PROLONGED INHIBITION OF CELL PROLIFERATION BY SHORT-TERM EXPOSURE TO CERTAIN ANTI-MITOTIC DRUGS

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Background: Mitotic inhibitors are widely used in cancer therapy to arrest rapidly dividing cells by disrupting spindle dynamics [1], yet most studies evaluate their effects under prolonged or continuous exposure, which does not reflect physiological conditions [2,3]. *In vivo*, mitotic inhibitors are rapidly cleared through metabolism and excretion, making actual tumor exposure transient. The long-term cellular consequences of such short-term exposures, particularly in resistant cancer cells, remain poorly understood.

Materials and methods: This study investigates how brief (2-hour) treatment with various mitotic inhibitors—nocodazole, paclitaxel, epothilone B, vinorelbine, and SB-743921—affects the fate and proliferative capacity of A549 lung carcinoma cells.

Results: At minimal mitostatic concentrations, all drugs effectively induced mitotic arrest, but their downstream outcomes differed. Epothilone B and vinorelbine promoted abnormal divisions and multinucleation, while SB-743921 primarily caused slippage, leading to large mononucleated cells. Despite drug washout and restoration of microtubule dynamics, normal mitosis remained suppressed for up to 6 days in most treatments except nocodazole. Life history analysis revealed delayed mitotic progression and abnormal outcomes after drug removal. Long-term monitoring showed delayed and drug-specific recovery: paclitaxel, vinorelbine, and SB-743921 led to gradual proliferation recovery, while epothilone B caused persistent arrest. Ki67 staining and β- galactosidase assays confirmed that short-term treatments induced prolonged proliferative arrest and senescence.

Conclusion: These findings challenge the assumption that sustained drug exposure is required for efficacy and emphasize the lasting impact of even brief mitotic inhibition. By revealing how short exposures affect recovery, this study supports the design of clinically relevant, personalized regimens that optimize tumor cell targeting while reducing toxicity and improving patient outcomes.

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Key words: Mitotic inhibitors, proliferation arrest, cell cycle, mitotic arrest

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