11th يوم البحث العلمي بكلية الصيدلة
College of Pharmacy Research Day

جامعة الملك سعود
King Saud University

The Potential Protective Role of Valsartan Against Dasatinib-Induced Cardiotoxicity

INTRODUCTION

- *Dasatinib* is a BCR-ABL tyrosine kinase inhibitor which target various types of cancers.
- Although rare, but *Dasatinib* has some serious cardiovascular toxicities and the rarity of it makes it more important to study.
- *Valsartan* is an antihypertensive medication that belongs to a class called Angiotensin II Receptor Blocker.
- *Valsartan* is known to reduce cardiotoxicity of other chemotherapeutic agents that might induce toxicities in similar ways.

OBJECTIVES

- Determine the toxic dose of *Dasatinib* that cause cardiotoxicity by measuring different parameters. And the survival rate of the model.
- Evaluate the efficiency of *Valsartan* against *Dasatinib-induced cardiotoxicity* after treating with different doses of *Valsartan*.
- Determine the underlying mechanisms by which *Valsartan* induce the protective effect against *Dasatinib-induced cardiotoxicity*.

METHODS

- Cell viability assay.
- Methyl thiazolyl tetrazolium (MTT) assay will be used to assess cell viability.
- Cell count by hemocytometer.
- H9C2 cells will be seeded into 6-well plates at a density of 2 × 105 cells/well for 24 hrs.
- Evaluation of apoptosis.
- Annexin V/propidium iodide staining will be used to detect apoptosis
- Reactive oxygen species (ROS) detection.
- Western blotting to identify protein levels of p21, p62, and p53 .
- LC3 and p62 are marker proteins for the autophagy pathway.

RESULTS

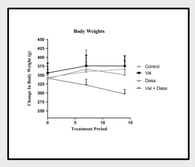

Figure 1: Changes in the body weight of experimental rats in various treatment groups. Body weight was measured every 5 days from day 1 of treatment initiation until day 14. No significant change in body weight was observed in rats treated with Val (30 mg/kg) or Val + Dasa (30 + 50 mg/kg, respectively). However, rats treated in Dasa monotherapy were associated with significant reduction in body weight.

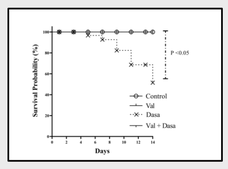

Figure 2: Kaplan-Meier plot to assess the survival probability of various treatment groups. In control and Val group, no rats were lost due to death. However, several deaths were recorded in rats treated with Dasa. On the other hand, no death was observed in rats pretreated with Val (30mg/kg) + Dasa (50 mg/kg). Statistical significance was assessed using log-rank test.

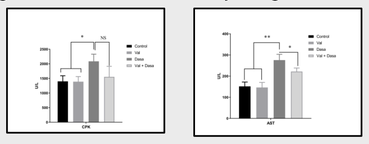

Figure 3: blood biomarkers analysis of liver and heart injuries. The levels of alanine aminotransferase (ALT), and creatine phosphokinase (CPK) were significantly increased after Dasa treatment. On the contrary, pretreated mice with Val **appeared** to have normal levels.

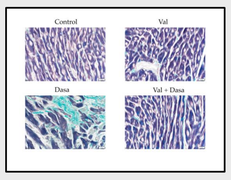

Figure 4 : Histopathological analysis of cardiac tissues. rats treated with Dasa showed chronic inflammation with presence of macrophages (arrowhead) in addition to signs of chronic myocardial infarction (arrow). Val + Dasa group showed minimal changes compared to control (magnification 60X).

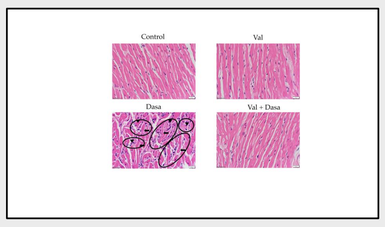

Figure 5: -Fibrotic changes of the cardiac tissue obtained from experimental rats. Control and Val groups showed no signs of fibrosis. Val + Dasa showed minimal fibrosis in the interstitial tissue and around the vasculature. However, Dasa group showed server fibrotic scarring (light green) and surrounding the cardiomyocytes in the intestinal tissue. Masson's trichrome staining; ×60 magnification

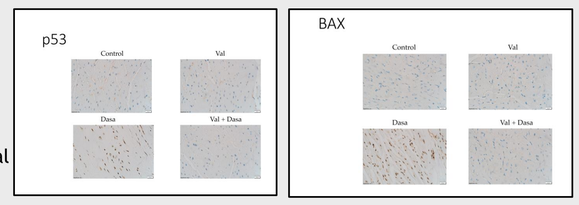

Figure 6: Immunohistochemical analysis of P53, BAX, and BCL-2 expression in cardiac tissue.

CONCLOSIONS

- In conclusion, our result suggests the cardioprotective effect of Valsartan against Dasatinib-induced cardiotoxicity through decreasing the cardiac enzymes like CPK and AST. Also, the histopathological and immunohistochemical findings indicate that Valsartan counteracts the detrimental effects of Dasatinib on cardiomyocytes.

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