CRIZOTINIB-INDUCED DOWNREGULATION OF ESSENTIAL RTKS IN RAT HEART

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INTRODUCTION: Selective ALK (anaplastic lymphoma kinase) inhibition is indicated for the treatment of non-small cell lung cancer. Except ALK, crizotinib also inhibits activity of following receptor tyrosine kinases (RTKs) – c-MET, RON, ROS. Limited data exist about crizotinib activity on the other RTKs. RTKs play a key role in development and function of myocardium and some of them are implicated in heart metabolism. RTKs activity could be affected by tyrosine kinase inhibitor crizotinib. This could be reflected by RTKs expression in heart. The aim of this work is to assess the effect of crizotinib treatment on expression of selected RTKs in rat heart and detect its metabolic consequences in subacute model. METHODS: Male Wistar rats were treated with crizotinib every 24 hours in a dose 25 mg/kg suspended in methylcellulose vehicle p.o. for 7 days. Controls got methylcellulose vehicle p.o. mRNA expression of selected RTKs and their ligands were assessed by RT-qPCR method. C-peptide and glucagon in plasma samples were determined by ELISA. RESULTS: Expressions of Insr, Igf-1r, c-Met, downstream molecule Akt2 and the receptor ligands Igf-1 and Hgf were decreased in rat heart. Expressions of Vegfr1, its ligand Vegf and RTKs Pdgfra and Her2 remain stable. C-peptide and glucagon plasma levels were not changed. CONCLUSION: Crizotinib decreases expression of cardiac RTKs after short-term treatment. Decrease in RTKs expression is specific for those RTKs which relate not only to growth and apoptosis but also glucose metabolism and insulin signalling. Plasmatic c-peptide and glucagon do not participate on this effect. Potential downregulation of assessed RTKs could determine toxic crizotinib effect on myocardium.