In Vitro Effects of BCR-ABL Tyrosine Kinase Inhibitors on Endothelial Cells Survival and Functions

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Published in:
Special Issue: Abstracts of the 64th Annual Meeting of the Scientific Standardization Committee of the International Society on Thrombosis and Haemostasis, July 18–21, 2018

Publication date:
2018

Document Version
Publisher's PDF, also known as Version of record

Thirty five of them have acquired risk factors (arterial hypertension, dyslipidemia, diabetes mellitus, atrial fibrillation, obstructive sleep apnea, smoking, oral contraceptives, family history) and hyperhomocysteinemia. The prevalence of acquired risk factors for stroke are significantly higher in ischemic stroke patients without thrombosis and clinically significant stenosis.

Conclusions: We found that thrombophilia could be a risk factor for thrombosis or severe stenosis in young patients with stroke.

PB497 | *In Vitro* Effects of BCR-ABL Tyrosine Kinase Inhibitors on Endothelial Cells Survival and Functions

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Background: BCR-ABL tyrosine kinase inhibitors (TKIs) are the mainstay of the treatment for chronic myeloid leukemia (CML). New generation TKIs (dasatinib, nilotinib, bosutinib and ponatinib) increase the risk of arterial thromboembolism in patients with CML. Clinical data suggest that new generation TKIs might accelerate atherogenesis.

Aims: This research aims to determine the effect of BCR-ABL TKIs on endothelial cell survival and major functions using an *in vitro* model (i.e. HUVEC).

Methods: Viability was assessed using MTS and LDH assays following standard protocols. Expression of 3 adhesion molecules (i.e. ICAM-1, VCAM-1 and E-selectin) was quantified by on-cell ELISA after 4-hour TNF-α activation. Endothelial cell migration was evaluated by scratch assays (i.e. monitoring of wound closure of a scratch on confluent monolayer).

Results: At high concentration, dasatinib, nilotinib and ponatinib reduce cell metabolism. Additionally, high-dose ponatinib induces necrosis as demonstrated by increased LDH release. On-cell ELISA demonstrates decreased expression of 3 adhesion molecules (i.e. ICAM-1, VCAM-1 and E-selectin) by dasatinib, nilotinib and ponatinib at high concentration. This diminution correlates with the decreased viability of endothelial cell with these 3 treatments. Imatinib and bosutinib have no or little impact on adhesion molecule expression. Finally, scratch assays indicate that high-dose dasatinib inhibits endothelial cell migration whereas other TKIs do not have any impact.

Conclusions: Over the 5 commercialized BCR-ABL TKIs, dasatinib, nilotinib and ponatinib possess the most impact on endothelial cells and possibly promote atherosclerosis development through impaired endothelium permeability, enabling migration and trapping of lipoprotein into the intima. Determination of mechanism(s) by which TKIs promote cardiovascular events is required to implement appropriate risk minimization measures and select patients to whom the prescription of these drugs should be avoided.

PB498 | Impaired Fibrinolytic Activity in Nigerian Myocardial Infarction Patients

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Background: Myocardial infarction (MI) is referred to as the changes that occur in cardiac muscle and the sudden deprivation of circulating blood leading to necrosis of myocardial tissue. The pathogenesis has been well documented in countries with advanced medical technologies while in developing countries such as Nigeria, MI as an unfolding major cardiovascular events leading to sudden death in most cases.

Aims: This study was designed to ascertain the fibrinolytic patterns in acute MI events with a view to indicate their possible role in diagnosis and management.

Methods: A total of 10 acute myocardial infarction (AMI) patients together with 20 age and sex -matched apparently healthy subjects as controls were studied. Blood samples were taken at the point of admission (Day 0), on the 4th and 7th day respectively after treatment has commenced. Fibrinolytic indices such D-dimer concentration (DDC) and Euglobulin lysis time test (ELT) were measured with standard laboratory methods.

Results: We observed a significantly increase in Euglobin lysis time as well as in increased D-dimer levels AMI patients on admission compared with controls ($P<0.05$, respectively). DDC became significantly lowered from the 4th day of admission while all the ELT remained significantly high until the 7th day of admission and treatment ($P<0.05$, respectively). On the other hand lipids such as Cholesterol and HDL remained relatively unchanged from admission and throughout the duration of the study.

Conclusions: Conclusively, impaired fibrinolytic activity could be a major associated risk of thrombosis in Nigerians with AMI. The role of lipids in AMI pathogenesis in Nigerians seem to be unpronounced.

PB499 | Shear Enhances Fibrin-induced GPVI Shedding and Platelet ADAM10 Function

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Background: Fibrin, shear stress and active Factor X (FXa) induce glycoprotein (GP) VI shedding independent of direct thrombin activity. **A** **D**isintegrin **A**nd **M**etalloproteinase (ADAM) 10 is the main sheddase releasing human platelet soluble GPVI ectodomain.

Aims: To assess molecular links between these agonists and ADAM10 activity.