Cancer-induced Hypercalcemia

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Abstract. Cancer-induced hypercalcemia (CIH) occurs in 5% to 30% of patients with cancer during the course of their disease, depending on the type of tumor. This review provides information on the pathophysiology and treatment of CIH. Enhanced bone resorption is the primary cause of CIH and the release of tumor-derived mediators induces this increase in osteoclast-mediated resorption. The interactions between osteoclasts and cancer cells are mainly mediated by parathyroid hormone-related protein (PTHrP), that activates osteoblasts to produce receptor activator of nuclear factor-κ ligand (RANKL) and osteoclast precursors, with subsequent bone osteolysis. Low parathyroid hormone serum levels together with high calcium levels in a cancer patient may suggest a CIH. There are two different therapeutic approaches for treating CIH, to increase the urinary excretion of calcium, or to inhibit osteoclastic bone resorption, RANKL or the action of PTHrP. In patients with CIH the first step of therapy is usually to restore renal function which is often impaired due to dehydration. Bisphosphonates administration is at present the mainstay of treatment, while calcitonin, gallium nitrate and mithramycin have limited activity and several side-effects. Anti-RANKL therapy (denosumab) and antibiotics against PTHrP are promising therapies, but their clinical use should be further explored to more clearly document the effects.

In 1941 Albright first proposed the term humoral hypercalcemia in patients with cancer and hypothesized that mechanisms different from direct bone resorption by tumor cells may cause such a complication (1). Cancer-induced hypercalcemia (CIH) occurs in 5% to 30% of patients with cancer during the course of their disease, depending on the type of tumor (2). CIH represents the most common paraneoplastic syndrome, with an incidence of 15 cases per 100,000 people per year (3, 4). Lung cancer, breast cancer and myeloma have the highest incidence of CIH, accounting for more than 50%, while the disease occurs rarely in patients with colorectal and prostate cancer (3). Except in patients with multiple myeloma and breast cancer, the prognosis of the cancer patients with CIH is usually poor, with a mean survival rate of 2-3 months (5). More than 30% of patients with multiple myeloma, 25% of those with squamous cell carcinoma and 20% of those with breast cancer may develop CIH (4). Enhanced bone resorption is the primary cause of hypercalcemia of malignancy and the release of tumor-derived mediators induces this increase in osteoclast-mediated resorption (4, 5). The mechanisms of osteoclast-mediated resorption are humoral effects of systemically elevated tumor-derived factors and local (autocrine or paracrine) effects of factors produced by the tumor cells metastasized to bone (i.e. direct bone resorption by lytic metastases), inducing osteolysis. Both normal and malignant bone and hemopoietic marrow cells interact together with a complex network of agents (i.e. interleukins [IL-1, IL-6], tumor necrosis factor alpha [TNF-α]), enhanced cancer growth and osteoclast activation as the ultimate outcome (2, 6).

Parathyroid Hormone-related Protein

Overall, about 80% of patients with CIH may have increased parathyroid hormone-related protein (PTHrP) serum levels. Other calcitropic hormones can also cause CIH, including parathyroid hormone (PTH) and 1-25(OH)2 vitamin D3 secreted by neuroendocrine tumors and increased 1α-hydroxilase activity in lymphoproliferative disorders, respectively (2, 4, 5). PTHrP is a distinct gene product with sequence homology to PTH only in a limited
domain at the amino-terminal end of the molecule (5). Both produce humoral hypercalcemia by increasing the resorption of bone throughout the skeleton and the renal resorption of calcium (7). However, PTH stimulates bone resorption and formation, while PTHrP stimulates only osteoclasts, showing a very low osteoblastic activity (7, 8). The best established role of PTHrP is to stimulate the proliferation of chondrocytes and suppresses their terminal differentiation (Figure 1). Interactions between osteoclasts and cancer cells are mainly mediated by PTHrP, that activates osteoblasts to produce receptor activator of nuclear factor-κ ligand (RANKL). RANKL activates osteoclast precursors and subsequent bone osteolysis, leading to the release of several bone-derived growth factors, including insulin-like growth factor (IGF1) and transforming growth factor-β (TGF-β), and raises extracellular ionised calcium concentrations, with subsequent activation of a Ca++ pump (10). The growth factors bind to receptors on the tumor cells’ surface and activate both cytoplasmic mediators of TGF-β and mitogen-activated protein kinase (MAPK). Signalling through this pathway promotes both cancer cell proliferation and PTHrP production, with subsequent increased calcium reabsorption (Figure 2).

Diagnosis and Treatment of Cancer-induced Hypercalcemia

Low PTH serum levels together with high calcium levels in a cancer patient suggest CIH. True ectopic secretion of PTH is rare and less than 5% of patients may have primary hyperparathyroidism (PHPT) together with CIH (11). Very high serum calcium levels are observed in patients with parathyroid cancer, but also the PTH levels are usually elevated (12). Unfortunately, the preoperative diagnosis of parathyroid cancer is difficult, because no sensitive tumor markers are available, although its localization is easy (13, 14). In patients with calcium concentrations over 3 mmol/L anorexia, nausea, polyuria, thirst and vomiting may be observed, while with serum calcium values above 4 mmol/L impairment of the conscious level usually occurs (15). Three different causes of hypercalcemia should be considered: PHPT, CIH and everything else (Table I). There are two different therapeutic approaches for treating CIH, to increase the urinary excretion of calcium, or to inhibit osteoclastic bone resorption, RANK ligand or the action of PTHrP (17).

The first step of management of hypercalcemia should be to assess the hydration state and saline infusion is currently the standard of treatment, depending upon the severity of dehydration. However, if employed alone, volume expansion is ineffective in restoring normocalcemia because rehydration does not interfere with osteoclastic function. Loop diuretics (i.e. furosemide) enhance calcium excretion only after normovolemia has been reached (18). Bisphosphonates (BP) represent at present the drugs of choice for treating patients with CIH. They inhibit osteoclasts, induce apoptosis in these cells and bind to bone, blocking osteoclastic resorption and osteolysis (19, 20). Once inside osteoclasts, BPs hamper
of RNA synthesis, but it is less effective and convenient for osteoclasts and inhibits bone resorption through the blocking Mithramycin is a cytotoxic antibiotic that has tropism for the still be used for salvage treatment of refractory patients. considered of second choice, although some of them may reductions are needed (28, 33). Other drugs are now concomitant nephrotoxic therapies and no dose patients with moderate renal impairment or those treated with teeth extractions or other invasive interventions on the jaw or maxilla bone (24). The first BPs etidronate and clodronate are now rarely used to treat CIH due to the availability of more potent compounds (25, 26). Pamidronate is able to normalize calcium levels in 80% to 100% of patients and the infusion time of 2-4 hours does not show a significant increment of nephrotoxicity (18). Randomized trials have proved that pamidronate is superior to clodronate, etidronate and mithramycin (26, 27). Zoledronate is a third-generation BP and can be administered in a dose 10 times lower than pamidronate (28, 29). It has been shown to be superior to pamidronate in the rate of normocalcemia, duration of control of CIH and time to relapse, therefore 4 mg zoledronate is the reference treatment for initial management of CIH, while higher doses can be used in relapsing or refractory patients (30). Its use is contraindicated if creatinine clearance is below 30 ml/min and/or if other nephrotoxic drugs are administered to the patient (28, 31). Ibandronate is especially useful in patients with breast or hematological cancer (18). A randomized trial comparing ibandronate and pamidronate showed a comparable activity of the two drugs in reducing calcium levels, while the median duration of response appeared to be longer for ibandronate (32). This drug has an extremely low rate of nephrotoxicity and represents the compound of choice for patients with moderate renal impairment or those treated with concomitant nephrotoxic therapies and no dose reductions are needed (28, 33). Other drugs are now considered of second choice, although some of them may still be used for salvage treatment of refractory patients. Mithramycin is a cytotoxic antibiotic that has tropism for the osteoclasts and inhibits bone resorption through the blocking of RNA synthesis, but it is less effective and convenient for patients compared to pamidronate (4, 27). Gallium nitrate may reduce solubilization of hydroxyapatite and tubular renal resorption, but does not inhibit the development or recruitment of osteoclasts and thus can be considered for the management of patients with CIH refractory to BP (34-36). Calcitonin may inhibit osteoclastic bone resorption and enhance renal excretion of calcium (25). Unfortunately, tachyphylaxis of receptors occurs frequently and it should be used only in selected cases, in combination with corticosteroids for patients with kidney failure (4, 37). The RANKL system is the central pathway leading to osteoclast differentiation and activation, and currently represents the most promising target for the treatment of CIH (4, 38, 39). An abnormal activation of RANKL (previously known also as osteoclastic differentiation factor [ODF]) is induced by circulating PTHrP or cytokines (i.e. IL-1, IL-6, TNF-α and TGF-[β] secreted locally by metastatic cells (39, 40). Osteoprotegerin (OPG), a protein of the TNF family, specifically binds to RANKL and therefore prevents differentiation of osteoclasts and promotes their apoptosis, blocking bone resorption by depletion of mature osteoclasts (21, 41, 42). OPG has induced a more rapid effect on bone resorption compared to BPs in experimental models of PTHrP-dependent CIH (42). The human monoclonal antibody named denosumab is another agent able to interfere with RANKL-RANK pathways. This agent, when administered to postmenopausal osteoporotic women, showed a rapid and sustained dose-dependent decrease of bone turnover (41-43). It was able to induce an early and sustained decrease of bone resorption in patients with bone localizations of multiple myeloma or breast cancer, but unfortunately the role of denosumab in the management of CIH has not yet been confirmed (29). Another attractive strategy consists in the development of antibodies directed against human PTHrP. A humanized anti-PTHrP antibody was tested in animal models of CIH and was found to be able to improve bone metabolism and calcium renal excretion, achieving a complete normalization of calcium levels (44, 45). It could be particularly interesting for subjects experiencing BP-refractory CIH (45). In conclusion, in patients with CIH the first step of therapy is usually to restore renal function which is often impaired due to
dehydration. Enhanced bone resorption represents the main cause of hypercalcemia and thus the second step is BP administration. Pamidronate, zoledronate and ibandronate are at present the main-stay of treatment. Non-BP drugs have limited activity and several side-effects. Anti-RANKL therapy and antibodies against PTHrP are promising therapies, but their clinical use should be further explored to more clearly document the effects.

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References


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