

Multiple myeloma - Section 2

Pathophysiology and diagnosis of multiple myeloma bone disease

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Osteolytic bone disease in multiple myeloma (MM) is due to increased osteoclastic bone resorption, diminished osteoblastic bone formation and impaired osteocyte function.¹ Myeloma cells disturb the balance between the receptor activator of nuclear factor-kappa B ligand (RANKL) and osteoprotegerin (OPG) in favor of RANKL, which results in osteoclast formation and activation.^{2,3} Other cytokines with osteoclast activity are also overexpressed in the myeloma microenvironment, including C-C motif ligand-3 (CCL-3),⁴ activin-A (which also inhibits osteoblast function),^{5,6} interleukin-6 (IL-6),¹ IL-1beta,¹ TNF-alpha,¹ CCL-20⁷ and others. Furthermore, the Wnt inhibitors dickkopf-1,⁸ sclerostin⁹ and secreted frizzled-related protein-2 orchestrate osteoblast dysfunction and apoptosis, while Notch signaling is implicated in osteocyte deregulation in MM.¹⁰ Based on biology advances the following novel agents are under clinical investigation: denosumab (anti-RANKL), romosozumab (anti-sclerostin), sotatercept (activin-A antagonist), BHQ880 (anti-Dkk1) and others. Modern imaging has entered into the diagnosis of bone disease in MM. Whole-Body Low-Dose Computed Tomography (WBLDCT) has increased sensitivity over conventional radiography for the detection of osteolytic lesions¹¹ and EMN has suggested that WBLDCT should replace conventional radiography for the work-up of myeloma patients.¹² Magnetic Resonance Imaging depicts accurately the marrow infiltration by myeloma cells and should be performed in all patients with no lytic lesions at diagnosis for the exclusion of symptomatic myeloma.^{13,14} Diffusion-Weighted Imaging (DWI) MRI is a novel MRI technique, which seems to better evaluate myeloma burden and MRI infiltration patterns. Positron Emission Tomography/CT (PET/CT) is a functional imaging technique, more sensitive than conventional radiography in the detection of lytic lesions, which probably allows better definition of complete response and minimal residual disease compared to all other imaging methods providing a tool for the follow-up of myeloma patients.¹⁵

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