HYPERCALCEMIA ASSOCIATED WITH MALIGNANCY pdf

1: Hypercalcaemia - Wikipedia

The most common cancers associated with hypercalcemia in the United States are breast, renal, and lung cancer and multiple myeloma. Malignancy is usually evident clinically by the time it causes hypercalcemia, and patients with hypercalcemia of malignancy often have a poor prognosis.

Hypercalcemia is a condition in which the calcium level in your blood is above normal. Too much calcium in your blood can weaken your bones, create kidney stones, and interfere with how your heart and brain work. Hypercalcemia is usually a result of overactive parathyroid glands. These four tiny glands are situated behind the thyroid gland. Other causes of hypercalcemia include cancer, certain other medical disorders, some medications, and taking too much of calcium and vitamin D supplements. Signs and symptoms of hypercalcemia range from nonexistent to severe. Treatment depends on the cause. Symptoms You might not have signs or symptoms if your hypercalcemia is mild. More-severe cases produce signs and symptoms related to the parts of your body affected by the high calcium levels in your blood. Excess calcium in your blood means your kidneys have to work harder to filter it. This can cause excessive thirst and frequent urination. Hypercalcemia can cause stomach upset, nausea, vomiting and constipation. In most cases, the excess calcium in your blood was leached from your bones, which weakens them. This can cause bone pain, muscle weakness and depression. Hypercalcemia can interfere with the way your brain works, resulting in confusion, lethargy and fatigue. It can also cause depression. Rarely, severe hypercalcemia can interfere with your heart function, causing palpitations and fainting, indications of cardiac arrhythmia, and other heart problems. When to see a doctor Contact your doctor if you develop signs and symptoms that might indicate hypercalcemia, such as being extremely thirsty, urinating frequently and having abdominal pain. Request an Appointment at Mayo Clinic Causes Besides building strong bones and teeth, calcium helps muscles contract and nerves transmit signals. Your bones to release calcium into your blood Your digestive tract to absorb more calcium Your kidneys to excrete less calcium and activate more vitamin D, which plays a vital role in calcium absorption This delicate balance between too little calcium in your blood and hypercalcemia can be disrupted by a variety of factors. Hypercalcemia is caused by: The most common cause of hypercalcemia, overactive parathyroid glands hyperparathyroidism can stem from a small, noncancerous benign tumor or enlargement of one or more of the four parathyroid glands. Lung cancer and breast cancer, as well as some cancers of the blood, can increase your risk of hypercalcemia. Spread of cancer metastasis to your bones also increases your risk. Certain diseases, such as tuberculosis and sarcoidosis, can raise blood levels of vitamin D, which stimulates your digestive tract to absorb more calcium. A rare genetic disorder known as familial hypocalciuric hypercalcemia causes an increase of calcium in your blood because of faulty calcium receptors in your body. People who have a condition that causes them to spend a lot of time sitting or lying down can develop hypercalcemia. A common cause of mild or transient hypercalcemia is dehydration. Having less fluid in your blood causes a rise in calcium concentrations. Certain drugs â€” such as lithium, which is used to treat bipolar disorder â€” might increase the release of parathyroid hormone. Taking excessive amounts of calcium or vitamin D supplements over time can raise calcium levels in your blood above normal. Risk factors Women older than 50 are at highest risk of overactive parathyroid glands. Complications Hypercalcemia complications can include: If your bones continue to release calcium into your blood, you can develop the bone-thinning disease osteoporosis, which could lead to bone fractures, spinal column curvature and loss of height. If your urine contains too much calcium, crystals may form in your kidneys. Over time, the crystals may combine to form kidney stones. Passing a stone can be extremely painful. Severe hypercalcemia can damage your kidneys, limiting their ability to cleanse the blood and eliminate fluid. Severe hypercalcemia can lead to confusion, dementia and coma, which can be fatal. Abnormal heart rhythm arrhythmia. Hypercalcemia can affect the electrical impulses that regulate your heartbeat, causing your heart to beat irregularly.

HYPERCALCEMIA ASSOCIATED WITH MALIGNANCY pdf

2: [Full text] Hypercalcemia of malignancy and new treatment options | TCRM

Hypercalcemia of malignancy is a common finding typically found in patients with advanced stage cancers. We aimed to provide an updated review on the etiology, pathogenesis, clinical presentation, and management of malignancy-related hypercalcemia. We searched PubMed/Medline, Scopus, Embase, and Web.

This article has been cited by other articles in PMC. Abstract Hypercalcemia of malignancy is a common finding typically found in patients with advanced stage cancers. We aimed to provide an updated review on the etiology, pathogenesis, clinical presentation, and management of malignancy-related hypercalcemia. Hypercalcemia of malignancy usually presents with markedly elevated calcium levels and therefore, usually severely symptomatic. Several major mechanisms are responsible for the development of hypercalcemia of malignancy including parathyroid hormone-related peptide-mediated humoral hypercalcemia, osteolytic metastases-related hypercalcemia, 1,25 Vitamin D-mediated hypercalcemia, and parathyroid hormone-mediated hypercalcemia in patients with parathyroid carcinoma and extra parathyroid cancers. Diagnosis should include the history and physical examination as well as measurement of the above mediators of hypercalcemia. Management includes hydration, calcitonin, bisphosphonates, denosumab, and in certain patients, prednisone and cinacalcet. Patients with advanced underlying kidney disease and refractory severe hypercalcemia should be considered for hemodialysis. Hematology or oncology and palliative care specialists should be involved early to guide the options of cancer targeted therapies and help the patients and their closed ones with the discussion of comfort-oriented care. Cancer, hypercalcemia, parathyroid hormone related peptide, vitamin D Introduction Hypercalcemia is defined as an increase in the serum calcium level above the upper limit of normal for a given reference value used in a laboratory. To answer this question, Hamilton et al. Patients with hypercalcemia comprised the minority but had higher rates of cancer diagnosis at 1-year 6. However, the retrospective methodology of this study should be kept in mind when interpreting the study results. Another important aspect to mention briefly is that not all hypercalcemia in cancer patients is secondary to malignancy, and this is discussed further in subsequent sections. The search terms were: The reference lists of the identified articles were further screened for potentially relevant articles that could be overlooked by an electronic search. The search methodology was adapted from the scientific search guidelines published in Second, we discuss the etiology and pathogenesis of hypercalcemia of malignancy. Third, we review the clinical presentation of hypercalcemia. Fourth, the diagnostic approach to hypercalcemia is addressed. Finally, the management of hypercalcemia of malignancy is discussed. Normal Regulation of Calcium Metabolism Calcium is an essential element that participates in various biochemical reactions, including muscle contraction, coagulation and bone development among others. Bone, where calcium is stored as hydroxyapatite salt that comprises the major part of body calcium, and plasma. PTH release reaches a peak when calcium falls below 7. PTH has several important actions focused on the increase of serum calcium. First, PTH activates the 1-alpha-hydroxylase enzyme located in the renal proximal tubules, which in turn converts hydroxyvitamin D into the more active 1,dihydroxyvitamin D. Third, PTH leads to calcium mobilization from the bone with the help of 1,dihydroxyvitamin D. All these actions aim to increase calcium concentrations, bringing them back to normal. Another key player in normal calcium metabolism is Vitamin D. Vitamin D or cholecalciferol sources in the body include synthesis in the skin from 7-dehydrocalciferol under the influence of ultraviolet light and dietary intake. Eventually, dihydroxycholecalciferol will be delivered into kidneys where it can be activated by the aforementioned 1-alpha-hydroxylase enzyme which is activated by PTH into 1,dihydroxycholecalciferol. However, tumors secreting calcitonin, such as medullary thyroid cancer, do not lead to low calcium levels. A possible explanation for the efficacy of calcitonin in patients with malignancy-related hypercalcemia could be related to secondary overzealous bone resorption and calcium release in these patients. Finally, it is necessary to discuss briefly the different roles of major bone cells and their interplay in bone turnover and calcium release. For this purpose, we focus on two cellular types: Osteoblasts derive from mesenchymal cells and osteoclasts originate from monocyte lineage that migrates into the bone environment from the bloodstream. Factors that exert the opposite effects on bone turnover such as

estrogens stimulate the release of osteoprotegerin from osteoblasts, binding RANKL, and preventing it from binding to RANK on the osteoclast precursor cell. Etiology and Pathobiology of Hypercalcemia of Malignancy There are several major mechanisms of hypercalcemia of malignancy, which are discussed here. Increased renal calcium reabsorption is another mechanism through which PTHrP leads to hypercalcemia. In the case of multiple myeloma, the local release of various cytokines, such as RANKL, interleukin-3 and -6, facilitate bone remodeling and resultant hypercalcemia. The third mechanism includes ectopic activity of 1-alpha-hydroxylase and the formation of 1,dihydroxycholecalciferol, common in lymphomas and in some ovarian germ cell tumors. The major mechanisms of malignancy-related hypercalcemia are emphasized in Figure 1.

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3: Hypercalcemia | Clinical Gate

hypercalcemia of malignancy abnormal elevation of serum calcium associated with malignant tumors, resulting from osteolysis caused by bone metastases or by the action of circulating osteoclast-activating factors released from distant tumor cells (known as humoral hypercalcemia of malignancy).

Advanced Search Abstract We present a case of undifferentiated pancreatic cancer associated with humoral hypercalcemia of malignancy HHM in which parathyroid hormone-related protein PTH-rP is identified as the causative factor of hypercalcemia. A year-old man was hospitalized with right hypochondralgia. Ultrasound examination and computed tomography demonstrated a large mass in the pancreatic head with liver metastases. Biopsy of the pancreatic tumor demonstrated undifferentiated carcinoma. Serum calcium level and PTH-rP were elevated. Bone scan with technetium demonstrated no accumulation in the bones. Immunohistochemical staining for PTH-rP was weakly positive in the tumor cells. This rare case was successfully treated with pamidronate disodium, which is a type of bisphosphonate derivative. We compared this case with previously reported cases. Local osteolytic hypercalcemia LOH is a complication of bone metastases, such as multiple myeloma, which locally release osteolytic proteins. Humoral hypercalcemia of malignancy HHM is a biochemical feature of cancer without bone metastases, reminiscent of primary hyperparathyroidism. HHM is relatively common in squamous cell carcinoma of the lung and larynx 2. In pancreatic cancer, endocrine pancreatic cancer associated with HHM is more common than exocrine pancreatic cancer. Fourteen cases of exocrine pancreatic cancer associated with HHM have been reported 3â€” Here, we present a case of undifferentiated pancreatic cancer associated with HHM in which PTH-rP was identified as the causative factor of hypercalcemia. Case Report A year-old man was hospitalized in February with right hypochondralgia, which he first noted in December He had a past history of duodenal ulcer. Ultrasound examination and computed tomography Fig. Initial laboratory data were as follows: Laboratory data related to Ca metabolism were as follows: Serum Ca level was increased to Thirst and loss of appetite were progressive. A 30 mg dose of parnidronate disodium by drip infusion normalized the serum Ca concentration. Although the effect of pamidronate disodium was temporary, it caused no major adverse effects and could be administered again. The patient died from the progressive cancer. A necropsy specimen of the pancreas Fig. Tumor cells had eosinophilic cytoplasm and clear nucleoli, similar to those in lymphoma. Interstitial tissue had vessels, necrosis and apoptosis. Diffuse proliferative tumor cells were loosely connected and classified as undifferentiated or anaplastic ductal carcinoma. Immunohistochemical staining for keratin and epithelial membrane antigen EMA was positive and that for leukocyte common antigen LCA , vimentin, NSE and chromogranin was negative not shown. These findings indicate that tumor cells were derived from epithelial cells, and a diagnosis of undifferentiated carcinoma originating from the exocrine pancreas was made. Figure 1 Computed tomography showed a tumor of the pancreatic head and liver metastases. Discussion Although the mechanism of hypercalcemia induced by a malignant tumor without bone metastasis, so-called humoral hypercalcemia of malignancy, has long been investigated, it has not yet been clarified. Figure 2 Necropsy specimen showed undifferentiated carcinoma. Fourteen cases of exocrine pancreatic cancer associated with HHM have been reported Table 1. Marked hypercalcemia in the presence of normal plasma concentrations of PTH and vitamin D3 without bone metastases is compatible with HHM. Moreover, the plasma PTH-rP level was markedly elevated in this patient. HHM is common in squamous cell carcinoma, such as that of the lung and larynx 2 , and is less common in pancreatic cancer. However, in pancreatic cancer, endocrine pancreatic cancer associated with HHM is more common than exocrine pancreatic cancer. Only one case of undifferentiated pancreatic cancer associated with HHM in which PTH-rP was identified as the causative factor of hypercalcemia has been reported Table 1 Reported cases of exocrine pancreatic cancer with humoral hypercalcemia of malignancy Table 1 Reported cases of exocrine pancreatic cancer with humoral hypercalcemia of malignancy Table 2 Reported cases of exocrine pancreatic cancer with hypercalcemia caused by PTH-rP Table 2 View large Download slide Reported cases of exocrine pancreatic cancer with hypercalcemia caused by PTH-rP Hypercalcemia in HHM is often resistant to treatment and its

prognosis is very poor. In our case, pamidronate disodium was effective in treating hypercalcemia. The concentration of Ca rapidly normalized. In conclusion, we have reported a rare case of undifferentiated pancreatic cancer associated with HHM. Pamidronate disodium, a type of bisphosphonate derivative, was effective in treating HHM. It had few adverse effects and improved the quality of life in this patient.

4: Malignancy-associated hypercalcemia - Cancer Therapy Advisor

A year-old woman with a history of breast cancer presents with confusion and dehydration. The serum calcium level is mg per deciliter.

Which Bisphosphonate is Best? Therapies for managing MAH emergently should focus on correcting the underlying mechanism, as outlined below with their respective causes: Patients with MAH are often dehydrated due to decreased oral intake and a renal water-concentrating defect directly caused by elevated calcium levels. Routine administration of loop diuretics, such as furosemide, has largely fallen out of favor unless the patient is volume-overloaded because of the concern of worsening volume depletion in this population. Several bisphosphonates are available in the US in IV formulations pamidronate, zoledronic acid, ibandronate, and etidronate. Of these, pamidronate, zoledronic acid, and etidronate are currently approved for MAH. Etidronate carries a higher risk of increasing serum creatinine than the other agents. Comparison of zoledronic acid and pamidronate Zoledronic acid is a third-generation bisphosphonate with potency approximately times that of pamidronate. Aside from potency, several important differences between the two exist 1 infusion time 2 preparation and 3 acquisition cost. The calcium concentrations at day four were only significantly different between the 8 mg zoledronic acid group and the pamidronate group. Zoledronic acid is only approved at a 4 mg dose in the US for MAH, and this dose did not show a difference in calcium concentrations at day 4 when compared to pamidronate. Additionally, the nadir calcium concentrations between zoledronic acid and pamidronate were 9. While this may have reached statistical significance, the clinical significance is questionable. Tolerability and incidence of adverse events were similar between the two agents in this trial. Intervention Single dose of zoledronic acid 4 mg or 8 mg IV over 5 minutes or single dose of pamidronate 90 mg IV over 2 hours; IV fluids also administered at time of study drug Comparison Active control in this trial was pamidronate group; study funded by Novartis Pharma, makers of Zometa zoledronic acid Outcomes Evaluated Primary: Time to relapse serum calcium greater than Additionally, some may extrapolate a faster infusion time with a faster onset of action. This is not the case. These agents take at least hours to work, with a nadir occurring between days four and seven. The formulation of zoledronic acid approved for use in MAH is a mL ready-to-infuse solution; pamidronate must be diluted in at least mL of fluid for infusion. The preparation of pamidronate is another way to provide fluid resuscitation to these often volume-depleted patients. One difference between the two agents that is fairly significant is cost. In the outpatient infusion setting, this may not matter as much when considering preparation, infusion time, and nursing care associated with a longer infusion. However, it is unlikely that this substantially higher cost carries the same value in the ED. Bottom Line Malignancy-associated hypercalcemia is an important cause of hypercalcemia encountered in the ED. ED management should focus on IV fluid resuscitation and initiation of bisphosphonate therapy. Although zoledronic acid is more potent and can be infused more rapidly, it appears that calcium-lowering effects do not differ clinically, and thus pamidronate may be considered a reasonable and more cost-effective alternative in the ED. Hypercalcemia associated with cancer. N Engl J Med. Grill V, Martin T. Rev Endocr Metab Disord. Metabolic emergencies in the cancer patient. J Clin Endocrinol Metab. Didronel R oral tablets, etidronate disodium oral tablets. Renal failure associated with intravenous diphosphonates. Rosner M, Dalkin A. Clin J Am Soc Nephrol. Toxic acute tubular necrosis following treatment with zoledronate Zometa. Zoledronic acid is superior to pamidronate in the treatment of hypercalcemia of malignancy: Single-dose intravenous therapy with pamidronate for the treatment of hypercalcemia of malignancy: Cheer S, Noble S. I have to admit, this was certainly an area that I had to read up on. My biggest question is the necessity of initiating biphosponate therapy in the ED. Can you clarify any relative or absolute contraindication? Additionally, what degrees of hypercalcemia do you recommend initiation on biphosphonate therapy? Should mild or asymptomatic hypercalcemia in the content of malignancy by considered? Finally, what other factors should be considered before initiation on therapy? How should renal function, albumin, phos and other electrolytes be taken into consideration? Overall, certainly an intriguing topic, well-written, and good flow to the article. I would love to have a little more information to

help EM physicians feel comfortable that they are making a well-educated and appropriate choice for their patients. Let me know if you have any questions or need any assistance.

HYPERCALCEMIA ASSOCIATED WITH MALIGNANCY pdf

5: Exported PTHRP MALIGNANCY-ASSOCIATED HYPERCALCEMIA

Malignancy-associated hypercalcemia is relatively common and presents in % of cancer patients. It occurs in both solid tumors and leukemias but is mostly associated with breast cancer, lung.

Hypercalcemia of malignancy affects up to one in five cancer patients during the course of their disease. It is associated with both liquid malignancies, commonly multiple myeloma, leukemia, and non-Hodgkins lymphoma and solid cancers, particularly breast and renal carcinomas as well as squamous cell carcinomas of any organ. The clinical manifestations of hypercalcemia are generally constitutional in nature and not specific to the inciting malignancy. Such physical manifestations can range from malaise to lethargy and confusion. Constipation and anorexia are common. Acute kidney injury is likely the most frequently encountered manifestation of end organ damage. Symptomatology is closely linked to both the absolute elevation of serum calcium levels and the rapidity of calcium rise. The majority of cases are humoral in etiology and related to parathyroid hormone-related protein PTHrP. The diagnosis of hypercalcemia of malignancy is confirmed either by an elevated PTHrP or by an evidence of bone metastasis in the appropriate clinical setting. Interventions are aimed at lowering the serum calcium concentration by inhibiting bone resorption and increasing urinary calcium excretion, the former accomplished via bisphosphonate therapy and the latter with aggressive hydration. Finally, anti-PTHrP antibodies have been successfully deployed in animal models of disease. Despite the efficacy of the above therapies, hypercalcemia of malignancy portends an ominous prognosis, indicating advanced and often refractory cancer with survival on the order of months. The goals of this paper include educating the clinician on the etiology, clinical presentation, and pathogenesis of hypercalcemia among cancer patients. Thereafter, the evaluation and management of such patients is reviewed for the practicing physician. Finally, a detailed summary of previous, current, and novel therapeutic options is described. Non-specific neuropsychiatric symptoms include malaise and lassitude with progression to lethargy, confusion, and coma in those with severe elevations. Constipation, anorexia, and nausea are frequent gastrointestinal expressions of disease with pancreatitis and peptic ulcer disease infrequently encountered. Renal dysfunction appears to be the most clinically important sequelae of hypercalcemia. Acute kidney injury, while not a symptom, is common and the product of direct renal vasoconstriction and natriuresis-induced volume contraction. Nephrolithiasis, while frequently cited, is an uncommon acute manifestation of hypercalcemia, and nearly always only found in those with longstanding disease. Mechanism of disease Hypercalcemia of malignancy occurs as the result of direct bone metastasis and via humoral mechanisms such as parathyroid hormone-related protein PTHrP or 1,dihydroxyvitamin D mediated pathways. Rarely, ectopic secretion of parathyroid hormone PTH has been implicated. Hypercalcemia due to osteolytic bone lesions is common in multiple myeloma, leukemia, and breast cancer. Humoral hypercalcemia is predominant in squamous cell, renal cell and ovarian cancers, and lymphomas are associated with 1,dihydroxyvitamin D mediated hypercalcemia. Physiologic bone turnover requires the complementary activity of osteoblasts â€" mesenchymal stem cell-derived bone-forming cells â€" and bone-resorbing cells of monocyte and macrophage lineage known as osteoclasts. Macrophage inflammation protein 1-alpha MIP 1-alpha may also play a role in hypercalcemia of malignancy at least in multiple myeloma patients. MIP 1-alpha is elevated in bone marrow of patients with active multiple myeloma, and MIP 1-alpha has been shown to stimulate osteoclastic formation in murine models as well as in human bone marrow cells. From this similar but non-identical structural profile, the distinct effects of PTHrP, a biochemical syndrome that shares many features with primary hyperparathyroidism, can be anticipated. This process is, in part, mediated by cytokines such as interleukin IL -1, prostaglandin, lymphotoxin, and tumor necrosis factor TNF. Both IL-1 and E series prostaglandins directly stimulate bone resorption. Moreover, lymphotoxin and TNF contribute to the recruitment, proliferation, and stimulation of osteoclasts. In contradistinction, metastases-induced hypercalcemia results in hyperphosphatemia. Finally, while PTHrP results in enhanced bone resorption and renal calcium reclamation â€" owing to the differences in structure with PTH â€" PTHrP does not augment 1,dihydroxyvitamin D production, and as a result does not increase intestinal calcium absorption. While 1,dihydroxyvitamin D may

also induce some bone resorption, this mechanism of disease is best conceptualized as an absorptive form of hypercalcemia. Ectopic production of PTH by malignant cells has been described in a handful of cases involving cancer of the ovary and lung, as well as neuroendocrine tumors and sarcoma. The epidemiology and natural history of both processes can assist in ascertaining the diagnosis prior to the acquisition of laboratory data. Among patients presenting to the hospital, hypercalcemia of malignancy is 2â€”3 times more common than primary hyperparathyroidism with the source of cancer often evident by history and physical examination. In contrast, findings that suggest primary hyperparathyroidism include mild elevations in serum calcium levels, an asymptomatic patient, a non-focal exam, and a patient without risk factors for cancer. A low to low-normal phosphorus and low 1,dihydroxyvitamin D confirms the diagnosis. Serum phosphorus is in the high-normal range if not frankly elevated. If hypercalcemia related to bone metastasis is suspected but not apparent, then evaluation for a monoclonal gammopathy should be initiated including serum and urine protein electrophoresis, serum-free light chains, and serum and urine immune fixation. A skeletal survey may also be employed. Lymphoma, a hypercalcemia due to 1,dihydroxyvitamin D mediated pathways, is implied by elevations in 1,dihydroxyvitamin D without concomitant elevations in hydroxyvitamin D. An important epidemiological caveat is the coexistence of hyperparathyroidism with hypercalcemia of malignancy. Therapy Treatment of hypercalcemia of malignancy is aimed at lowering the serum calcium concentration by targeting the underlying disease, specifically by inhibiting bone resorption, increasing urinary calcium excretion, and to a lesser extent by decreasing intestinal calcium absorption. Because definitive serologic diagnosis takes several days, treatment is begun empirically at the time of presentation with adjustments occurring as laboratory information becomes available. The urgency and aggressiveness of treatment is predicated on both the serum calcium and importantly, the symptoms manifest. Symptomatology, in turn, is a function of both the absolute serum calcium concentration and the rate of rise of serum calcium. Given the efficacy, tolerability, and cost effectiveness of the treatments involved, it may be reasonable to treat such individuals similar to those with more severe degrees of hypercalcemia. Table 1 summarizes the various pharmacologic treatments available. IV, intravenous; q, every; SQ, subcutaneous. Such therapies include hydration with isotonic fluid if admitted , avoidance of thiazide diuretics, and a low-calcium diet. Conceptually, treatment consists of temporizing measures such as volume expansion and calcitonin with concurrent bisphosphonate therapy for targeted and definitive treatment. Parenteral fluid administration is effective at lowering serum calcium in those with acute kidney injury as well as in patients with preserved glomerular filtration rates. It corrects the decline in glomerular filtration rate mediated by the direct renal vasoconstriction of hypercalcemia as well as the natriuresis-induced volume contraction of hypercalcemia. It also addresses the polyuric state consistent with diabetes insipidus that hypercalcemia provokes. If oliguric renal failure or congestive heart failure is present, the addition of a diuretic should be considered. In those with severe elevations in serum calcium and minimal comorbidities, 4â€”6 L can be safely administered over the first 24 hours. Initially employed to augment renal calcium losses, the routine use of loop diuretics has fallen out of favor with the advent of bisphosphonate therapy. Given the attendant electrolyte complications associated with the high doses employed, the need for even more frequent monitoring and the potential for worsening hypovolemia, loop diuretics should be reserved for patients with congestive heart failure and evidence of symptomatic volume overload or in cases of oliguric renal failure with the same. Since the approval of etidronate for hypercalcemia of malignancy in the late s, bisphosphonates have become the standard of care in the treatment of cancer-associated hypercalcemia providing safe, effective, and sustained reductions in serum calcium levels. In a randomized double blind trial of 50 patients with hypercalcemia of malignancy mean serum calcium Reductions in calcium began 2 days after administration with normocalcemia maintained for 10â€”13 days after infusion. In all treatment groups, serum calcium began to decline within 48 hours with normalization beginning to occur by day 4. The duration of sustained normocalcemia was 32 and 43 days in the zoledronic acid 4 and 8 mg groups, respectively, and 18 days in the pamidronate 90 mg arm. Nonetheless, they are subject to certain side effects and limitations. Most importantly, the administration of bisphosphonates has been associated with significant nephrotoxicity, specifically pamidronate-induced collapsing focal segmental glomerulosclerosis and acute tubular necrosis ATN with zoledronate. The risk of renal failure is directly

related to the drug infusion time and dosage. Multiple case series have documented the development of collapsing focal segmental glomerulosclerosis in cancer patients, mostly myeloma, having received more than 1 year of high-dose pamidronate. ATN has been associated with zoledronic acid with acute kidney injury developing within a few doses of therapy. With both medications, renal impairment has been severe enough to result in permanent dialysis dependence. Side effects of such treatment include hyperglycemia, and further immunosuppression. Although withdrawn from the US market in , gallium nitrate is likely as effective an anti-hypercalcemic agent as bisphosphonates inhibiting both osteoclast and PTHrP-mediated elevations in calcium. Owing to its extended administration time, the advent of even more potent bisphosphonates, and a side effect profile including ATN and hypophosphatemia, gallium nitrate is no longer available within the US, but should be considered in bisphosphonate and denosumab refractory disease. Since the introduction of bisphosphonate therapy, the need for hemodialysis to control hypercalcemia of malignancy has diminished. However, indications remain and include those individuals with oliguric renal failure whose volume status cannot be managed with diuretics alone. Additional categories include patients with severe symptomatic ie, coma elevations in serum calcium despite hydration and high-dose bisphosphonate therapy. In such cases, dialysis is indicated for symptom relief and control of hypercalcemia until chemotherapy has been administered. Given that humoral hypercalcemia is often accompanied by hypophosphatemia and the lack of phosphorus in standard dialysate solutions, hemodialysis-induced hypophosphatemia should be monitored and corrected for. In , the fully human monoclonal antibody denosumab was approved for the treatment of osteoporosis and the prevention of skeletal-related events in patients with solid tumors. In , it was subsequently approved for bisphosphonate refractory hypercalcemia. In case reports, denosumab demonstrated noteworthy anti-hypercalcemic effects in patients with refractory disease despite high-dose bisphosphonate therapy. In an open label, single arm phase two study, 33 patients with a mean serum calcium of However, denosumab must be used with caution in such patients because the risk of hypocalcemia is augmented in patients with impaired calcium homeostasis characteristic of renal failure. However, it is useful to note that in patients with preexisting hypercalcemia of malignancy treated with denosumab, only 2 of 33 patients developed mild hypocalcemia. However, the use of oral vitamin D supplements should be carefully considered against the risks of exacerbating underlying hypercalcemia. Approved in for secondary hyperparathyroidism of renal failure and parathyroid carcinoma, cinacalcet is a calcimimetic that interacts with the calcium sensing receptor on parathyroid cells leading to the downregulation of PTH with an attendant decline in serum calcium levels. A future molecular target for the treatment of hypercalcemia of malignancy involves PTHrP-related antibodies. Using chimeric anti-PTH antibodies, murine models of hypercalcemia suggest infusions of PTHrP antibodies both corrects hypercalcemia and suppresses the release of malignancy associated cytokines such as TNF and multiple interleukins. Moreover, attenuation of these cytokines was accompanied by improvement in appetite, weight, and energy. In a recent study of patients with humoral hypercalcemia of malignancy, the median survival was 52 21â€” days from the time the PTHrP level was obtained. As such, while the aforementioned therapies have markedly decreased the symptoms of hypercalcemia, there is little evidence to suggest that such modalities affect the natural history or mortality rates associated with the underlying malignancy. Disclosure Dr Ilya Glezerman has received institutional research support from and had served on advisory board for Amgen Inc. Dr Hillel Sternlicht reports no conflicts of interest in this work.

HYPERCALCEMIA ASSOCIATED WITH MALIGNANCY pdf

6: Management of Hypercalcemia of Malignancy

The History of Malignancy-Associated Hypercalcemia. Malignancy is the second most common cause of hypercalcemia in the general population and by far the most common cause among inpatients.

What every physician needs to know. Malignancy-associated hypercalcemia results from increased bone resorption and release of calcium from bone secondary to four different mechanisms present in underlying malignant processes. Local osteolytic hypercalcemia results from boney metastasis. These cells cause a local release of cytokines, such as TNF and IL-1, which then stimulate the differentiation of osteoclast precursors into mature osteoclasts and increase bone resorption; it is mostly seen in breast cancer and non-small cell lung cancer. Other osteoclast activating factors such as IL-1 beta, lymphotoxin, TNF and IL-6 stimulate osteoclastogenesis in multiple myeloma and some cases of lymphoma. Tumor secretion of parathyroid hormone-related protein PTHrP also known as "humoral hypercalcemia of malignancy". PTHrP has some homology with PTH and binds to the same receptors as PTH thus increasing bone resorption as well as reabsorption of calcium in the distal tubules of the kidney along with inhibition of phosphate transport in the proximal tubules. This results in hypercalcemia and hypophosphatemia similar to hyperparathyroidism. Interestingly, increased calcitriol production is also responsible for hypercalcemia related to granulomatous diseases such as sarcoidosis and tuberculosis where the liver enzyme hydroxylase responsible for activating Vitamin D is upregulated. Finally, in rare instances, tumors such as ovarian carcinoma, lung carcinoma, or primitive neuroectodermal tumors can secrete ectopic PTH and cause hypercalcemia also known as "ectopic hyperparathyroidism". Are you sure your patient has Malignancy-Associated Hypercalcemia? Total and sometimes ionized calcium levels should be ordered to confirm presence of hypercalcemia and estimate severity of the disease. The mnemonic "moans, groans, stones, and bones with psychic overtones" describes the clinical manifestations of hypercalcemia. Abdominal pain and constipation, muscle or joint pains, boney pain, polyuria, nephrolithiasis, neuropsychiatric symptoms such as depression, headache, fatigue, confusion, cognitive dysfunction are a few of the clinical manifestations that can be present in patients with hypercalcemia depending on the severity and acuity of the disease. It occurs in both solid tumors and leukemias but is mostly associated with breast cancer, lung cancer, and multiple myeloma. Competing diagnoses that can mimic Malignancy-Associated Hypercalcemia. Hypercalcemia resulting from hyperparathyroidism, granulomatous disease, or excessive intake of vitamin D or calcium are other competing diagnoses which need to be ruled out. Mild elevations in calcium levels are usually asymptomatic. With moderate to severe hypercalcemia, especially if the calcium level rises rapidly, patients can present with altered mental status, confusion or even coma. Nonspecific abdominal pain or flank pain with radiation to groins concerning for kidney stones may be present. Proximal muscle weakness and pain on palpation or joint pain are other physical exam findings. Hyperreflexia and tongue fasciculation can also be present in hypercalcemia. Additionally, findings related to the underlying malignancy such as cachexia, lymphadenopathy, hepatomegaly, splenomegaly, and masses can be present. What diagnostic tests should be performed? Many patients presenting with malignancy-associated hypercalcemia have known underlying malignancy in which case further diagnostic testing is not always necessary. What laboratory studies if any should be ordered to help establish the diagnosis? How should the results be interpreted? Intact PTH is very helpful in diagnosing malignancy-associated hypercalcemia if inappropriately low. PTHrP can be obtained if malignancy is suspected. However, PTH is elevated or normal which in the majority of cases and is related to concomitant primary hyperparathyroidism, although ectopic PTH secretion is possible. If lymphoma or granulomatous diseases are suspected, then plasma 1,hydroxy vitamin D level can be obtained to establish the diagnosis of tumor production of calcitriol. What imaging studies if any should be ordered to help establish the diagnosis? Imaging studies are not diagnostic for hypercalcemia and are only useful in diagnosing any underlying malignancy associated with hypercalcemia. PTHrP is an over-utilized laboratory value which is usually obtained on presentation for further workup. Usually, the mechanism of hypercalcemia can be elucidated with obtaining PTH alone and PTHrP is useful only in the minority of cases where the mechanism

remains unknown after initial testing. ECG is often obtained with acute hypercalcemia in the inpatient setting and can be associated with some abnormalities such as QTc shortening and fist degree AV block. Occasionally, the ST segment can be depressed. Life-threatening cardiac arrhythmias secondary to hypercalcemia are unusual. Management of malignancy-associated hypercalcemia is usually guided by the severity of the hypercalcemia determined by the calcium level as well as presenting symptoms and laboratory findings. Generally, neurologic and renal complications of hypercalcemia increase with increasing severity of hypercalcemia. Mild hypercalcemia with calcium levels Medications associated with hypercalcemia such as lithium, thiazide diuretics, vitamin D and calcitriol if present should also be withheld. Treatment of moderate hypercalcemia with calcium levels Generally, intravascular volume repletion is sufficient in these patients to increase calciuresis and decrease calcium levels by increasing glomerular filtration rate and the filtered load of calcium as well as inhibiting reabsorption of calcium in the proximal tubules. If more severe symptoms are present, calcitonin can be used along with intravascular volume repletion to decrease calcium levels more rapidly. Loop-diuretics can be used in certain instances after complete intravascular volume repletion in order to increase calciuresis or when saline infusion is limited by renal failure or heart failure; however, their use has fallen out of favor given potential for intravascular volume depletion and worsening of renal dysfunction and hypercalcemia. Bisphosphonate therapy which blocks osteoclastic bone resorption is the main and most effective long-term treatment of malignancy-associated hypercalcemia and is usually initiated in patients with mild to severe hypercalcemia on presentation. Glucocorticoids can be used in cases of hypercalcemia associated with calcitriol production. In severe and symptomatic hypercalcemia also known as "hypercalcemic crisis", immediate intravascular volume repletion with normal saline at a rate of ml per hour should be initiated and continued until patient is adequately volume resuscitated and has good urine output of ml per hour. Furosemide therapy can be used thereafter to increase calciuresis but is generally discouraged if patient can tolerate volume repletion. Often tachyphylaxis to the effects of calcitonin develops within 48 hours of initiation of therapy. Physical Examination Tips to Guide Management. Monitoring volume status is essential in guiding management of hypercalcemia with aggressive intravascular volume repletion. Jugular venous distention, lung exam, oxygen saturation, and urine output should be followed closely while administering IV saline to avoid volume excess. If patient fails to improve with successful treatment of hypercalcemia, brain imaging should be considered to rule out other intracranial process such as metastatic disease, CVA or intracranial bleed. Typically, calcium and phosphate levels as well renal function are followed to monitor response to therapy. Potential survival benefits had been reported with bisphosphonate use in breast cancer and multiple myeloma in the past but more recently evidence is developing for prolonged survival and symptom relief independent of type of malignancy or calcium levels prior to treatment. Management should focus on anti-neoplastic therapy when indicated or comfort care in patients with advanced disease. In the palliative care population, it seems reasonable to offer antihypercalcemic therapy with bisphosphonates if consistent with goals of palliative and comfort care. There appears to be a larger survival benefit with greater reduction of calcium levels after bisphosphonate treatment. Older patient age and history of recurrent episodes of hypercalcemia seem to be associated with less response and worse outcome. Common Pitfalls and Side-Effects of Management. Inadequate intravascular volume repletion. Administration of loop diuretics such as furosemide before adequate volume repletion can lead to worsening renal function and hypercalcemia. Volume overload with aggressive IV saline administration especially with patients with renal dysfunction or cardiovascular disease. If indicated and consistent with goals of care, dialysis to remove calcium should be entertained in patients with a glomerular filtration rate of less than ml per minute. No change in standard management. Systolic and Diastolic Heart Failure. Again, rate and volume of intravascular saline infusion may be limited by volume overload. In these cases, consider concomitant administration of loop diuretics if necessary. In severe cases, dialysis may be necessary to remove calcium if patient is hemodynamically stable. Diabetes or other Endocrine issues. Monitor closely for hypoglycemia or hyperglycemia in patients with decreased oral intake in setting of mental status changes resulting from hypercalcemia. Antihyperglycemic agents will likely need to be held, especially metformin and sulfonylureas in setting of renal insufficiency possibly resulting from hypercalcemia. Insulin doses will need to be decreased as well to avoid prolonged

hypoglycemia with decreased renal clearance of insulin. Hyperglycemic side effects should be anticipated and managed accordingly if use of glucocorticoids is considered for the treatment of hypercalcemia. Consider use of glucocorticoids in certain malignancies such as lymphomas associated with tumor production of calcitriol. Otherwise, no change in standard management. Immunosuppression HIV, chronic steroids, etc. No change in standard management unless patient has cor pulmonale secondary to severe pulmonary hypertension resulting from pulmonary fibrosis. In this case, again aggressive and complete intravascular volume repletion may be challenging in setting of heart failure. Gastrointestinal or Nutrition Issues. Hematologic or Coagulation Issues. Patients may be more prone to developing neuropsychiatric symptoms of hypercalcemia and may require treatment with lower calcium levels. Also, potential use of concomitant medications such as lithium which can exacerbate hypercalcemia and sedating medications which can alter mental status may complicate the clinical picture. Sign-out considerations While Hospitalized. Aspiration and fall precautions in setting of altered mental status, continue NPO status until improved. Monitor volume status closely while on IV fluids, consider furosemide or discontinuation of saline infusion if patient develops shortness of breath, orthopnea, or hypoxia. Clear sign-out of CODE status and resuscitation orders in case of cardiopulmonary arrest. Anticipated Length of Stay. Anticipate days of hospitalization depending on severity of hyperglycemia and symptoms. With new malignancy diagnosis, the length of stay may be longer for staging, oncology consultation, and initiation of anti-neoplastic therapy. When is the Patient Ready for Discharge. Resolution of symptoms and decrease in calcium level with trend towards improved renal function are goals of hospitalization. Patient should be ready for discharge after discontinuation of IV saline with decreasing calcium levels and normalization of mental status. Arranging for Clinic Follow-up. Depending on goals of therapy, patient should either have oncology or primary care clinic follow up. If not enrolled in hospice prior to admission, consider hospice referral on discharge. When should clinic follow up be arranged and with whom.

HYPERCALCEMIA ASSOCIATED WITH MALIGNANCY pdf

7: Hypercalcemia - Symptoms and causes - Mayo Clinic

Hypercalcemia Associated with Cancer BASIC INFORMATION Description Certain cancers may cause calcium levels in the blood to become elevated (hypercalcemia). When.

The consequences of abnormally high serum calcium can range from asymptomatic to life-threatening. In addition, excessively high serum calcium causes clinical manifestations that affect the neuromuscular, gastrointestinal, renal, skeletal, and cardiovascular systems. Because some tumor cells can resorb or destroy bone tissue, hypercalcemia of malignancy develops more rapidly and more aggressively than hypercalcemia related to other conditions, and includes the classic symptoms of dehydration, anorexia, nausea, vomiting, constipation, confusion, and polyuria. In multiple myeloma, for example, malignant myeloma cells secrete a cytokine-interleukinthat activates osteoclasts in the vicinity of the myeloma cells, leading to bone resorption. Hypercalcemia is a common complication of various types of cancer, including squamous-cell carcinoma, multiple myeloma, T-cell lymphoma, and breast carcinoma. Epidemiology and Etiology The most common causes of hypercalcemia in the United States are primary hyperparathyroidism and malignancy. Many cancer cells secrete parathyroid-hormone-related protein PTHrP , which binds to the parathyroid receptors in bone and renal tissues, resulting in increased bone resorption and renal tubular reabsorption. Local osteolytic hypercalcemia is typically associated with breast cancer, multiple myeloma, and lymphoma. The normal range for total serum calcium is 8. The severity of hypercalcemia is classified into 3 categories based on the level of total serum calcium Figure. Patients with mild hypercalcemia, defined as total serum calcium of The mnemonic "stones, bones, abdominal moans, and psychic groans" represents the constellation of symptoms and signs of hypercalcemia. The clinical manifestations of hypercalcemia can involve many body systems. Central nervous system effects include lethargy, impaired concentration, fatigue, and muscle weakness. Renal effects include dehydration, polyuria, nephrolithiasis resulting from hypercalciuria, nephrogenic diabetic insipidus, and nephrocalcinosis. Gastrointestinal symptoms include nausea, vomiting, anorexia, weight loss, constipation, abdominal pain, pancreatitis, and peptic ulcer disease. Cardiovascular effects include hypertension, shortened QT interval, cardiac arrhythmia, and vascular calcification. Other symptoms include bone pain, arthritis, and osteoporosis. Treatment Options This section addresses treatment options for hypercalcemia, including dose, frequency, and titration parameters; expected effects and anticipated time to resolution; special or target populations for specific therapies; and side effects and their management. The optimal therapy for hypercalcemia of malignancy varies according to the severity of hypercalcemia and the underlying causes. Hypercalcemia related to malignancy may resolve with definitive antitumor therapy directed at the underlying cancer, such as surgery or chemotherapy. Withholding antihypercalcemic therapy may result in a life-threatening emergency such as coma and death. Asymptomatic patients with mild hypercalcemia serum calcium level, Calcitriol-mediated hypercalcemia is treated with intravenous glucocorticoid therapy plus limitation of calcium intake to inhibit vitamin D conversion to calcitriol. Hydration with Normal Saline Followed by Low-Dose Furosemide Most patients with hypercalcemia associated with malignancy are dehydrated as a result of renal dysfunction induced by hypercalcemia and by decreased oral fluid intake resulting from nausea and vomiting. Therefore, the cornerstone of initial treatment of hypercalcemia in these patients is volume expansion with intravenous normal saline to increase the glomerular filtration rate and renal calcium excretion. However, aggressive hydration can exacerbate heart failure in elderly patients; thus, the use of hydration is limited in patients with congestive heart failure. Furosemide blocks calcium reabsorption in the loop of Henle and increases urine output, which may necessitate increased saline administration, inducing further renal excretion of calcium. The maximum effect generally occurs within 4 to 7 days after initiation of therapy. Denosumab binds to RANKL soluble protein essential for the formation, function, and survival of osteoclasts and inhibits osteoclast activity, resulting in decreased skeletal-related events and tumor-induced bone destruction. This agent decreases serum calcium by inhibiting osteoclast activity. Because of the requirement for continuous intravenous infusion, gallium nitrate is not used frequently. However, mithramycin is not often recommended for patients with malignancy-related

hypercalcemia because of dose-related adverse effects such as nausea, vomiting, stomatitis, thrombocytopenia, renal symptoms, and hepatotoxicity. It is currently not being manufactured in the United States. Conclusion Hypercalcemia is a common complication of cancer. Hydration is key, and bisphosphonates are the most popular first-line agents. Denosumab, although expensive, is a valid option for patients with renal impairment. Hypercalcemia of malignancy is a severe complication of cancer that should be treated quickly and appropriately. Author Disclosure Statement The authors have no conflicts of interest to report. A practical approach to hypercalcemia. Hypercalcemia associated with cancer. N Engl J Med. Aredia pamidronate sodium [package insert]. Novartis Pharmaceuticals Corp; Zometa zoledronic acid [package insert]. Miacalcic salcatonin [package insert]. Gallium nitrate; [cited Aug 21]. Denosumab in hypercalcemia of malignancy: J Oncol Pharm Pract. Denosumab should be the treatment of choice for bisphosphonate refractory hypercalcaemia of malignancy. Prolia denosumab [package insert].

8: Malignancy-associated hypercalcemia - The Clinical Advisor

Malignancy is associated with hypercalcemia in 20% to 30% of cases, and represents the most common etiology of hypercalcemia in the inpatient setting.

9: BMJ Best Practice

Hypercalcemia is when a person has a higher than usual level of calcium in the blood. About 10% to 20% of people with cancer develop hypercalcemia.

HYPERCALCEMIA ASSOCIATED WITH MALIGNANCY pdf

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