Soluble molecules and bone metabolism in multiple myeloma: a review

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Summary

Bone metabolism and turnover are strongly altered in multiple myeloma, as a consequence of the proliferation of malignant cells resembling plasmacells in the bone marrow. By both direct or indirect secretion of several molecules, and cell-to-cell interactions, multiple myeloma cells lead to severe and disabling skeletal alterations, such as osteolytic lesions, pathologic fractures, and osteoporosis. In this review, we summarize the studies concerning the soluble molecules which are supposed to have a role in this pathological process. We then consider the substances that, either in serum or urine specimens, can be dosed in the affected patients, thus giving an indirect measure of their altered bone turnover. In the last part of our review, we discuss the potential action of the new anti-myeloma drug bortezomib (Velcade®, Janssen-Cilag), in opposing and maybe reverting, through a possible direct "pro-osteoblastic" effect, the deranged bone turnover which characterizes this disabling and unavoidably deathly disease.

KEY WORDS: multiple myeloma, bone, turnover, soluble, bortezomib.

Introduction

Multiple myeloma (MM) is a haematological neoplasia whose hallmark is an abnormal proliferation of monoclonal cells resembling mature plasmacells inside the bone marrow (1). MM is characterized by skeletal alterations, such as bone pain, osteolytic lesions, pathologic fractures, and hypercalcemia (1-3). Up to 80% of the patients experience these complications sooner or later during the course of their disease (2). In patients affected by MM, osteoclastic activity enhancement (4-6), paralleled by diminished osteoblastic function (6, 8, 9, 12, 15, 17-27), results in bone tissue rarefaction. This pathologic process brings to focal osteolysis (the so-called "punched-out lesions") and to bone architecture generalized impoverishment, namely, osteoporosis. Bone turnover is strongly altered in patients affected by MM. This phenomenon appears to be related to both direct secretion of substances by MM cells and the alterations which occur in the microenvironment surrounding them, following direct cell-to-cell interactions between malignant cells and stromal ones. In these last few years research efforts have been focused on the molecules acting in MM (4, 5, 7-11, 13, 17, 18, 21-25, 28-38), and on their effects towards blocking osteoblastic activity and enhancing osteoclast mediated bone resorption. Many of the investigated substances can also be measured in urine or serum samples of the patients diagnosed with MM, along with bone turnover molecular by-products, and could prove to be useful markers for prognosis and response to treatment (28, 39-52). So far, traditional agents targeting MM cells were not able to restore normal bone turnover, as they possess, with the possible exception of the immunomodulatory drugs (IMiDs, thalidomide and lenalidomide (Revlimid®, Celgene), a mainly cytolytic activity. Bisphosphonates have represented a step forward in preventing MM bone complications, but this drug class does not enhance bone regeneration. The first therapeutic molecule which could have direct "pro-osteoblastic" properties is the proteasome inhibitor bortezomib (Velcade®, Janssen-Cilag) (53-61). This review will summarize the major advances in understanding the molecular bases of the deranged bone turnover which characterizes MM, with particular attention on the studies concerning the role of soluble molecules in bone metabolism, and their possible role in clinical practice. The potential of bortezomib to act on MM deranged bone turnover will also be discussed.

Bone turnover in multiple myeloma

The pathogenesis of MM bone disease is complex: it encompasses both increased osteoclastic activation mechanisms, and impaired osteoblastic function ones, thus leading to a sort of "uncoupling" of the physiologic osteonic functional unit (6, 12, 14, 16, 62). The bone marrow microenviroment surrounding MM cells is made up of cells like fibroblasts, osteoblasts, osteoclastic precursors, mature osteoclasts and endothelial cells. Direct secretion of cytokines and other substances by MM cells, and cell-to-cell interactions between neoplastic cells and the surrounding environment, induce a distorted production of osteoclast activating factors (OAFs). Amongst the most investigated ones, there are molecules like Interleukin (Il)-1, Il-3, Il-6, Il-7, Il-11, Tumour Necrosis Factor (TNF)-α, Macrophage Colony-Stimulating Factor (MCSF), PTH-related Peptide (PTHrP), Hepatocyte Growth Factor (HGF), Macrophage Inflammatory Protein (MIP)-1α, MIP-1β and Matrix Metalloproteinases (MMPs) (4, 5, 11, 18, 31, 63). These factors are deemed to concur in raising the production of a major osteoclastogenic factor, called receptor activator of NF-kB ligand (RANKL) (7), by both neoplastic and "by-stander" stromal cells. Normally, RANKL and its "decoy" soluble receptor, Osteoprotegerin (OPG), keep under control bone resorption (15), positively (RANKL) or negatively (OPG) regulating the growth and activity of osteoclasts. MM cells break the balance between RANKL and OPG in favour of the first molecule (9, 10, 34, 50), possibly with a direct contribution to its secretion (13) and to the degradation of OPG (34). As a consequence, MM cells enhance the development, maturation and activity of the osteoclasts, with a net increase in bone resorption (9, 10, 32, 35, 36).
On the other hand, both *in vitro* and *ex vivo* studies showed

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that, inside the bone milieu, MM cells act by decreasing the number, activity and viability of osteoblasts, and by inducing their apoptosis, *via* both direct interaction with these cells and by secreting a number of inhibiting soluble factors (6, 17, 19, 20, 23, 26). Among the various molecular networks involved, the inhibition of the Wingless-type (Wnt) signalling pathway seems to play an important role in blocking osteoblastic survival and differentiation (64). This event may occur through the abnormal secretion, by MM cells, of molecules such as Dickkopf (Dkk)-1 (21, 38) and Soluble Frizzle-Related Protein (sFRP)-2 (25), which behave as Wnt pathway inhibitors. Other soluble factors, like Il-7 and Il-3, were correlated, *in vitro*, with osteoblastic differentiation arrest (17, 24), even though experimental evidences about the occurrence of this phenomenon *in vivo* are still lacking.

Clinical expressions of altered bone turnover

In serum or urine samples many substances, directly or indirectly related to bone metabolism, can be quantified and are altered in MM. For the sake of simplicity, and far from being exhaustive (since the number of discovered molecules in this field is growing steadily), they can be classified and listed in four broad groups, as follows:

1. Osteoclastic activity markers: serum Tartrate Resistant Acid Phosphatase (TRAP)-5b (65), urinary or seric bone collagen degradation products, like total Pyridinoline (T-Pyd), Deoxypyridinoline (T-Dpd), cross linked N-telopeptide (Ntx), C-telopeptide (Ctx) of type I collagen and immunologic free Deoxypyridinoline (f-Dpd) (49), measurable in urinary samples, or C-terminal and N-terminal Telopeptides of type I collagen (S-CTX and S-NTX) and bone sialoprotein, which can be assessed in serum specimens (thus circumventing some of the limitations of urinary measurements) (41).
2. Osteoblastic activity markers: Osteocalcin (OC) (48), bone Alkaline Phosphatase (bALP), Bone Morphogenetic Protein (BMP)-2, which can be dosed in serum (30).
3. Molecules with inhibitory activity towards osteoblasts, or whose decreased production ultimately results in impaired behaviour of osteoblasts: DKK-1 (21, 64), sFRP-2 (38), Il-3, Il-7 (23, 25), OPG reduced synthesis (these molecules can be measured in serum samples too) (9, 10, 33, 34, 50).
4. Molecules with stimulating and activating properties towards osteoclastic precursors and mature osteoclasts: Il-1, Il-3, Il-6, Il-11, TNFα, MCSF, PTHrP, HGF, MIP-1α, MIP-1β, MMPs, RANKL (serum samples) (4, 5, 11, 18, 31, 35, 37, 63).

Correlation between MM treatment and bone disease

During the last few years, many clinical studies assessed the levels of various parameters of bone turnover, as the ones summarized above, in patients with MM, finding the most of them to be considerably altered. Their levels were often found to correlate with activity, stage, or progression of MM (8, 28, 29, 36, 40, 42-45, 49, 51, 65-67), but so far none of them has entered validated prognostic scores. The described bone metabolism derangements provided the rational basis for treatment of MM bone disease with bisphosphonates (68, 69). These drugs act mainly by inhibiting osteoclasts (70), and possibly via a direct effect against MM cells (71, 72), but they are not efficacious in restoring osteoblastic activity. Moreover, the use of such agents is sometimes associated with severe complications, like acute systemic inflammatory reactions, ocular inflammation, renal failure, nephrotic syndrome, electrolyte imbalance, and jaw osteonecrosis (73), so it is not advisable, according to the available data, to prolong indefinitely therapy with bisphosphonates. Few clinical studies were published, which took into account different markers of bone resorption in MM patients treated with various chemotherapeutic regimens or with autologous stem cell transplantation. Some of them did indeed show a reduction in indirect osteoclast activity indexes, an amelioration of bone turnover markers, and modifications of some of the aforementioned OAFs after treatment (38, 39, 46, 74). However, no traditional drug employed in MM therapy has been linked with a direct activity on osteoblastic function so far. Among the signalling pathways, considered as target candidates of drugs in MM, the inhibition of degradation of ubiquitinized proteins with molecules like bortezomib (75), which acts by blocking the proteasome machinery, was found to be related, both in *in vitro* (17, 27, 53, 58, 76, 77), in murine models (57), and in *ex vivo* (27, 53, 57, 58) studies, with modifications of the osteonic balance in favour of osteoblastic activity. Bortezomib could also exert a direct stimulatory effect on osteoblasts (58), and an inhibitory one on osteoclasts (77). As expected result, the treatment with bortezomib should lead to a significant improvement of deranged bone turnover, indirectly measurable with biochemical parameters as the ones cited above. A few recent conducted studies have actually demonstrated that treatment with bortezomib not only results in lowering OAFs and osteoclast activity markers, but also in raising pro-osteoblastic soluble factors and osteoblast function serum markers (52, 54-57, 59, 78). These studies looked for various markers modifications in the course of regimens containing bortezomib, either alone or combined with other drugs (54, 55). Some of them were group-controlled: age matched healthy subjects (56) or patients treated with non-bortezomib-containing schemes (78). The results tend to confirm the "pro-osteoblastic" *in vitro* activity of bortezomib, even though a major pitfall of these studies is that they could not directly measure modifications in bone quality. In this regard, an exception is a clinical work by Giuliani et al. (58), in which osteoblasts and their precursors were found to be increased in number, as directly assessed in bone marrow biopsies obtained from patients that had undergone treatment with bortezomib.

Conclusions

MM has profound effects on bone metabolism. The very nature of this incurable disease leads to the severe and disabling bone complications that afflict MM patients. Apart from targeting MM cells directly, blocking bone destruction must be a major goal in therapy. Ideally, treatment should be aimed in eradicating neoplastic cells, but since this is almost impossible in most patients, restoring normal bone turnover would still be a step forward in treatment. Bisphosphonates have an important role in MM bone disease, but their activity is mainly directed towards blocking osteoclastic activity. These drugs do not enhance osteoblastic functions, which are impaired in MM. The discovery of bortezomib *in vitro* properties has prompted a great interest in research. However, *in vivo* evaluation of bortezomib "pro-osteoblastic" activity must take into account several difficulties, and raises many questions: first of all, which technique is the most suitable in the assessment of patients' "bone quality" before and after treatment with bortezomib? Dual Emission X-Ray Absorptiometry (DEXA) is the standard for measuring bone density in patients with osteoporosis, but it is not sensible enough to observe subtle density modifications during the few months of treatment with bortezomib. Moreover, sampling areas could be infiltrated by MM lesions, thus making DEXA not reliable for routinary use in patients affected by MM (46). New imaging technologies, like quantitative ultrasound, quantitative computed tomography, peripheral quantitative tomography, micro-computed tomography, and magnetic reso-

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nance (79) are neither widely available nor standardized yet. Direct count of osteoblasts and their precursors in biopsies obtained from the patients treated with bortezomib seems to be the most precise and reliable search performed so far (58). Another problem to be considered when planning studies aimed in assessing bone quality modifications before and after treatment with drugs like bortezomib is the choice of the patients to enroll: including patients that were already pre-treated with many drugs, or that did not receive similar doses of corticosteroids and bisphosphonates, introduces heavy biases in the study itself, and this could bear unreliable and not easily interpretable data. A last, but not less important doubt rises from the real importance of dosing some (but which ones?) of the newly discovered soluble factors involved in bone metabolism. Do they, and if so, which ones, really correlate with modifications of "bone quality"? May they have a value in the prognostic assessment or in the follow-up of patients affected by MM? In conclusion, many molecules have been recently found to be involved in normal and pathologic bone turnover, and to be altered in MM natural course and during treatment. It may be that new proteasome inhibitors like bortezomib retain a distinct activity in bone "reverse remodelling", not typical of other drug classes currently used in MM treatment. Further studies are needed to elucidate the usefulness of dosing bone metabolism soluble molecules in patients treated with this new drug, to clarify the molecular bases of bortezomib properties, and to assess the clinical impact of its supposed "pro-osteoblastic" action. Should this last assumption prove to be true *in vivo*, research will have to focus, in the near future, on the development of new bortezomib-like agents, targeted not only at blocking MM disease, but also at promoting the normalization of the deranged bone turnover, which is so dramatically altered in this severe and incurable neoplasia.

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