Integrative in Silico Repurposing of Kinase Inhibitors for Gastric Cancer Using a Multi-Target Precision Medicine Strategy

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Abstract

With molecular heterogeneity, late diagnosis, and resistance to treatment being some of the driving forces behind gastric cancer burden worldwide, precision oncology approaches with multi-target capabilities are becoming increasingly desirable. Drug repurposing allows faster and cheaper access to clinically approved candidate molecules with already established safety profiles and pharmacokinetics (PK) parameters. In this study, we developed a pipeline of in silico methods to assess the multi-target drug repurposing landscape of five approved kinase inhibitors - crizotinib, dasatinib, erlotinib, imatinib, and venetoclax against four gastric cancer-related kinases chosen based on their biological importance in cancer cell proliferation, metastasis, and therapeutic resistance. The AutoDock Vina combined with replicate docking and clustering analysis, enabled the identification of both high-affinity and reproducible binding modes, emphasizing the importance of binding stability in functional target engagement. The docking protocol was successfully validated by re-docking each protein's native ligand. Cross-target binding relationships were also noted, indicating structural promiscuity typical of kinase inhibitors. Multi-Parametric ADMET profiling, including gastrointestinal absorption, P-glycoprotein substrate status, cytochrome P450 inhibition, and toxicity prediction across SwissADME, pkCSM, and ADMETlab 3.0 was used to filter drugs with undesirable pharmacokinetics and drug efflux properties. Overall, dasatinib possessed the most optimal drug profile with stable binding across predicted targets and favorable ADMET properties while, erlotinib demonstrated target interactions relevant to brain metastasis and cancer-of-origin pharmacology. This pipeline identified dasatinib as a prime candidate for gastric cancer drug repurposing efforts and can be readily applied to other targets for precision oncology and drug repurposing efforts.

Keywords

Drug repurposing, gastric cancer, molecular docking, admet profiling, multi-target therapy.