114 CYTOGENETIC ABNORMALITIES IN A COHORT OF 175 PATIENTS WITH WALDENSTROM'S MACROGLOBULINEMIA BEFORE TREATMENT: CLINICAL AND BIOLOGICAL CORRELATIONS

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Introduction:
WM cells present with a reduced expression of miRNA-9* that has been predicted to target histone acetylation regulatory genes. Importantly, it has been shown that epigenetic regulation of gene-expression, such as histone-acetylation, is commonly deregulated in tumors. We therefore looked at miRNAs as possible regulators of histone-acetylation in WM.

Material and methods: miRNA- and gene-expression-profiling have been performed on primary CD19+ cells isolated from bone marrow of patients with WM as clinical implications for familial WM disease need to be clarified.

Chromosomal abnormalities were compared to adverse characteristics described by Morel et al (Blood 2009,113,4163-70): age >65y, hemoglobin (Hb) <11.5g/dL, platelet count <100x10^9/L, b2microglobulin (b2M) >3mg/L, and IgM >7g/dL.

Conclusions:
Patients with > 1 case of WM in their family. Among 924 consecutive patients seen at our center, 254 (27.4%) reported familial disease.

115 MICRONR-9* REGULATES HISTONE ACETYLATION IN WALDENSTROM’S MACROGLOBULINEMIA

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Material and methods: miRNA- and gene-expression-profiling have been performed on primary CD19+ cells isolated from bone marrow of patients with WM as clinical implications for familial WM disease need to be clarified.

Conclusions: Familial predisposition is common in WM, and associated with an inferior treatment outcome. Prospective studies examining the impact of familial disease status on treatment outcome in WM are warranted.

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Introduction: The impact of cytogenetic abnormalities on therapeutic response in pts with MM is well-established. Bortezomib (BTZ) overcomes the adverse impact of several common unfavorable cytogenetic features, as do lenalidomide (LEN) /dexamethasone, and pomalidomide, albeit to a lesser extent. CFZ is a novel, highly selective epoxyketone proteasome inhibitor with durable single-agent activity. This analysis evaluated the influence of cytogenetics in a large phase 2b study (PX-171-003-A1) of single-agent CFZ in pts with R/R MM.

Methods: 229/266 pts enrolled were response evaluable and had available metaphase cytogenetic data (200 pts [75%]) and/or fluorescence in situ hybridization (FISH) data (205 pts [77%]). Unfavorable cytogenetic abnormalities were defined per mSMART criteria: del 17p, t(4;14), and t(14;16) by FISH; hypodiploidy and chr 13 deletions by metaphase cytogenetics. All pts received CFZ at 20 mg/m² IV on days 1, 2, 8, 9, 15, and 16 of a 28-day cycle (C) in C1 followed by 27 mg/m² in C2–12. The overall response rate (ORR) by International Myeloma Working Group criteria and the clinical benefit response rate (CBR) were assessed by investigators and confirmed by Independent Review Committee.

Results: Pts had relapsed disease after 2 regimens including BTZ and either thalidomide (THAL) or LEN, and were refractory to their last regimen. In this heavily pre-treated pt population, 99.6% of pts previously received BTZ, 74% received prior THAL, 94% prior LEN, and 74% prior stem cell transplantation. The ORR (≥ PR) for pts with available cytogenetic/FISH data was 25% and the CBR was 36%. 71/229 pts (31%) had ≥1 abnormality. These were detected by metaphase analysis in 47 pts (60%), by FISH in 44 (62%), and by both in 20 (28%). The presence of del13, hypodiploidy, del17p13, t(4;14), or t(14;16) did not significantly impact responses – updated data will be presented. The ORR was 28% in pts with ≥1 abnormality; 24% in those with 0. The CBR was similarly unaffected. The median OS for pts with ≥1 unfavorable abnormality 6 mo (95% CI 4–10); and for those with 0, 8 mo (95% CI 6–10).

Conclusions: CFZ demonstrated comparable, durable activity in pts with R/R MM in both the absence and the presence of cytogenetic abnormalities. This study suggests that responses to CFZ and DOR in heavily pretreated pts are not impacted by poor prognostic cytogenetic features. The authors wish to acknowledge the support of the Multiple Myeloma Research Consortium (MMRC).

Background: A proliferation inducing ligand (APRIL/TNFSF13) is a TNF member implicated in plasma-cell survival.

Methods: In order to study the in vivo role of APRIL in multiple myeloma (MM) development, we used two new multiple myeloma models, one xenogeneic based on the backcrossing of APRIL-/- mice onto an immunodeficient background, and one syngeneic based on the selection of a variant (MOPC-315BM) of the MOPC-315 plasmocytoma cell line able to invade mouse BM following intravenous injection.

Results: In the xenogenic model, we are showing for the first time that lack of APRIL severely impacts the in vivo development of multiple myeloma (MM). We recently showed that the bone marrow (BM), the orthotropic site of MM development, is an organ constitutively rich in APRIL. Indeed, the most abundant hematopoietic precursors, i.e. myeloid precursors, constitutively secrete high levels of APRIL. In the syngeneic model, we further observed that MOPC-315BM selectively protects APRIL-producing myeloid precursors in an IL-6 dependent manner upon BM invasion, while all other hematopoietic precursors are downregulated. This process insures a stable level of APRIL expression in MOPC-315BM-invaded BM.

Conclusion: Our present study shows how MM selectively deviates hematopoiesis to maintain a favorable cytokine milieu for a maximal BM invasion. Hematopoietic reconstitution is mandatory for patients’ recovery to multiple myeloma treatments. The link demonstrated here between hematopoiesis and multiple myeloma development may explain why multiple myeloma is still an incurable disease.