MMSL
Military Medical Science Letters
Since 1925

Mil. Med. Sci. Lett. (Voj. Zdrav. Listy) 2022, 91 (supplementum 1)
ISSN 0372-7025 (Print)
ISSN 2571-113X (Online)

MEETING ABSTRACTS

GK-667 - A NEW PROMISING CARDIOPROTECTANT AGAINST CHRONIC ANTHRACYCLINE CARDIOTOXICITY *IN VIVO*

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Anthracyclines (ANT) are very effective anticancer drugs, but they are feared for their cardiotoxicity. The only drug approved to counteract this severe side effect in clinical settings is a bisdioxopiperazine dexrazoxane (DEX). However, another bisdioxopiperazine agent ICRF-193 was recently shown to be more effective than DEX *in vitro*. Its poor water-solubility was solved by design of its prodrugs, from which GK-667 was selected for *in vivo* studies. The aim of this study was to examine cardioprotective effects of GK-667 on a rabbit model of chronic ANT cardiotoxicity *in vivo*. Cardiotoxicity was induced with daunorubicin (DAU; 3 mg/kg, *i.v.*, weekly, 10 weeks) and GK-667 (1 or 5 mg/kg, *i.v.*) was administered 30 min before each DAU dose. DAU-induced mortality, blood congestion and left ventricular (LV) dysfunction were completely prevented with GK-667. Dose-dependency of the effects was visible on molecular markers of cardiac damage and dysfunction. GK-667 prevented p53-mediated DNA damage response induced in LV by the chronic, as well as acute DAU administration (single dose). This was attributable to topoisomerase IIβ inhibition provided by active metabolite of GK-667 (ICRF-193). In addition, the plasma pharmacokinetics of DAU and its main metabolite was not altered by GK-667 administration *in vivo* and it also did not reduce anticancer effect of DAU *in vitro*. Therefore, GK-667 is a promising drug candidate for further research and development.

Supported by the Project InoMed CZ.02.1.01/0.0/0.0/18_069/0010046 co-funded by the ERDF and the project GAČR No. 21-16195S.

Keywords: anthracycline; cardioprotection; cardiotoxicity; dexrazoxane; ICRF-193