1. BIOLOGY AND PRECLINICAL

CYTOKINE AND BONE MICROENVIRONMENT PROFILES REFLECT DISEASE STAGE AND OSTEOLYTIC INVOLVEMENT IN MULTIPLE MYELOMA

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Background. Myeloma bone disease (MBD) is a hallmark of multiple myeloma (MM) and is present in up to 80% of newly diagnosed patients. The extent of osteolytic bone involvement varies and generally correlates with advanced disease stages. MBD results from an imbalance in bone homeostasis, characterized by increased bone resorption and suppression of bone formation. The aim of this study was to evaluate selected biochemical markers, serum cytokines, and bone marrow microenvironment parameters in relation to osteolytic involvement and MM disease stage.

Methods. A total of 121 patients with monoclonal gammopathies were assessed, including 77 patients with active MM (at diagnosis or relapse), 14 patients with smoldering multiple myeloma (SMM), and 30 patients with monoclonal gammopathy of undetermined significance (MGUS). The following biochemical parameters, serum cytokines, and bone marrow microenvironment markers associated with MBD were analyzed: calcium (Ca^{2+}), phosphorus (P), parathyroid hormone (PTH), calcitonin, 25-hydroxyvitamin D_2, 1,25-dihydroxyvitamin D_3, alkaline phosphatase (ALP), procollagen type I N-terminal propeptide (P1NP), C-terminal telopeptide of type I collagen (CTX-1), cross-linked telopeptide of type I collagen (ICTP), osteoprotegerin (OPG), osteocalcin (OCN), nuclear factor kappa B (NF-κB), receptor activator of nuclear factor κB (RANK), receptor activator of nuclear factor κB ligand (RANKL), macrophage inflammatory protein-1α (MIP-1α), Dickkopf-1 (DKK-1), osteopontin (OPN), hepatocyte growth factor (HGF), matrix metalloproteinase-9 (MMP-9), secreted Frizzled-related protein-1 (sFRP-1), runt-related transcription factor 2 (RUNX2), tartrate-resistant acid phosphatase 5 (TRAP5), semaphorin, and syndecan-1. These parameters were evaluated according to disease stage using the Durie–Salmon (DS) and International Staging System (ISS), as well as according to the extent of skeletal involvement (0, 1, 2, or ≥3 osteolytic lesions).

Results. Significant differences across Durie–Salmon stages were observed for P1NP ($p = 0.0069$), ICTP ($p = 0.0003$), CTX-1 ($p < 0.0001$), HGF ($p = 0.0004$), MIP-1α ($p = 0.0379$), syndecan-1 ($p < 0.0001$), DKK-1 ($p < 0.0001$), NF-κB ($p = 0.0335$), and OPN ($p = 0.0498$). Across ISS stages, significant differences were identified for P1NP ($p = 0.0056$), ICTP ($p < 0.0001$), CTX-1 ($p < 0.0001$), 25-hydroxyvitamin D_2 ($p = 0.0027$), 1,25-dihydroxyvitamin D_3 ($p = 0.0084$), HGF ($p < 0.0001$), MIP-1α ($p = 0.0092$), syndecan-1 ($p < 0.0001$), OPG ($p = 0.0242$), DKK-1 ($p = 0.0011$), NF-κB ($p = 0.0008$), and OPN ($p = 0.0199$). The extent of radiographically detected skeletal involvement correlated significantly with phosphorus ($p = 0.0050$), ICTP ($p = 0.0225$), CTX-1 ($p = 0.0002$), OCN ($p = 0.0086$), HGF ($p = 0.0250$), syndecan-1 ($p = 0.00004$), OPG ($p = 0.0267$), DKK-1 ($p = 0.0202$), and RANK ($p = 0.0083$).

Conclusions. Several evaluated biomarkers showed significant correlations with the extent of skeletal involvement, supporting their role in the development and progression of myeloma bone disease. In addition, multiple parameters correlated with both Durie–Salmon and ISS staging, indicating accelerated bone destruction in patients with advanced stages of multiple myeloma. *With support of MH CZ – DRO (FNOl, 00098892) and IGA_LF_2025_005.*