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Evaluation of NAV2729 in combination with imatinib in apoptosis induction in chronic myeloid leukemia cells (K562), an *in vitro* study

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Despite the clinical success of imatinib in chronic myeloid leukemia (CML), drug resistance and adverse effects remain significant challenges, driven in part by tumor-derived extracellular vesicles (TEVs) that promote drug efflux and intercellular survival signaling. While TEV inhibition represents a promising strategy to augment therapy, no studies have yet explored targeting the ARF6-mediated TEV pathway in CML or evaluated its synergy with tyrosine kinase inhibitors. This study addresses this critical gap by investigating the novel combination of imatinib and NAV2729 a selective ARF6 inhibitor known to block TEV release in solid tumors but untested in hematological malignancies to overcome resistance and enhance therapeutic outcomes. The K562 CML cell line was treated with imatinib, NAV2729, or a combination of both for 48 h. Cell viability and metabolic activity were assessed using trypan blue exclusion assay and MTT assay, respectively. Apoptosis was analyzed through Annexin V/PI staining, while gene expression levels were determined using real-time PCR. EV size distribution and concentration were evaluated by dynamic light scattering. The combination treatment demonstrated superior efficacy in reducing cell viability and metabolic activity compared to either drug alone. Furthermore, the combination therapy induced apoptosis by upregulating the anti-apoptotic *BCL-2* and the pro-apoptotic *BAX* gene. Notably, the combined treatment also significantly reduced the number of EVs released by K562 cells. These findings suggest that targeting both CML cells and their secreted EVs with a dual therapeutic approach may enhance the efficacy of Imatinib therapy and potentially overcome drug resistance. Additionally, EVs could serve as valuable biomarkers for monitoring disease progression and treatment response in CML.

Keywords: ARF6 inhibition, Drug resistance, Tyrosine kinase inhibitor, Apoptosis, Tumor microenvi