ANTHRACYCLINES AND THE PROBLEM OF DOSES: LESSONS FROM A TRANSLATIONAL MODEL OF HUMAN HEART

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Background: The antitumor anthracycline, doxorubicin (DOX), can cause heart failure (HF) upon cumulative administration. Lowering the cumulative dose of DOX proved useful to minimize HF risk and yet, there is a growing concern that HF might occur after doses of DOX that were thought to be safe. Clinical trials that prospectively address such concerns are lacking. Studies of laboratory animals would be of uncertain exploratory value as they are limited by species- and strain- related differences in the levels of formation of toxic metabolites. Because HF risk correlates with cardiac exposure to DOX, cumulative doses associated with HF risk were re-explored by modelling the accumulation of anthracycline pools in human myocardium.1

Methods: Ex vivo myocardial samples were used in vitro to simulate clinical pharmacokinetics of DOX rapid infusions, liposomal DOX infusions, or DOX slow infusions. The accumulation of anthracycline pools was measured and incorporated into newly developed equations from which risk versus dose curves were obtained.

Results. For DOX rapid infusion the experimental curve identified a 5% risk dose that was congruent with a previously reported clinical value (380 versus 400 mg/m2, respectively); however, 1-2% risk occurred after lower doses than reported. Simulations of gain-of-function polymorphism of carbonyl reductase increased the conversion of DOX to its unclearable polar metabolite, doxorubicinol (DOXOL), and expanded anthracycline pools. This caused the 5% risk dose to decrease to 330 mg/m2 and 1-2% risk to occur after doses as low as 180-230 mg of DOX/m2. Replacing DOX rapid infusion with slow infusions or liposomal DOX caused formation of smaller anthracycline pools, did not generate DOXOL, increased the 5% risk dose to 750-800 mg/m2, and prevented HF risk aggravation by carbonyl reductase polymorphism.

Conclusions: Modelling human myocardium exposure to DOX rapid infusions supports concerns about HF risk from “safe” cumulative doses of DOX. Further dose reductions would limit the oncologic efficacy of DOX but cardioprotective options should be given to all patients candidate for anthracyclines.2 Liposomal formulations and slow infusions merit considerations in these settings.

1. Salvatorelli E., Menna P., Chello M., Covino E. and Minotti G. (2017) submitted

2. Menna P. and Salvatorelli E. (2017) Chemotherapy 62:159-168.