Dissecting the Cellular Mechanisms of Cardiotoxicity by Anthracycline and Tyrosine Kinase Inhibitors

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Background. Cardiomyopathy and symptomatic Congestive Heart Failure (CHF) have limited the clinical use of Anthracyclines (DOXO). However, Tyrosine Kinase Inhibitors (TKIs) have been also implicated in cardiovascular events.
DOXO is known to cause irreversible cardiotoxicity most often manifesting years after treatment. This phenomenon has been attributed to free radical formation and metabolic dearrangement in cardiomyocytes. In addition, DOXO interacts with DNA by intercalation and stabilizes topoisomerase II complex after its breaking action on the DNA chain for replication.
TKIs represent a decisive turning point in the modern medicine and exert antineoplastic action by targeting multiple receptor kinases. Although these drugs directly aim oncogenic pathways, the clinical use of TKIs resulted in alteration of cardiac function. TKIs toxic effect seems to be manageable and reversible, however the development of late cardiovascular sequelae is more than speculative.
Aim. The mechanisms of cardiotoxicity by DOXO and TKI are poorly defined. Based on the recently introduced concept that the heart is not a post mitotic organ and contains a stem cell pool responsible for tissue homeostasis, we hypothesized that the myocardial progenitor cell compartments represent a complementary cellular target of anticancer therapy beyond cardiomyocytes.
Methods. To test this hypothesis, studies were performed on human and rat drug-induced cardiomyopathy. Human myocardial samples were obtained from cancer patients who died as a consequence of DOXO or Imatinib Mesylate (IM) administration. In young rats treated with different doses of DOXO and IM, cardiac function and changes in myocardial cell compartments were evaluated. In addition, the in vitro effects of the two drugs on human and rat Cardiac Progenitor Cells (CPCs) and human blood and lymphatic endothelial cells was investigated.
Result. In human and experimental rats, DOXO induced dilated cardiomyopathy, heart failure and necrotic and apoptotic cell death. Multiple foci of inflammatory damage resulting in scattered focal collagen deposition were present. A 2-fold increase in arteriolar and lymphatic density with a reduction of capillaries was present. The number of c-kit+CPC in DOXO treated hearts was not significantly affected, however the fraction of senescent and apoptotic cells was several fold higher than controls.
Experimentally, IM treatment developed a cardiomyopathy characterized by a restrictive type of LV remodeling with impaired cardiac function. No significant myocardial fibrosis was observed. Morphometric analysis indicated that IM induces a significant decrease in arteriolar and lymphatic vessels. The number of c-kit+ CPC and PDGFR+ progenitors was significantly reduced in the myocardium. TEM analysis and immunogold staining of IM treated human and rat myocardium documented severe mitochondrial damage consistent with autophagy in cardiomyocytes, arterioles and lymphatics.
In vitro cytotoxic effect of DOXO or IM on CPC showed differences in kinetic and molecular pathways implicated in cell death, proliferation and DNA damage/repair. Both drugs to a different extent affected these cellular processes, however DNA repair was allowed in IM treated cells whereas restoration of genotoxic damage upon DOXO exposure was blunted even after drug washout. Importantly, in agreement with in vivo data, autophagy was a prominent feature of IM treated CPC. Altered endothelial cell function by IM was confirmed *in vitro* by wound healing and matrigel tube formation assays on lymphatic and blood cells.
Conclusion. Our study by documenting the different cardiotoxic effects of DOXO and IM, provides strong evidence of a common alteration of myocardial cell homeostasis. If our hypothesis is correct, the possibility of preventing cardiotoxicity by preservation and/or expansion of the resident stem cell pool responsible for cardiac repair may open new therapeutic options for this emerging clinical issue.