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POSTER ABSTRACTS

652.MULTIPLE MYELOMA: CLINICAL AND EPIDEMIOLOGICAL

Genomic and Immune Determinants of Resistance to Anti-CD38 MoAb Based Therapy in Relapsed Multiple Myeloma

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INTRODUCTION: Anti-CD38 monoclonal antibody (MoAb)-based treatment (e.g. daratumumab), especially when used in combination, have significantly improved the outcomes in patients with multiple myeloma (MM). However, despite the good results with this combination, a notable fraction of patients inevitably experiences relapse.
METHODS: To characterize the genomic and immune microenvironment factors associated with resistance to daratumumab, lenalidomide and dexamethasone (dara-Rd), we integrated whole genome sequencing (WGS) and flowcytometry data generated from a longitudinally cohort (N=32) of relapsed/refractory MM (RRMM) patients (NCT03848676). WGS was performed in 28 patients, with 6 patients having samples collected before treatment and at the time of progression. To explore the impact of pretreatment bone marrow (BM) and peripheral blood (PB) immune composition, samples from both compartments were captured at baseline for each patient and investigated by flowcytometry (N=64). Additionally, to characterize the dara-Rd-induced immune modulation over time, flowcytometry was used to profile PB samples collected every 3 months after treatment start until progression for each patient (N=170). This project was funded and supported by Associazione Italiana per la Ricerca sul Cancro (AIRC IG 20541).
RESULTS: Single base substitutions (SBS) signature APOBEC (SBS2 and SBS13), and SBS18 (oxygen radical stress) were significantly associated with shorter progression free survival (PFS; p=0.047, p=0.03 respectively). Furthermore, shorter PFS was also observed in patients harboring del1p22.1 (*RPL5*, p=0.031), del17p13.1 (*TP53*, p=0.015), del16p13.3 (*CREBBP*, p=0.034) and del10p15.3 (p=0.006). Of note, all patients with *TP53* deleted progressed. Moreover, 6/7 of patients with structural variants involving *MYC* progressed (p=0.00016). Chromothripsis was detected in 10/28 (36%) patients, with 7 experiencing early progression (p=0.05). Reconstructing the genomic evolution between baseline and progression, patterns of branching evolution were observed in all 6 patients, without any recurrent genomic events positively selected or acquired at relapse.
The BM and PB immune cell composition at baseline showed high concordance (p<0.001). In both PB and BM baseline samples, patients that progressed were characterized by higher levels of exhausted T cells (T cytotoxic TIM3+), lower presence of T helper cells, and higher proportion of CD38+ NK cells compared to the progressors (p<0.05). Investigating dynamic PB immune changes during treatment with dara-Rd; we detected a significant depletion and CD38+ down-modulation of NK cells (p<0.0001). This observation combined with the impact of NK cells at baseline reflects a scenario where dara bind both myeloma cells and NK cells, promoting NK fratricide, potentially limiting the immune activity against the myeloma cells. In line with this model, proliferative NK cells were characterized by a higher expansion at 3 months compared to cytotoxic

NK cells ($p<0.0001$), in particular among non-progressed patients ($p=0.046$). Similar to NK cells, CD38+ T regs drastically decreased ($p=0.003$) between baseline and 3 months. Finally, our immune longitudinal analysis revealed relevant findings such as enrichment of exhausted T helper and T cytotoxic cells, as well as T regs and granulocytic myeloid-derived suppressor cells (MDSC) in progressive patients ($p<0.05$).
By integrating WGS and flowcytometry data we were able to define associations between unfavorable genomic features and immune environment patterns. Specifically, patients with high APOBEC contribution and MYC SV were characterized by increased T cell exhaustion (T helper and T cytotoxic TIM3+ cells; $p<0.05$). MYC SV were also associated with a low number of naïve and central memory T cells ($p=0.018$, $p=0.048$). Furthermore, patients with del_1p22.1 exhibited a low number of T regs CD38+ and a high presence of monocyte-MDSC ($p<0.05$). Finally, low numbers of cytotoxic NK cells at baseline were observed among patients with any of the high-risk genomic feature listed above ($p=0.009$).
CONCLUSION: Overall our data revealed that the MM resistance and progression to dara-Rd in RRMM patients is driven by a complex interplay between high genomic complexity and an immune-exhausted microenvironment.

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