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MEETING ABSTRACTS

COMPARISON OF TOPOISOMERASE 2 INHIBITORS DEXRAZOXANE AND XK469 FOR THE PREVENTION OF ANTHRACYCLINE CARDIOTOXICITY

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Despite its unprecedented efficacy against some cancers, anthracycline cardiotoxicity represents the main limitation of its clinical use. Its' mechanisms are elusive, but quite recently TOP2B was addressed as a possible target in cardiomyocytes (1). This study introduces the putative TOP2B selective inhibitor XK469 (2) as a potential cardioprotective agent in the management of anthracycline cardiotoxicity. Its' potential was compared with the cardioprotection of the only approved cardioprotective drug dexrazoxane (DEX, ICRF-187) (3). Initially, the selectivity of XK469 and the character of TOP2 inhibition were re-examined *in vitro* using isolated TOP2A and TOP2B isoforms and the detection of DNA-TOP2 covalent complexes. Contrary to XK469 original presentation, we found it rather non-selectively targets both enzyme isoforms and does induce only very little covalent complexes. Consequently, *in vitro* pilot results suggested that XK469 was protective against daunorubicin (DAU)-induced cardiotoxicity *in vitro* in a slightly higher concentration than DEX. Nevertheless, *in vivo* XK469 was not cardioprotective in both acute and chronic settings. This can be partly explained by marked differences in the pharmacokinetics of the two agents. Modified incubation protocol in neonatal cardiomyocytes reflecting the longer half-life of XK469 revealed an increased trend in its toxicity. Thus, despite the promising characteristics of XK469, the cardioprotective ability of XK469 was not confirmed.

Keywords: Anthracycline cardiotoxicity; DNA topoisomerase II; dexrazoxane; XK469

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