcitonin 200 IU SC every 8h for 7 days (N=5) vs. Salmon calcitonin 200 IU SC every 8h for 7 days + oral prednisolone 40 mg/day (N=5)	CRITICAL OUTCOMES • Serum calcium: ○ By day 5 serum calcium levels were significantly higher in patients who received calcitonin alone (p<0.01; reported in figure) ○ Normocalcemic response by day 7: 0/5 vs. 4/5 • Duration of effect: not reported • Adverse events: not reported IMPORTANT OUTCOMES • Quality of life: not reported • Symptoms of hypercalcemia: not reported	Level of evidence: unclear risk of bias • Unclear randomisation method and allocation concealment • Unclear blinding, but unlikely
Wimalawansa 1997 Study 3	• Design: RCT • Funding: not reported; CoI: not reported • Setting: single university centre, US • Sample size: N=14 • Duration: follow-up 8 days	• Eligibility criteria: patients with solid tumors and cancer-associated hypercalcemia who did not have gross renal impairment (serum creatinine <90 µmol/l) • *A priori* patient characteristics: reported for study 1, 2 and 3 together ○ Median age 65y ○ Solid tumors: breast N=9, head/neck N=7, lung N=7, kidney N=1	Full rehydration with normal saline Pamidronate 60 mg IV over 6h (N=7) vs. Pamidronate 60 mg IV over 6h + salmon calcitonin 200 IU SC every 8h for 7 days (N=7)	CRITICAL OUTCOMES • Serum calcium: ○ In days 1 and 2, patients who received combined therapy had significantly lower serum calcium levels than the group treated with pamidronate alone (p<0.05) • Duration of effect: mean 14 vs. 13 days, NS • Adverse events: not reported IMPORTANT OUTCOMES • Quality of life: not reported • Symptoms of hypercalcemia: marked reduction of symptomatology that included most symptoms attributable to hypercalcemia in combination group	Level of evidence: unclear risk of bias • Unclear randomisation method and allocation concealment • Unclear blinding, but unlikely

Abbreviations: 95%CI: 95% confidence interval; AUC: area under the curve; CoI: conflict of interest; IM: intramuscular IV: intravenous; M/F: male/female; MD: mean difference; NS: not significant; po: per os; RCT: randomised controlled trial; RR: relative risk; SC: subcutaneously; SD: standard deviation; US: United States.

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