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The impact of rosuvastatin and omeg-3 on the antitumoral activity and cardiotoxicity of doxorubicin compared to captopril effect in experimentally-induced hepatocellular carcinoma in mice

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Background: Despite its usefulness as an antineoplastic agent, doxorubicin (DOX) has been associated with the development of acute and chronic cardiotoxicity.

Aim: The present study for the first time was undertaken to evaluate and compare the potential antitumoral effects of three drugs; (captopril, rosuvastatin and omega 3) in combination with DOX against diethylnitrosamine (DEN)-induced hepatocellular (HCC) in mice, in an attempt to achieve an improved antitumoral effect devoid of cardiotoxicity.

Methods: The effect of combined treatments was evaluated by analyzing cell viability *in vitro*, studying tumor apoptosis (Bcl-X and Bak) and angiogenesis (VEGF) *in vivo*, assessing cardiac inflammation (TNF-α) and oxidative stress (MDA,GSH, SOD), and evaluating variations of heart weight/body weight ratio as a general indicator of animal health status. Histopathological assessement of liver and heart were also performed.

Results: Compared to the DEN group, administration of doxorubicin (12 mg/kg ip) resulted in a significant increment in Bak expression and a significant decrease of hepatic VEGF level. Furthermore, captopril (25 mg/kg, *po*), rosuvastatin (20 mg/kg, *po*) and omega-3 (1gm/kg, po) treated groups were shown to have more pronounced reduction of hepatic VEGF measured. Marked cardioprotection was noticed with the combination regimen.

Conclusion: The antitumoral, apoptotic and antiangiogenic effects demonstrated by the combined treatment with rosuvastatin, captopril or omega 3 and DOX, is further emphasized by lack of toxicity. The most promising results were obtained with rosuvastatin and captopril treatment. These data raise important issues that may impact how these drugs can best be included in chempotherapy regimens.

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