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REVIEW

The role of markers of bone remodeling in multiple myeloma

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Summary Osteolytic bone disease is a frequent complication of multiple myeloma, resulting in skeletal complications that are a significant cause of morbidity and mortality. A characteristic feature of myeloma bone disease is that the lesions rarely heal and bone scans are often negative in myeloma patients who have extensive lytic lesions, offering very little in the follow-up of bone disease. X-rays are also of limited value in monitoring bone destruction during anti-myeloma or anti-resorptive treatment. Biochemical markers of bone turnover, such as N- and C-terminal cross-linking telopeptide of type I collagen (NTX, CTX/ICTP, respectively), and newer ones such as the tartrate resistant acid phosphatase isoform 5b, provide information on bone dynamics that in turn may reflect disease activity in bone. Several studies have shown bone markers to be elevated in myeloma patients and reflect the extent of bone disease, while in some of them bone resorption markers correlate with survival. These markers may also be helpful in identifying those patients likely to respond to bisphosphonate treatment, and monitoring the effectiveness of bisphosphonate therapy in the management of myeloma bone disease. This review attempts to summarize the existing data for the role of markers of bone remodeling in assessing the extent of bone destruction in myeloma and monitoring bone turnover during specific anti-myeloma treatment. We also discuss some novel markers that may be of particular interest in the near future.

Introduction

Multiple Myeloma (MM) is a clonal plasma cell disorder characterized by bone destruction, immunodeficiency, and renal impairment. Nearly 3500 people in the UK are diagnosed with MM each year. This accounts for 10% of blood cancers and 1% of all cancers. More than 55% of patients who present with MM are aged 60 or older, while less than 3% of MM occurs in patients younger than 40 years; median survival ranges between 3.5 and 5 years.[1,2] A cure in MM appears to be achievable only by allogeneic transplantation, which is not the treatment of

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choice for the majority of patients due to high rate of transplant-related mortality.[3] A major clinical feature of MM is the presence of osteolytic bone disease and generalized osteoporosis, which can lead to severe bone pain, pathologic fractures, spinal cord compression, and hypercalcemia. Over 85% of myeloma patients have bone disease. It thus represents a major cause of morbidity and mortality.[4] Progression of skeletal disease is often not affected by chemotherapy even in responding patients.[5] The mechanisms of bone destruction appear to be related to increased osteoclastic bone resorption, which is not accompanied by a comparable increase in bone formation.[6] Thus, a characteristic feature of myeloma bone disease is that the lesions rarely heal even when the patients are in complete remission.[7] This finding is in keeping with the observation that bone scans are often negative in myeloma patients who have extensive lytic lesions, and offer very little in the follow-up of bone disease in these patients.[8] Furthermore, a recent study has shown that sequential measurement of bone mineral density (BMD) using DEXA-scans produced heterogeneous local BMD changes and the available data do not support routine use of sequential DEXA-scans in MM.[9] The bone disease in MM is usually assessed by X-rays of the skeleton. X-rays are useful in the diagnosis of osteolytic lesions, but do not give any dynamic information on the ongoing bone resorption. In contrast, biochemical markers of bone metabolism specifically reflect bone resorption or bone formation rates and are strongly affected by the processes active in myeloma bone disease. Therefore, biochemical markers of bone remodeling are used more often nowadays in an attempt to improve monitoring of bone destruction in MM.

In addition, strategies that target osteoclast activation and proliferation represent an important approach to the management of myeloma bone disease. Bisphosphonates consist of a heterogeneous group of agents that affect bone metabolism and regulation of calcium homeostasis, mainly through an inhibitory effect on osteoclasts.[10] Several studies have demonstrated their efficacy in myeloma bone disease and therefore they are included in all therapeutic regimens for stage II/III myeloma patients.[11,12] Biochemical markers of bone resorption and formation have also been used to follow up myeloma bone disease during bisphosphonates administration. This review attempts to summarize the existing data for the role of markers of bone remodeling in assessing the extent of bone destruction in myeloma and monitoring bone turnover during specific anti-myeloma chemotherapy or bisphosphonates administration. We also discuss novel markers that may be of particular interest in the near future.

Pathogenesis of bone disease in multiple myeloma

Although the mechanisms responsible for the development of myeloma bone disease currently remain unclear, several studies have begun to shed new light on this process. Histomorphometric studies have demonstrated that myeloma bone destruction is related to increased osteoclastic activity, which is not accompanied by a comparable increase in osteoblast formation. This uncoupling of resorption and formation leads to rapid bone loss.[13] A number of cytokines and growth factors that are produced either by myeloma cells or by stromal cells, due to interactions between them, have been implicated in the increase in osteoclast formation and activity in MM. The adherence of myeloma cells to bone marrow stromal cells results in enhanced production of cytokines, such as interleukin-6 (IL-6), interleukin 1-β (IL-1β), interleukin 11 (IL-11), tumor necrosis factors α and β (TNFα, TNFβ), basic fibroblast growth factor (bFGF), macrophage-colony stimulating factor (M-CSF), which stimulate human osteoclast formation.[4] IL-6 also acts as a survival factor for myeloma cells.[14] Furthermore, stromal cells also produce receptor activator of nuclear factor κ-B ligand (RANKL), a member of the tumor necrosis factor (TNF) gene family. Following activation of the cellular receptor RANK on osteoclasts by its ligand, RANKL, differentiation, proliferation, and survival of osteoclasts is enhanced, osteoclast fusion and activation is promoted, and osteoclastic apoptosis is suppressed, leading to a dramatic increase of the number and activity of osteoclasts.[15,16] In addition, production of osteoprotegerin (OPG), a soluble decoy receptor of RANKL produced by marrow stromal cells, is suppressed through the above interactions and has been found to be reduced in patients with MM.[17–19] The mechanisms through which OPG levels are decreased have not been clearly defined yet, but a study by Standal et al.[20] has shown that OPG is bound, internalized, and degraded by the myeloma cells through CD138. The ratio RANKL/OPG is reversed in myeloma, leading to osteoclast activation and bone destruction.[15,19,21–24] Several reports have suggested that myeloma cells also produce RANKL and that the expression of RANKL by human myeloma cells mediates osteoclast formation in vitro and correlates with bone destruc-