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Effects of Combined Doxorubicin and Chloroquine in the Lung of Mice with Ehrlich Ascites Carcinoma

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Objectives: Combined usage of chemotherapeutic agents and autophagic inhibitors represents a new treatment strategy. One of the commonly used chemotherapeutic drugs in cancer treatment is Doxorubicin (DOXO). Autophagy inhibitor Chlorokine (CQ) has recently been used in combination with chemotherapeutic drugs to improve the effectiveness of cancer treatment. Nitric oxide (NO) is a signaling molecule associated with angiogenesis and tumor development. Indication of the presence of continuous NO changes is important to determine the development of lung tissue damage. We aimed to reveal any ameliorative potential of combined usage of doxorubicin (DOXO) and chloroquine (CQ) in the lung of mice with Ehrlich Ascites Carcinoma (EAC) by using histology, immunohistochemistry and some cellular injury markers.

Methods: One control (n=8) and eight experimental groups (n=10) of Adult female BALB/c mice were inoculated with 2.5x106 EAC cells subcutaneously. Two different doses of DOXO (1.5 mg/kg and 3 mg/kg) and CQ (25 mg/kg and 50 mg/kg) alone or in combination were applied intraperitonally on days 2, 7, and 12 after inoculation, while physiological saline was injected to control group. Sacrificed animals lung tissue samples on day 14 were subjected to histology and immunohistochemistry for inducible and endothelial nitric oxide synthase (iNOS and eNOS, respectively). Serum catalase, glutathione peroxidase, and malondialdehyde levels were measured by ELISA.

Results: Immunohistochemistry results indicated decreased iNOS and eNOS levels in the groups receiving 1.5 mg/kg DOXO ($p<0.05$, eNOS), alone and in combination with 25 mg/kg ($p<0.05$, iNOS; $p<0.05$, eNOS) and 50 mg/kg ($p<0.01$, iNOS; $p<0.001$, eNOS) CQ. Disrupted alveolar structure observed in the control group was partially recovered in all the groups receiving combined DOXO and CQ. Although not significant, catalase and glutathione peroxidase levels increased in the group receiving combined 3 mg/kg DOXO and 25 mg/kg CQ, while malondialdehyde levels significantly decreased ($p<0.01$) in the group receiving combined 1.5 mg/kg DOXO and 25 mg/kg CQ.

Conclusion: By lowering nitrosative stress, combined usage of DOXO and CQ has ameliorative effects on diseased lung tissue.

Keywords: Doxorubicin, chloroquine, lung, mouse, iNOS, eNOS