The clinically active PARP inhibitor olaparib ameliorates doxorubicin-induced cardiotoxicity in both in vitro and in vivo model

D. Chen¹, A. Croft¹, T.J. Haw¹, C. Kelly¹, A. Leong¹, A. Sverdlov¹, D. Ngo¹

¹University of Newcastle, Newcastle, Australia

Funding Acknowledgements: Type of funding sources: Foundation. Main funding source(s): Australia Heart Foundation

Introduction: Inhibition of poly (ADP-ribose) polymerase (PARP) has been shown to be cardioprotective in acute and chronic myocardial injury. Additionally, PARP inhibitor, Olaparib, is a clinically effective anti-cancer agent. Activation of PARP pathway has been suggested to be involved in cardiotoxicity arising from Doxorubicin (DOX, one of the most used anticancer drugs). It is thus, entirely possible that PARP inhibition could be a novel pathway to prevent DOX-induced cardiotoxicity (DIC).

Purpose: To determine the cardioprotective effects of Olaparib in preventing DOX-induced cardiotoxicity in in vitro and in vivo models.

Methods:
In vitro: Human cardiomyocytes (HCMs) were treated with DOX at 1uM (EC50) +/- various doses (15.6nM, 1uM, 80uM, 100uM and 150uM) of Olaparib at 72hrs. Cell viability was assessed via CellTiter-Glo®. The mRNA expressions of treated HCMs were performed by qPCR.

In vivo: Female C57BL/6 mice (6-8 weeks old) were administered: A) DOX at 5mg/kg/week for 6 weeks via IP injections, B) vehicle of 0.9% saline and 5% DMSO in PBS, C) Olaparib at 50mg/kg was administered 3 times/week, D) Olaparib at 50mg/kg was administered 3 times/week, followed by DOX treatments. Cardiac function was assessed by echocardiography at baseline and end of 6 weeks’ treatment.

Results: For the in vitro model, Doxorubicin induced marked reduction in HCMs cell viability. Concomitant Olaparib treatment at higher doses (80uM, 100uM, 150uM) significantly preserved DOX-induced cell viability after 72 hours of treatment. Molecular analysis in HCMs showed DOX-induced upregulation of mRNA gene expressions for apoptosis: Casp3, DNA damage: BBC3, and cardiac remodelling: TGF-β; all of which were reversed by Olaparib. In vivo: we found significant reduction of left ventricular function and increased ventricular wall thickness in DOX treated group after 6 weeks’ treatment compare to baseline [LVEF%: 52.4±1.3 vs. 56.5±2.0, P=0.02; FS%:16.7±1.4 vs. 20.1±1.3, P=0.03; Total Wall thickness (mm):2.1±0.1 vs. 1.9±0.1, P<0.05]; whereas the mice pre-treated with Olaparib in combination with DOX showed preservation of cardiac functions between endpoint and baseline.

Conclusion: Olaparib protected HCMs against DIC and improved cardiac function in DIC mice model. Our findings indicate that Olaparib could provide cardioprotection in DOX-induced cardiotoxicity.