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651.MULTIPLE MYELOMA AND PLASMA CELL DYSCRASIAS: BASIC AND TRANSLATIONAL

Association between BCL2, BCL2 E17, MCL1 and BAX Protein Expression, Bone Marrow Microenvironment Histological Features, Clinical Presentation, Therapeutic Outcome, and the Overall Survival in Newly Diagnosed Multiple Myeloma

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Abstract We evaluated the correlation between immunohistochemical BCL2, BCL2 E17, MCL1 (Bcl2-related protein family) and BAX (effector proapoptotic protein) expression and intensity of staining in plasma cells (PC) in MM patients (pts) who were eligible for autologous stem cell transplantation (ASCT) with DD4, CD8, and FOXP3 positive Tregs lymphocytes in bone marrow (BM) microenvironment, morphologic features of PC, clinical parameters, and outcomes.

Immunohistochemical staining of BCL2, BCL2 E17, MCL1, BAX, CD4, CD8, FOXP3 and Ki67 was performed in BM biopsy of 36 newly diagnosed MM patients who were eligible for ASCT between 2012-2017 at University Hospital Merkur. Pearson's and Spearmans's coefficients of correlation, t-tests, one-way independent sample ANOVAs, mixed ANOVAs, moderation analyses, chi-square tests of independence and Cox's proportional hazards were used to analyze the data.

Median age of pts was 57 years (95% CI 52-60), 15 pts were female with equal distribution in rISS I-III (12 pts). Twelve (33%) pts had high risk cytogenetics: del 13q34 (8 pts; 22%), del 17p (5 pts, 13,8%), t(4; 14) (4 pts; 11.1%); t(16;14) (4 pts; 11.1%); 4 pts (11.1%) had t(11;14). The median percentage of PC (PC ptc) in BM was 60 (95% CI 45 - 80); 25 pts (69.4%) had diffuse type of infiltration (TI) in BM; and 23 pts (63.8%) had high grade of PC differentiation (grade 2/3). The median percentage of Ki67 in PC was 3% of PC (95% CI 2 - 4, range 1 - 80). The median percentage of BCL2 positive PC in BM was 50 (95% CI 25 - 60) with high intensity of staining in 23 pts (63.8 %); BCL2 E17 positive PC in BM was 60 (95% CI 60 - 70) with high intensity of staining in 33 pts (91.6%); MCL1 positive PC in BM was 40 (95% CI 20 - 60) with high intensity of staining in 21 pts (58.3%); and BAX positive PC in BM was 17.5 (95% CI 6 - 40) with high intensity of staining in 18 pts (50%). Median CD4 positive T-cells was 8.5 (95% CI 4 - 18); CD8 T-cells 24 (95% CI 18 to 37); and FOXP3 Tregs 1 (95% CI 1 - 2, range 1 - 31). Nineteen pts (52.7 %) underwent tandem ASCT, 34 pts (94.4%) received VCD induction; 2 pts received MP induction; and 1 pts received VD induction. Overall response rate (≥partial response) to induction therapy was 94.4%; ≥ very good partial response rate was 80.5%. Overall response rate (≥partial response) to ASCT was 86.1%; complete response rate was 50%. Median overall survival time was 35.40 months (95% CI 26.61-165.39).

Expression of BCL2, BCL2 E17, MCL1 and BAX proteins was significant and positively, moderately to strongly associated ($p < 0.05$), except for BCL2E17 and BAX association ($r(36) = 0.319$, $p = 0.058$). BCL2 and MCL-1 expression was more correlated when PC were well differentiated, grade 1 ($p = .016$). Higher PC pct was correlated with higher intensity of BLC2 staining ($t(34) = 2.51$, $p = 0.017$). Patients with Ki67 >10% had a higher PC pct in BM ($t(34) = 2.04$, $p = 0.049$). Higher grade of PC in BM correlated with higher PC pct in BM ($t(34) = 2.63$, $p = 0.012$). A higher MCL1 expression was found in MM with high-risk cytogenetic changes ($t(34) = 2.09$, $p = 0.045$). Cytoplasmic granular MCL1 staining had greater MLC 1 staining intensity than the diffuse TI ($\chi^2(1) = 6.60$, $p = 0.017$).

Low BCL2, BCL2E17, MCL1 and BAX expression was found in MM stage rISS1 compared to rISS3 ($p < 0.05$), and low BCL2 and MCL-1 expression in MM stage rISS1 compared to ISS2 ($p < 0.05$). Patients with non-diffuse TI had worse response to ASCT compared to their response to induction therapy than patients with diffuse TI ($\chi^2(2) = 6.39$, $p = 0.041$).
Although we observed high number of CD4 and CD8 T-cell in BM microenvironment and aberrant CD4:CD8 ratio in favor to CD8 positive T-cell, it had no impact on other variables in study. We found significant correlation between BCL2E17 expression and response to ASCT ($r_s = -0.417$, $p = 0.011$), with higher protein expression being associated with worse outcomes. BCL2 contributed to worse survivability ($\chi^2(1) = 7.18$, $p = 0.007$), while BCL2 E17, MCL1 and BAX expression, as well as the number of CD4 and CD8 T-cells, did not predict survival ($p > 0.05$).
Results showed aberrant expression of the BCL2 family members that may plays a role in application strategies for MM therapy. Bcl-2 inhibits Bax but we found aberrant BAX expression in MM that may be result of pre-condition or hormesis like responses in stressful micro-environments that serve to increase apoptotic resistance. Further investigation of the role Bcl2-proteins family in the biology of MM and its impact on clinical and therapeutic outcomes is warranted.

Disclosures Jaksic: *Roche, Oktal-Pharma/Celtrion, Sandoz:* Consultancy, Honoraria.

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