Bone disease in multiple myeloma: Pathophysiology and treatment strategies.

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Introduction

Multiple myeloma (MM) is a hematologic malignancy characterized by the clonal proliferation of plasma cells in the bone marrow. One of the most debilitating complications of MM is bone disease, affecting nearly 80% of patients during the course of their illness. This bone involvement leads to skeletal-related events (SREs), including pathological fractures, severe bone pain, hypercalcemia, and spinal cord compression, significantly impacting patient quality of life and survival outcomes [1].

The bone disease in MM results from an imbalance between osteoclast-mediated bone resorption and osteoblast-driven bone formation. Malignant plasma cells stimulate osteoclast activity while inhibiting osteoblast differentiation, leading to excessive bone degradation without compensatory bone formation. Key factors involved include receptor activator of nuclear factor kappa-B ligand (RANKL), macrophage inflammatory protein-1 alpha (MIP-1α), and Dickkopf-1 (DKK1). RANKL, secreted by stromal and myeloma cells, binds to its receptor RANK on osteoclast precursors, promoting osteoclastogenesis. Simultaneously, DKK1 inhibits the Wnt signaling pathway, suppressing osteoblast function and bone repair [2].

Patients with MM often present with bone pain, particularly in the spine, ribs, and pelvis. Lytic bone lesions detectable through imaging, pathological fractures, and osteoporosis are common. Vertebral compression fractures can lead to spinal deformities and nerve compression. Additionally, bone destruction often results in hypercalcemia, manifesting as nausea, confusion, and renal dysfunction, further complicating disease management [3].

Accurate diagnosis of bone involvement in MM requires a combination of imaging techniques. Conventional skeletal surveys are commonly used but have low sensitivity. Advanced imaging modalities such as low-dose whole-body CT, MRI, and PET-CT offer higher sensitivity in detecting lytic lesions and early bone marrow involvement. Biomarkers like elevated serum calcium, increased bone resorption markers (e.g., C-terminal telopeptide), and suppressed bone formation markers (e.g., osteocalcin) can support diagnosis and monitoring [4].

Bisphosphonates, such as zoledronic acid and pamidronate, are the cornerstone of therapy for myeloma-related bone disease. They inhibit osteoclast-mediated bone resorption by inducing osteoclast apoptosis and reducing bone turnover. Clinical trials have shown that bisphosphonates reduce SREs, alleviate bone pain, and improve quality of life. However, prolonged use can lead to complications like osteonecrosis of the jaw (ONJ) and renal toxicity, necessitating regular monitoring [5].

Denosumab, a monoclonal antibody targeting RANKL, offers an alternative to bisphosphonates, especially for patients with renal impairment. By inhibiting RANKL, denosumab prevents osteoclast formation and activity, reducing bone resorption. Studies have demonstrated its efficacy in lowering SRE risk and controlling hypercalcemia in MM patients. Its reversible effects upon discontinuation require careful management to prevent rebound bone loss [6].

Emerging therapies focus on restoring the balance between bone resorption and formation. Agents targeting DKK1 and sclerostin aim to stimulate osteoblast activity and bone formation. For example, anti-DKK1 antibodies have shown promise in preclinical studies by enhancing bone repair. Additionally, proteasome inhibitors like bortezomib indirectly promote bone formation by reducing osteoclast activity and stimulating osteoblasts [7].

Localized radiation therapy is effective for pain control and preventing fractures in patients with focal bone lesions. Surgical interventions, including vertebroplasty and kyphoplasty, provide mechanical stabilization for vertebral compression fractures, offering rapid pain relief and improved mobility. Orthopedic surgery may be necessary for long bone fractures or impending fractures to prevent further complications [8].

Effective pain management is critical in MM-related bone disease. Analgesics, including nonsteroidal anti-inflammatory drugs (NSAIDs), opioids, and adjuvant medications like antidepressants and anticonvulsants, are commonly used. Interventional pain procedures, such as nerve blocks and spinal cord stimulation, can offer relief in refractory cases. Addressing pain not only improves patient comfort but also enhances physical function and overall well-being [9].

Controlling the underlying myeloma is essential for managing bone disease. Standard therapies, including immunomodulatory drugs (lenalidomide), proteasome inhibitors (bortezomib), and monoclonal antibodies (daratumumab), reduce myeloma burden and indirectly mitigate bone damage. Autologous stem

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cell transplantation, when appropriate, can further improve disease control and reduce skeletal complications [10].

Conclusion

Bone disease in multiple myeloma represents a major challenge, significantly affecting morbidity and mortality. A deep understanding of the pathophysiological mechanisms driving bone destruction has led to effective therapies, including bisphosphonates, denosumab, and emerging bone-modifying agents. Integrating bone-targeted treatments with systemic antimyeloma therapies is crucial for improving patient outcomes. Ongoing research and novel therapeutic strategies continue to offer hope for better management of bone disease in multiple myeloma, ultimately enhancing patient quality of life and survival.

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