

MECHANISM OF ACQUIRED RESISTANCE TO ABT-199 (VENETOCLAX) IN MV4-11 CELL LINE

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ABSTRACT

Venetoclax (ABT-199) is a highly selective B-cell lymphoma 2 (BCL-2) inhibitor. It recently received accelerated US FDA approval for use in combination with hypomethylating agents or with low-dose cytarabine in elderly or acute myeloid leukemia (AML) patients unfit for other treatment. Venetoclax-based AML treatment showed a tolerable safety and favorable overall response rate in elderly patients with AML. The acquisition of resistance to Venetoclax in AML is the leading cause of treatment failure. Resistance to ABT-199 is generally attributed to increased levels of MCL-1 and/or BCL-XL, or acquisition of mutations in the BCL-2 gene. To study the mechanisms of acquired ABT-199 resistance, we created ABT-199 resistant MV4-11 cells by treating MV4-11 cells with incremental doses of the drug starting from 1nM to 100nM for eight weeks. Five ABT-199 resistant MV4-11 clones were then isolated after culturing the cells in methylcellulose based medium. (MV4-11 ABT-199/R1 through 5). The MV4-11 ABT-199R clones demonstrated 160 – 350-fold higher resistance to ABT-199 than the parental cells. Microarray-based gene expression profiling of the two resistant clones (ABT-199/R1, ABT-199/R2) in comparison to the parental cell line (MV4-11) showed downregulation of BAX gene expression. We subsequently performed genomic DNA PCR for the BAX gene that revealed a micro-deletion in the resistant clones that included the promoter region and the first three exons of the BAX gene. Due to BAX gene deletion, the resistant clones also demonstrated co-resistance to ABT-737 (BCL-2 and BCL-XL inhibitor), S63845 (MCL-1 inhibitor), and S55746 (BCL-2 inhibitor).

In summary, we are reporting a novel mechanism of Venetoclax resistance by genomic deletion of BAX in MV4-11 cells. As a result of BAX gene deletion, the inhibitors of BCL-2, BCL-XL, and MCL-1 are rendered ineffective in inducing apoptosis. Alternative mechanisms of apoptosis induction need to be explored to overcome BAX deletion-induced resistance. Screening of BAX gene locus in patients showing ABT-199 resistance is advised.