**CARDIOVASCULAR EFFECTS OF CARFILZOMIB, A NEW PROTEASOME INHIBITOR, ON CORONARY ARTERY RESISTANCE, VASCULAR TONE AND VASCULAR REACTIVITY**

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*Background:*Carfilzomib (CFZ) is a proteasome inhibitor which was recently approved in the United States as a single agent for the treatment of patients with relapsed and refractory Multiple Myeloma (MM). Chemically it is a tetrapeptide epoxyketone and an analog of epoxomicin. A recent cross-trial analysis examining the safety profile of single agent carfilzomib in patients with relapsed and refractory MM reported an incidence of aggregated cardiac-failure events (including congestive heart failure, pulmonary edema, and decreased ejection fraction) of 7.2%. Of note, the use of CFZ is not contraindicated in patients with recent myocardial infarction/unstable angina who had been excluded in phase II safety trials.

*Aim of study***:** To investigate whether CFZ can exert *in vitro* effects on vascular tone and reactivity, as well as endothelial function.

*Methods and Results:*CFZ-mediated cardiovascular toxicity and potential pathophysiological mechanisms were assessed in an isolated experimental model of rabbit thoracic aortic-strips. In a first set of experiments, we evaluated the effect of single injections of CFZ on the basal tone of isolated aortic strips (n= 6) placed in 10 ml organ bath at 37°C containing Krebs-Henseleit solution. Vasoconscriction, as documented by an overall increase in tension of 0.5 g, was observed with increasing concentrations of CFZ (from 1 x 10-9 to 10 -7 mol/L; p:0.041). In a second set of experiments, the effect of three different spasmogenic agents [potassium chloride (KCl) (n= 6), noradrenaline (NA) (n= 6), and angiontensin II (A) (n= 6)] on naive aortic strips (group 1) was compared to that on aortic strips pretrated for 60 minutes with CFZ at a concentration of 15 nmol/L (group 2). Pretreatment with CFZ resulted in amplified vasocostriction (2.4±0.4 g vs 2.1±0.3 g for KCl administration; 2.5±0.3 g vs 2.0±0.2 g for NA; 2.6±0.2 g vs 2.0±0.2 g for A; all p<0.005) and impaired vasodilation following administration of nitroglycerin (NTG) on the plateau of contraction induced by each spasmogenic agent (100% vs 82% for KCl; 100% vs 67% for NA and 100% vs 51% for A; all p<0.05). In a third and final set of experiments, aortic strips pretreated with CFZ exhibited impaired relaxation, as compared to naive strips (100 % versus 40% in tension reduction; p:0.028), following administration of acetylcholine (Ach), an endothelium-dependent vasodilating agent, on the plateau of NA contraction.

*Conclusions:*Our findingsshowed that CFZ exerts significant *in vitro* effects on vascular tone and reactivity. CFZ increased the resting vasoconstricting tone and amplified the spasmogenic effect of different agents. Moreover, preincubation with CFZ decreased the anti-spasmogenic activity of NTG and reduced by over 50% the vasodilating effect of Ach, suggesting that CFZ can impair vasodilation by inducing endothelial dysfunction. Further studies are therefore warranted to better elucidate the vascular effects of CFZ, above all in the coronary vasculature, in order to establish its clinical safety in patients with known CAD and prior history of coronary spasm.