Systems pharmacology analysis of oncology drug combinations to evaluate adverse events due to drug-drug interactions

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Objectives: Targeted therapy drug (TTD) side effects are frequently unexpected and long-term toxicities detract from otherwise impressive tolerability and exceptional efficacy of new TTDs. Efficacy of TTDs is compromised by an additional host factor, i.e. serious drug-drug interactions (DDI). Using a systems pharmacology approach and trastuzumab-drug pairs, the objectives were i) to investigate the underlying molecular mechanisms triggering cardiotoxicity, one of its most severe adverse drug reaction (ADR) of trastuzumab and ii) to compare findings from trastuzumab (#1) alone and in combination with doxorubicin (#2), tamoxifen (#3), paroxetine (#4) and/or lapatinib (#5).

Methods: The data analytical platform “Molecular Analysis of Side Effect” (MASETM) was used to analyze data from the FDA Adverse Event Reporting System and link those findings to chemical and biological databases for molecular pathway and target evaluation. MASETM uses the proportional reporting ratio to assess the statistical relevance of the ADR occurrence and the molecular mechanisms causing a specific ADR. The established hypotheses of molecular causation of cardiotoxicity were evaluated through literature findings and compared to our findings.

Results: We found the combination therapy of #1 and #2 induced a synergistic effect of mitochondrial dysfunction in cardiomyocytes through different molecular pathways such as BCL-X and PGC-1α proteins, leading to a synergistic effect of cardiotoxicity. We found, on the other hand, #1-induced cardiotoxicity was diminished by concomitant uses of #3, #4 and/or #5 during treatment with #1. Each of both #3 and #4 caused less cardiotoxicity through an increase in the antioxidant activities such as glutathione conjugation. #5 decreased the apoptotic effects in cardiomyocytes by altering the effects of #1 on BCL-X proteins.

Conclusions: This systems-based approach provides an exemplar for a detailed investigation of an ADR, i.e. cardiotoxicity, due to a DDI at the pathway and target level and provides a process to better understand drug pair adverse events.