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Perspectives and Commentaries

Cancer Hypercalcemia: Recent Advances in Understanding and Treatment

JEAN-JACQUES BODY

Service de Médecine et Laboratoire d'Investigation Clinique H. Tagnon, Institut Jules Bordet, Centre des Tumeurs de l'Université Libre de Bruxelles, 1, rue Héger-Bordet, 1000 Bruxelles, Belgium

HYPERCALCEMIA is not a rare complication of cancer: about 10% of cancer patients develop hypercalcemia [1], and cancer is the most frequent cause of hypercalcemia in hospitalized patients [2]. It is generally a sign of advanced disease, but not necessarily a sign of terminal disease: according to a recent study, two-thirds of the patients will survive for more than 1 yr if they receive adequate treatment [3]. I wish to briefly review here the major progress that has recently been accomplished in the understanding and in the treatment of cancer hypercalcemia.

Development of hypercalcemia in the setting of a malignancy is due to an increase in bone resorption that is not followed by a similar increase in bone formation, as is the case for other diseases characterized by an augmented bone resorptive activity, such as Paget's disease of bone. This 'uncoupling' between bone formation and bone resorption has been confirmed by modern histomorphometric techniques [4]. Other sources of calcium than bone are much less important in the pathogenesis of cancer hypercalcemia. Isotopic studies suggest that intestinal calcium absorption is decreased in hypercalcemic cancer patients [5], and the concentration of the active vitamin D metabolite that stimulates intestinal calcium absorption is also lowered [6]. Thus the gut is not the source of the increased calcium load, although this concept has recently been challenged by the demonstration in an animal tumor model that hypercalcemia was dependent on the dietary calcium intake [7]. Renal calcium reabsorption is also decreased in hypercalcemia accompanying bone metastases [8]; so the kidney is also not the cause of hypercalcemia, at least as long as the renal function is normal and the increased calcium load from bone can be excreted. But any decrease in glomerular filtration rate—induced by dehydration, vomiting, nephrotoxic drugs, etc.—can precipitate hypercalcemia by increasing tubular reabsorption of sodium, and thus of calcium. Hypercalcemia itself will then result in a fall in the glomerular filtration rate and create a vicious spiral.

Classically, cancer hypercalcemia is attributed either to bone destruction by metastases or to a paraneoplastic secretion of an osteolytic substance (the 'humoral type' of cancer-associated hypercalcemia). This separation is supported by recent biochemical data: Stewart *et al.* have observed in the humoral type only an increase in urinary cyclic AMP (adenylate cyclase-stimulating activity), and a decrease in serum phosphorus due to a reduced renal threshold [6]. These characteristics are common to primary hyperparathyroidism and could thus justify the use of the old term of 'pseudohyperparathyroidism' to describe the syndrome of paraneoplastic hypercalcemia. These patients even have a circulating substance that is active in parathyroid hormone (PTH) bioassays and it very probably binds to PTH receptors [9, 10]. Nevertheless, it is now almost certain that authentic PTH is not the mediator of paraneoplastic hypercalcemia: the substance in question has a different molecular weight [10] and is not recognized by various PTH antisera [6], and the PTH messenger RNA has not been found in tumor extracts from these patients or from the animal models [11].

Circulating prostaglandins are also not the cause of paraneoplastic hypercalcemia, except perhaps for some rare individual cases [12]. The

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increased urinary excretion of prostaglandins found in some patients [13] could be a consequence rather than a cause of bone destruction [14]. It is, however, probable that prostaglandins have a key role in the local stimulation of bone resorption: for example, inhibitors of their synthesis are able to block tumor-stimulated bone resorption *in vitro* [15]. The role of prostaglandins is nevertheless far from clear, and the recent demonstration of their potential bone formation-stimulating activity adds a new dimension to the action of this important type of mediator [16]. Osteoclast-activating factor is another candidate. It is a lymphokine produced by stimulated peripheral lymphocytes, and by malignant myeloma and lymphoma cells; it is a potent stimulator of bone resorption, but so far has only been implicated in hematological malignancies [17].

So, what is (are) the substance(s) responsible for the humoral hypercalcemia accompanying solid tumors? It still remains "a syndrome in search of a hormone" [18], but major progress is to be expected in the near future. The adenylate cyclase-stimulating activity reported above has now been extracted from various tumors, and this property should help in the isolation of the substance(s) at cause [19]. On the other hand, attention is also focusing on a new class of substances, transforming growth factors. Some of these factors can produce osteolysis *in vitro* [20] and potentiate the osteolytic activity of osteoclast precursors [21], and a tumor-derived growth factor has been implicated in the genesis of hypercalcemia in an animal tumor model [22]. The relation of such tumor growth factors to the adenylate cyclase-stimulating activity is unknown.

If the substance responsible for the humoral type of cancer hypercalcemia is still unknown, the mechanism of hypercalcemia in the case of bone metastases is no better understood. It is naive to believe that there is just a mechanical or ischemic destruction of bone produced by the metastasis. Cancer cells can probably resorb bone [23], but the real problem lies in the activation of normal bone-resorbing cells, the osteoclasts [24]. Such an activation could be mediated locally, or even at a distance, by a substance released by the cancer cells. Very little is known about this or these substance(s), but it is not impossible that both types of cancer hypercalcemia—due to bone metastases or of the 'humoral type'—share the same pathogenetic factor(s), acting either locally or systemically.

Treatment of cancer hypercalcemia has remained unchanged in clinical practice for several years, but will undoubtedly undergo major changes in the near future.

Several drugs more or less toxic can be successfully used to temporarily control hypercalcemia in the cancer patient, but the only current way of obtaining long-term control of serum calcium is to significantly reduce the tumor burden. This can be especially important in chemotherapy-sensitive tumors such as lymphomas, where appropriate antineoplastic treatment will frequently normalize serum calcium.

Rehydration should be part of the initial treatment, since hypercalcemia is almost always associated with hypovolemia, which leads to a further increase in serum calcium and is in itself responsible for some of the symptoms of hypercalcemia. One common mistake is to give a loop diuretic, such as furosemide, before rehydration is completed; it will further deplete the extracellular fluid volume and aggravate the hypercalcemia. Three or four liters of saline a day will reduce serum calcium in a majority of moderately hypercalcemic patients, but normocalcemia will rarely be obtained and the increased calcium load from bone is, of course, maintained [25, 26]. Forced saline diuresis (more than 10 l/day with considerable doses of furosemide) [27] is no longer recommended: it is difficult, dangerous and frequently ineffective.

Corticosteroids are frequently used by clinicians, even though their reported efficacy varies considerably [28, 29]. The most consistent results have been obtained in lymphomas, myelomas, and less in breast cancer; in these tumors, steroids can have a direct antineoplastic effect and could also inhibit the action of osteoclast-activating factor, which is produced by malignant hematological cells [17]. Calcitonin is another therapeutic weapon. It is a non-toxic drug that acts very rapidly. Therefore it is an excellent emergency treatment, especially when there is cardiac or renal insufficiency; doses recommended vary from 4 to 8 U/kg, 2–4 times a day [30]. Combining corticoids with calcitonin has been reported to permit a much prolonged effect by preventing the escape phenomenon to calcitonin [31].

There is no longer much place for therapeutic measures such as low-calcium diet, mithramycin, indomethacin, chelating agents or intravenous phosphates. Intestinal calcium absorption is already lowered in hypercalcemic cancer patients [5, 6], and a low-calcium diet will just reduce the quality of the food intake. Mithramycin is a toxic drug, acts relatively slowly, and is contraindicated when renal function is altered; one injection (15–25 μg/kg) can, however, be helpful in some acute situations and, as such, has been successfully and safely used [32]. Inhibitors of prostaglandin synthesis, such as indomethacin or aspirin, are too rarely effective to be recom-

mended. Intravenous phosphates can lead to serious damage by causing extraskeletal precipitation; they must be used very cautiously and only when serum phosphate is low. However, oral phosphate remains a good treatment for chronic moderate hypercalcemia [33].

There are surprisingly very few comparative studies between all these therapeutic possibilities, and none are valid enough to permit strong recommendations. It is, however, doubtful that many will ever be done because of the recent introduction of diphosphonates in the therapeutic armamentarium.

Diphosphonates (also called biphosphonates) are new and promising agents that can block bone resorption very efficiently. Their mechanism of action is not completely elucidated: in addition to their well-known stabilizing effect on the hydroxyapatite crystal, they have also intracellular effects on bone resorbing cells or on their precursors [34]. The only commercially available diphosphonate, 1-hydroxyethylidene-1,1-diphosphonate (EHDP), is unfortunately the least potent; moreover, it inhibits the mineralization of newly formed bone, and high doses or prolonged treatment can lead to osteomalacia. Used intravenously, it has nevertheless permitted interesting results in cancer hypercalcemia [35]. Dichloromethylidene disphosphonate (Cl_2MDP) acts faster than EHDP [35], does not cause osteomalacia and several well-controlled studies have demonstrated a remarkable efficiency [35–37]. However, Cl_2MDP has been withdrawn from clinical trials, at least temporarily, because of concern about a possible leukemogenic effect in Paget's disease of bone. Lastly, 3-amino-1-hydroxypropylidene-1,1-diphosphonate (APD) has only been investigated in Europe, although it seems to be the most potent and probably the least toxic of the current diphosphonates. APD normalized serum calcium in 16 of 19 hypercalcemic cancer patients when used orally [8] and in 29 of 30 when used intravenously [26]. The results obtained with the intravenous route are particularly impressive: normocalcemia is reached after a few days, no toxic effect is apparent, a prolonged action is possible and accompanying biologic abnormalities such as hypomagnesemia and reduced glomerular filtration rate are also improved [26]. A multicenter trial is currently underway using intravenous APD in cancer hypercalcemia. When commercialized, this diphosphonate or a newly developed analog [38] will undoubtedly improve and simplify the management of hypercalcemia. Moreover, diphosphonates also seem to have the capacity of slowing or even preventing the development of osteolytic bone metastases [39]; this potential major advance in oncology is currently under active investigation.

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