Cardiotoxic Effects of Doxorubicin In a Short-Time Mouse Model

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Doxorubicin (DOXO) is widely used for its anti-cancers activity. Its main side effect is cardiotoxicity, which can be acute that is dose-independent, characterized by arrhythmias, congestive heart failure and conduction disorders or chronic, that is dose-dependent, with irreversible effects like heart failure.

This work was aimed to evaluate the early effects of DOXO in a short-time murine model, taking into account the main indicators of cardiotoxicity, such as pro-inflammatory cytokines, calcium homeostasis proteins, cardiac function. DOXO has been administered to C57B6 mice in two dosages (0.2 or 1 μg/mouse) and the effects were observed in three experimental times (24h, 3 or 7 days).

Echocardiogram, performed before DOXO administration and before mice sacrifice, showed that DOXO reduces Ejection Fraction, a main parameter of cardiotoxicity, in a dose- and time-dependent manner. ELISA test demonstrated an increase in IL-6, IL-17, TNF-α levels. The relationship between cardiotoxicity and inflammation was supported by an increase of nitrites levels and by IKK and INOS expression alterations in DOXO-treated mice. Western blot analysis showed alterations in the expression of proteins involved in calcium homeostasis: reduced SERCA-2 and, at the same time, increased phospholamban expression. It was also observed a dose- and time-dependent reduced expression of Connexin43, an important protein involved in cell to cell communication and with a cardioprotective role.

In conclusion, this work shows that, in our model, DOXO cardiotoxicity is an early event which involves the expression of important factors implicated in inflammation and in calcium homeostasis that may lead to several and irreversible effects.