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641.CHRONIC LYMPHOCYTIC LEUKEMIAS: BASIC AND TRANSLATIONAL

The Unique BCR Inhibiting Properties of BMS-986205 in Chronic Lymphocytic Cells

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B cell receptor (BCR) signaling is recognised as a central pathway in the pathogenesis of chronic lymphocytic leukaemia (CLL), the most common leukemia in the western world. In CLL, the BCR pathway is activated by antigens in the tissue microenvironment to promote the maintenance and expansion of leukemic cells. The impressive inhibition of clonal expansion of CLL cells and the disease control achieved with tyrosine kinase inhibitors that block BCR signaling provided further evidence of the role of BCR in CLL. Indoleamine 2,3-dioxygenase 1 (IDO1) is the inducible and rate-limiting enzyme involved in the catabolism of tryptophan to kynurenine. It was discovered as a modulator of the innate immune response during infection. Subsequent discoveries have implicated IDO1 as a player in acquired immune tolerance. IDO1 activity has been identified in several types of cancer cells as well as in their tumor-surrounding microenvironment. We have previously investigated and characterized the impact of IDO1 expression in CLL. Our results show that CLL microenvironmental stimuli positively modulate IDO1 expression in leukemic cells and that increased IDO1 activity leads to sustained survival of malignant lymphocytes and impaired drug sensitivity through the autocrine/paracrine activation of the aryl hydrocarbon receptor by kynurenine (Atene CG et al. 2022). To assess the functional and clinical significance of IDO1 enzymatic activity in CLL, we used several inhibitors that are currently in late-stage clinical trials. Using BMS-986205 (BMS), an irreversible inhibitor of IDO1 with the best cell-based potency, in primary patient cells, we observed not only a reduction in kynurenine production due to enzymatic inhibition of IDO1, but also lower levels of IDO1 RNA and protein following BCR stimulation with α-IgM. As we have previously shown that BCR activation can induce IDO1 expression, we treated CLL cells with increasing doses of BMS for 3 hours and then added α-IgM to the culture. BMS is able to counteract the pro-survival effect of BCR triggering, leading to significant apoptosis of CLL cells, while the viability of CLL cells in the absence of external stimuli was not significantly modulated. Focusing on the complex signaling cascade activated by BCR engagement, we observed that BMS impaired the phosphorylation of upstream kinases such as SYK and BTK, but also CD79a, CD19 and BLNK, in addition to downstream effectors such as AKT. We therefore investigated which factors that negatively regulate the BCR pathway are modulated by BMS treatment. By analyzing both mRNA and protein levels, we measured a significant induction of the phosphatases PTPN6, PTPN22 and SHIP1. Since BMS also showed a downregulation of total SYK expression, we are analyzing the expression of the proto-oncogene CBL, an E3 ubiquitin ligase known to be involved in the negative regulation of SYK. Further studies should be undertaken to determine whether, in addition to its role as an IDO1 inhibitor, BMS may also have the ability to indirectly modulate and disrupt BCR signaling. Efforts are underway to identify the proteome-wide direct target of BMS in CLL cells. In conclusion, our limited and preliminary data suggest that BMS could be considered as a potential therapeutic strategy to target CLL cells with a double hit: by blocking the pro-survival effect of BCR signaling, one of the driving forces for CLL cell survival and proliferation, and by inhibiting IDO1/kynurenine action to restore sensitivity to key leukemia treatments.

Disclosures Luppi: *Jazz Pharma:* Membership on an entity's Board of Directors or advisory committees; *MSD:* Membership on an entity's Board of Directors or advisory committees; *Daiichi-Sankyo:* Membership on an entity's Board of Directors or advisory committees; *Sanofi:* Membership on an entity's Board of Directors or advisory committees; *Abbvie:* Membership on an entity's Board of Directors or advisory committees; *Novartis:* Membership on an entity's Board of Directors or advisory

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