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Brusatol induces apoptosis in aggressive lymphoma cells in vitro and synergizes with Venetoclax

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Aggressive lymphomas are the most common lymphoid malignancies in adults with an increasing incidence. Despite the available therapy, one third of DLBCL patients experiences treatment failure. One step forward seems to be Venetoclax, an FDA-approved Bcl-2 inhibitor. Here, we investigated the potential of Brusatol in the treatment of aggressive lymphoma cells as a single agent or in combination with Venetoclax. In ten cell lines representing different types of lymphomas, Brusatol induced cell growth inhibition in a concentration-dependent manner. Based on the results of apoptosis assays, they can be grouped into cell lines more and less sensitive to Brusatol. Cell cycle analysis showed an increased cell number in the subG1 phase in more sensitive cell lines. Western blot results of the more sensitive cell lines revealed reduced levels of Bcl-2, Bcl-XL, Mcl-1, p53 and Myc. Interestingly, the protein expression profile of untreated cells indicated that cell lines with higher Myc levels were more sensitive to Brusatol. mRNA expression analysis showed that the reduction of affected proteins occurred mainly at the protein level. Thus, we examined the effect of Brusatol on protein biosynthesis using click chemistry and observed inhibition of protein translation. Furthermore, co-treatment of Brusatol with Bcl-2, Bcl-XL and Mcl-1 inhibitors, respectively, revealed a higher apoptotic effect compared to these substances alone. Finally, the combination of Brusatol and Venetoclax synergistically increased lymphoma cell killing. Our data indicate that Brusatol efficiently induces cell death by reducing the expression of prosurvival proteins in aggressive lymphoma cells, especially in these with higher Myc levels. Additionally, the combination of Brusatol with Venetoclax results in enhanced induction of apoptosis. Thus, our study suggests that Brusatol, alone or in combination with Venetoclax, represents a very interesting agent for development of novel anti-lymphoma therapies.