

## 2. NEWLY DIAGNOSED MULTIPLE MYELOMA

**MONOCLONAL AND POLYCLONAL CIRCULATING PLASMA CELLS ARE ASSOCIATED WITH DISEASE DISSEMINATION IN MULTIPLE MYELOMA**

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Multiple myeloma (MM) is a hematological malignancy characterized by clonal expansion of plasma cells (PCs) in the bone marrow (BM), with occasional detection in peripheral blood (PB) as circulating plasma cells (CPCs). Although patient (pt) outcomes have markedly improved over the last decade due to novel therapeutic strategies, most pts eventually relapse. This may reflect the ability of BM-resident PCs to escape the BM niche, giving rise to CPC clones that promote extramedullary spread and systemic disease dissemination. This study aimed to investigate the association between CPCs and disease dissemination assessed by diffusion-weighted magnetic resonance imaging (DWI) and 18F-FDG PET (PET), and to compare pts with aberrant monoclonal CPCs (mCPCs) versus polyclonal CPCs (pCPCs). A total of 140 newly diagnosed (ND) MM pts were enrolled. BM aspirates and PB samples were collected at diagnosis together with DWI, PET, and baseline clinical and genomic data. CPCs were quantified and characterized by multiparametric flow cytometry with a sensitivity  $\geq 10^{-5}$ . pCPCs were defined by a cytoplasmic Ig $\kappa$ /Ig $\lambda$  ratio between 0.5 and 4. CPCs were detected in 112/140 pts (80%), with a median frequency of 0.02% (range 0.002-17.84%), while 28 pts (20%) had no detectable CPCs. Among CPCs-positive pts, 83 (74%) harbored mCPCs (median 0.025%, range 0.002-17.84%) and 29 (26%) had pCPCs (median 0.018%, range 0.002-0.34%). Pts with CPCs showed higher genomic risk according to the IMWG Consensus Genomic Staging (CGS;  $p=0.044$ ) and worse biochemical parameters, including lower hemoglobin, higher calcium, reduced albumin, and increased  $\beta_2$ -microglobulin ( $p<0.004$ ), indicating that CPCs presence per se

identifies a more aggressive disease. Imaging analyses confirmed this association: CPCs correlated with diffuse BM PET uptake ( $p=0.028$ ), positive DWI ( $p=0.01$ ), increased osteolytic lesions ( $p=0.013$ ), and higher PET SUV values ( $p=0.043$ ). CPC-positive pts more frequently exhibited 4-10 ( $p<0.001$ ) or  $>10$  ( $p=0.004$ ) DWI focal lesions, particularly in the extremities ( $p<0.001$ ), confirmed by PET ( $p=0.014$ ). Compared to pCPCs, mCPCs were associated with worse clinical and biochemical features ( $p<0.037$ ), higher-risk CGS ( $p=0.032$ ), increased DWI focal lesions ( $p=0.027$ ), and higher FDG uptake ( $p=0.041$ ). Among mCPCs-positive pts, higher mCPCs levels ( $>0.02\%$ ) correlated with high-risk CGS ( $p=0.026$ ), PET positivity ( $p=0.025$ ), extremity involvement on DWI ( $p<0.0001$ ), and lack of CD56 expression ( $p=0.022$ ). Importantly, pCPCs were also associated with adverse imaging features compared to pts without CPCs ( $p=0.035$ ). Finally, despite the limitations of a short follow-up, the presence of CPCs, both mCPCs and pCPCs, appears to be associated with higher risk of relapse ( $p=0.05$ ). To date, 23 pts have relapsed: 16 out of 83 (19%) mCPCs pts, 5 out of 29 (17%) pCPCs pts, and 2 out of 28 (7%) pts without detectable CPCs. In conclusion, the presence of CPCs significantly correlates with more widespread disease and increased skeletal involvement, suggesting the role of these cells in driving dissemination and progression in MM. Interestingly, even the presence of polyclonal CPCs was associated with a worse clinical profile compared to pts without detectable CPCs at diagnosis.

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