ANALYSIS OF MICROTUBULE TARGETING DRUGS AND MITOTIC SLIPPAGE

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Introduction: Microtubule (MT) inhibiting drugs are widely used in cancer treatment due to their ability to interfere with cell proliferation, cell cycle and cause cell death. MT drugs have a striking effect on cell cycle via mitotic arrest, this often leads to a mitotic slippage, when a cell fails to divide and forms a polyploid multinucleated cell, the phenomenon is not widely described. Some sources reported that Taxol treated cells acquire micronuclei after the mitotic slippage, however further information is mostly unknown. Thus, in this work we investigated MT-targeting drugs' effects on cancer cells describing the process of mitotic slippage and identified mitostatic, cytotoxic doses and concentration ranges, where mitotic slippage was common.

Methods: In order to define how human cancer cells (A549, HaCaT, U118, PC-3 and HT1080) respond to different MT-inhibiting agents (Nocodazole, Taxol, and Vinorelbine), they were visualized for 72 hours by time-lapse microscopy (on EVOS FL Auto 2) with 10 minutes intervals and analyzed using FIJI ImageJ software.

Results: We identified particular drug concentrations for each cell line that correspond to a mitostatic concentration, where at least half of cells divided after significant delay (more than three-fold, in comparison with normal mitosis), and a cytotoxic concentration, where more than half of mitotic cells died. The ratio between cytotoxic and mitostatic concentrations are 10-30 fold for Taxol and Nocodazole and 30-300 fold for Vinorelbine. There was no direct correlation between dose, drug type, or cell line and duration of mitotic arrest. In this range we frequently observed mitotic slippage, characterized either by the absence of cytokinesis, or as a result of incomplete cytokinesis when daughter cells fused with each other. After the mitotic slippage, cells commonly had multiple nuclei (>3) and never form single large nucleus as reported elsewhere. The size and number of the nuclei in the post-slippage cells did not depend on the drug type or concentration.
Conclusion: Mitotic slippage is a common outcome of mitotic arrest by anti-MT drugs applied in a concentration above mitostatic threshold. Viability of the cells after mitotic slippage requires further elucidation.