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Blood 142 (2023) 3319–3320

The 65th ASH Annual Meeting Abstracts

POSTER ABSTRACTS

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

Targeted Inhibition of Myeloperoxidase (MPO): A New Therapeutic Strategy for the Treatment of Multiple Myeloma

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Despite major improvements in therapeutic strategies for patients with multiple myeloma (MM), effective treatment still remains a persistent challenge, as patients ultimately relapse and succumb to the disease. In the last decade, studies have highlighted the reciprocal interaction between MM plasma cells (PC) and the bone marrow (BM) microenvironment in regulating immune evasion, disease progression and persistence. As MM PC rely on BM stromal cells and their secreted factors for their survival and growth, the therapeutic targeting of the BM microenvironment may prove to be a novel and successful strategy for myeloma care in the future. Myeloid-derived suppressor cells (MDSC), a heterogenous population of myeloid cells are described to promote MM progression through immunosuppression and induction of angiogenesis. Myeloperoxidase (MPO), a key inflammatory enzyme important in host defence, is reported to be the most highly upregulated gene in MDSCs in murine cancer models. Recently, the accumulation of MPO within the tumour microenvironment has attracted much attention with a number of studies describing a role for MPO in regulating cancer development due to its potent pro-oxidative and proinflammatory properties.

Our most recent findings have revealed new functional roles for myeloid-derived MPO in the BM microenvironment of MM. Specifically, we demonstrate that myeloid cell populations are increased within the BM of 5TGM1 tumour-bearing mice and that MM PC may directly influence *Mpo* gene expression in BM-derived myeloid cells. Mechanistically, we report that MPO has the capacity to induce the expression of key MM growth factors, and exerts potent immune suppression by inhibiting anti-tumour T-cell responses. Remarkably, in the syngeneic KaLwRij/5TGM1 mouse model of MM, targeted inhibition of MPO with the suicide substrate 4-Aminobenzoic acid hydrazide (4-ABAH) demonstrated a significant reduction in overall MM tumour burden.

Here, we investigate for the first time the efficacy of an orally bioavailable irreversible small molecule inhibitor of MPO (MPOi) in the preclinical Vk*MYC murine model of myeloma. Twelve-week-old C57BL/6J mice were intravenously inoculated with Vk*MYC (Vk14451-GFP) cells and tumour progression was monitored by serum paraprotein electrophoresis (SPEP), whilst endpoint GFP+ tumour cells in the bone marrow were quantitated by flow cytometry. To characterise myeloid cell populations and associated *Mpo* expression in the Vk*MYC tumour landscape, we utilised flow cytometry to quantitate CD11b+ cells and used magnetic activated cell separation to isolate these populations and characterise the expression of *Mpo* by qPCR. Our studies confirm that CD11b+ myeloid cells are significantly increased in the BM of Vk*MYC tumour-bearing mice ($p<0.01$), accompanied by an upregulation of *MPO* mRNA expression ($p<0.001$). To assess the efficacy of MPOi in MM, mice were treated with MPOi or vehicle alone twice daily by oral gavage, with treatment initiated at the time of Vk*MYC inoculation. Notably, mice receiving MPOi presented with significantly reduced endpoint tumour burden (9 weeks post tumour cell inoculation). We observed a 15.2% and 31.4% reduction in MM tumour as determined by hind limb GFP% ($p<0.05$) and SPEP ($p<0.01$) respectively, compared to vehicle control. Additionally, mRNA analysis of complete BM revealed an upregulation of the critical cytokine IFN gamma ($p<0.05$) and the downregulation of the potent proangiogenic factor VEGF ($p<0.05$) in mice treated with MPOi, suggesting MPO inhibition in MM may be an advantageous means to regulate the BM microenvironment and impede disease progression. However, when MPOi treatment was initiated at first signs of detectable disease, (as identified by the presence of a monoclonal spike by SPEP; 5 weeks post tumour cell inoculation), no difference in endpoint tumour burden was observed. This suggests that targeted inhibition of MPO using MPOi may be more effective in at early stages of MM development. In conclusion, the findings presented in this study indicate that inhibiting MPO activity with MPOi, as

a single agent therapy, attenuates MM tumour growth in the Vk*Myc mouse model. With limited therapies used in the clinic that target the stromal microenvironment, these findings suggest MPOi could be investigated as a potential novel treatment option that may be included in combination with current frontline therapeutic agents.

Disclosures No relevant conflicts of interest to declare.

https://doi.org/10.1182/blood-2023-179196