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The anti-proliferative and pro-apoptotic effect of topotecan in combination with thymoquinone in acute myelogenous leukemia

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Context: Topotecan (a novel topoisomerase I inhibitor and a water-soluble camptothecin analog) is active against numerous human tumor cell lines, and has shown promising antineoplastic activity in solid tumors and acute leukemia. Due to the primary dose-limiting toxicity of topotecan which is myelosuppression, it is necessary to identify other chemotherapeutic agents that can work synergistically with topotecan, potentially increasing its efficacy while limiting its toxicity. Many studies showed synergism upon combination of topotecan with other chemotherapeutic agents like Gemcitabine, bortezomin and CP-4055. Other studies report the increase in growth inhibition of gemcitabine or oxaliplatin when cells are pre-exposed to naturally occurring drugs such as thymoquinone.

Objective: The aim of this project is to study the mode of action of topotecan, in comparison with thymoquinone, on survival and apoptosis pathways in AML cell lines, and to investigate the potential synergistic effect of thymoquinone on the anti-tumor activity of the chemotherapeutic agent topotecan.

Methods: U 937 cells were incubated with different topotecan and thymoquinone concentrations for 24 and 48 hours, separately, and in combination. Cell proliferation was determined using the WST-1 reagent. The effect of the drugs on the expression of proteins involved in apoptosis, namely Bax, Bcl2 and p53 was determined by western blot analysis.

Results: Thymoquinone and topotecan exhibit dose and time dependent anti-proliferative effects on U937 cells when applied separately. In combination, the reduction in proliferation was extremely significant, even in non-cytotoxic doses; addition of thymoquinone (10 μM) to topotecan (50 μM), lead to a reduction in proliferation from approximately 100 to 54 % after 24 hours, and from 42 to 17 % after 48 hours. The combination of thymoquinone with topotecan exhibited a major increase in the expression levels of Bax/Bcl2, pointing out to the pro-apoptotic effect of the drugs on the cells. Moreover, the up-regulation of p53 upon combined treatment demonstrates a p53 dependent pro-apoptotic effect of the drugs on AML cells *in vitro*.

Conclusion: In summary, thymoquinone, when combined with topotecan in non-cytotoxic doses, produced synergistic anti-proliferative and pro-apoptotic effects in AML cells.

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