Cardiovascular functional and structural alterations induced by VEGFR-2 inhibitors axitinib and lenvatinib

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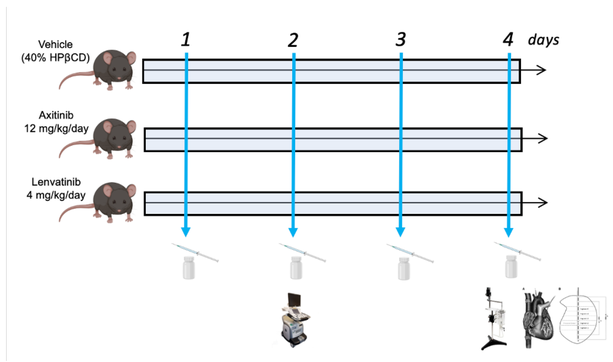
INTRODUCTION

Antiangiogenic therapies, also known as vascular endothelial growth factor receptor inhibitors (VEGFRIs), represent a novel approach in cancer treatment that has significantly improved cancer prognosis and survivorship. However, several cardiovascular complications have been identified as associated to these therapeutics, without being anticipated during preclinical evaluations[1]. The lack of clarity regarding the mechanisms and the extent to which VEGF inhibitors impact cardiovascular function complicates the therapeutic management of cancer patients who develop such adverse effects[2]. As a result, this study aims to characterise the impact of RTKIs targeting VEGFR-2 on cardiovascular physiology, as well as to improve the predictive value of existing preclinical approaches, in order to better define and limit the cardiovascular toxicities of these drugs.

METHODS

Male 10-week-old C57BL/6J mice were dosed with axitinib (12mg.kg^{-1}), lenvatinib (4mg.kg^{-1}) and vehicle (40% HPβCD) as an intravenous injection for 4 consecutive days. On day 2 of the treatment period, echocardiography was performed on all the groups. On day 4 animals were randomly divided into two clusters: cardiac function was assessed *in vivo* via PV-loop experiments and vascular reactivity was investigated *ex vivo* using isolated organ baths.

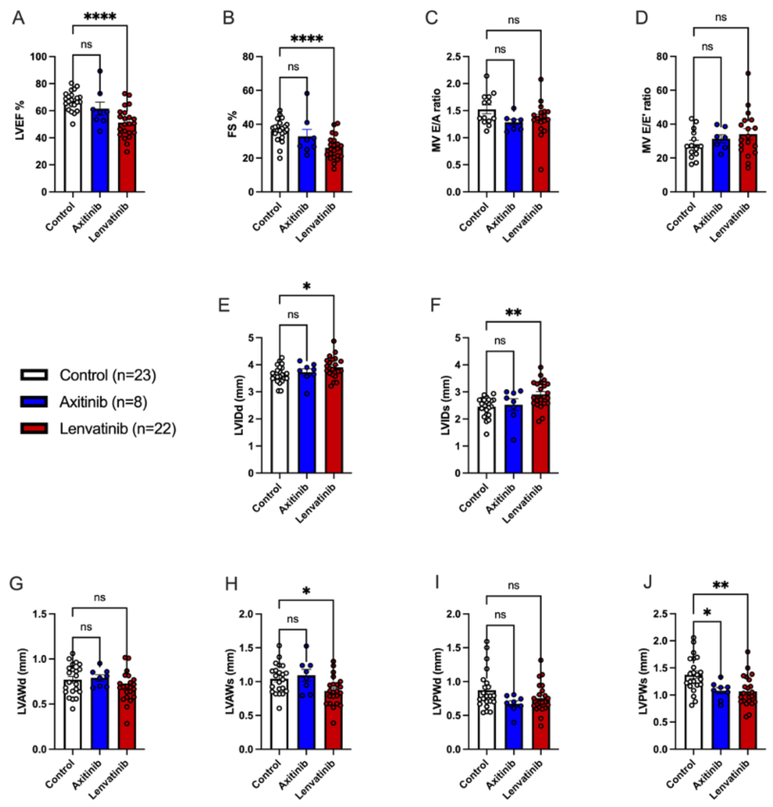


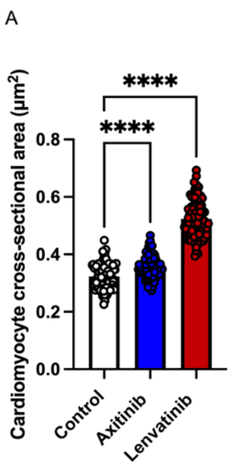
CONCLUSION

This study showed that lenvatinib treatment is associated with systolic dysfunction and enlargement of the left ventricle, while also determining cardiomyocyte hypertrophy. These features are suggestive of dilated cardiomyopathy. Conversely, axitinib did not impact cardiac performance. In terms of vascular reactivity, neither axitinib and lenvatinib were associated with alteration of aortic stiffness or endothelial dysfunction. Having characterised the cardiac and vascular changes induced by axitinib and lenvatinib, the next approach will involve the investigation of possible mechanisms underlying the cardiovascular responses induced by these anticancer therapies.

RESULTS

Figure 1. Echocardiographic changes in mice following 2-day treatment with vehicle, axitinib and lenvatinib. The systolic measurements (LVEF% and FS%) taken on parasternal long-axis and short-axis views at the level of the papillary muscles did not show significant changes in the axitinib-treated mice when compared to the vehicle group, while lenvatinib determined a significant loss of systolic function at day 2 of treatment, with a drop of 24% and 28% for LVEF and FS, respectively (***p<0.001, ****p<0.0001, Figure 1A-B). The evaluation of diastolic function by measuring intracardiac flows in Doppler mode did not reveal significant alterations of MV E/A ratio and MV E/E' ratio among the three groups (Figure 1C-D).
The left ventricular internal diameter at diastole and systole (LVIDd and LVIDs) of lenvatinib-treated mice was significantly enlarged when compared to the vehicle-receiving animals (7.3% increase for LVIDd and 18.6% increase for LVIDs) (Figure 1E-F). In addition, the left ventricular anterior and posterior wall systolic (LVAWs and LVPWs) thickness was significantly reduced in the lenvatinib-treated mice, with a reduction of 17.3% for LVAWs and 22.3% for LVPWs (Figure 1H-J).





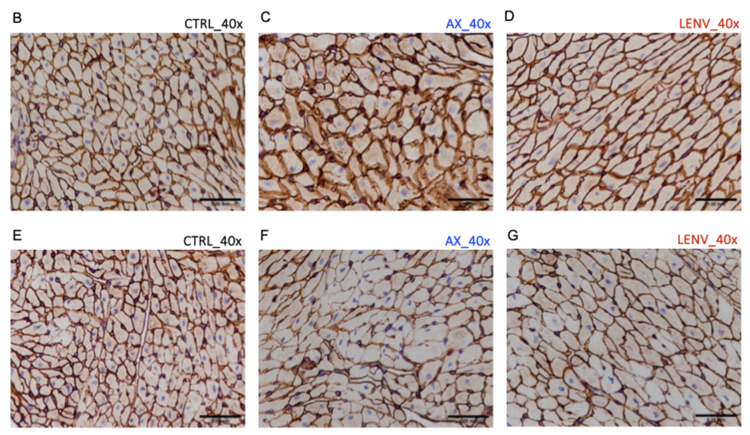


Figure 2. Laminin immunohistochemical staining of mice hearts to quantify cardiac hypertrophy by evaluation of cardiomyocyte cross-sectional area (2A). Representative images of cardiomyocyte cross-sectional area following 4-day treatment with vehicle (2B, E), axitinib (2C, F) and lenvatinib (2D, G). Both the treatment with axitinib and lenvatinib was associated with cardiomyocyte hypertrophy, with an increase of the cross-sectional cardiomyocyte area of 10.3% for axitinib and 62% for lenvatinib compared to the control group (****p<0.0001, Figure 2A).

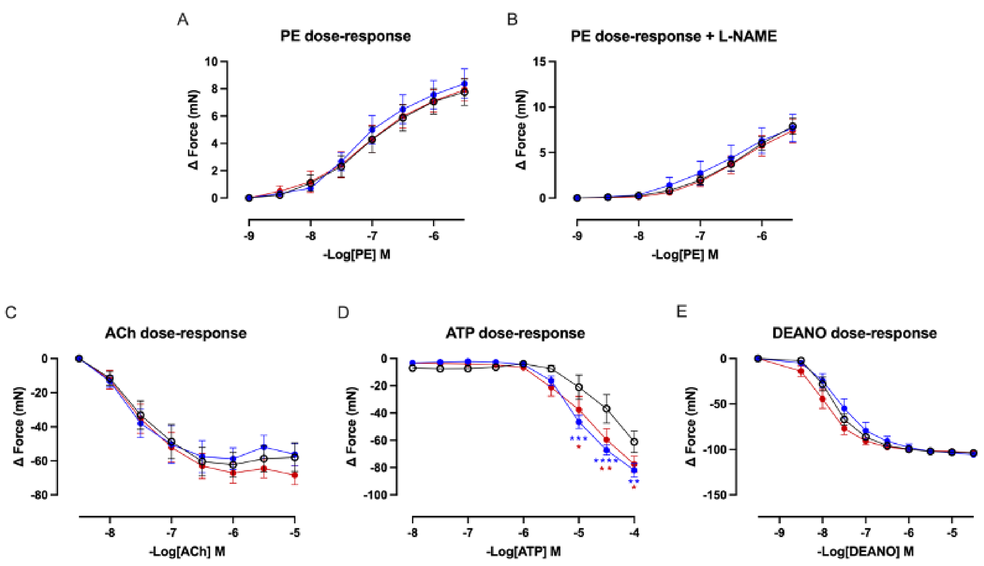


Figure 3. Contraction and relaxation of thoracic aortic segments of mice following 4-day treatment with vehicle, axitinib and lenvatinib. The contractile response of thoracic aortic segments to PE following a 4-day period of treatment in C57BL/6J mice did not reveal any differences between the treated groups and the control. The same observation applied for the segments pre-treated with L-NAME. The isometric measurements of Ach concentration-response vasodilation in aortic rings, where no differences were reported between control and treated samples, suggests the absence of endothelial dysfunction in response to the treatment. Endothelium-independent relaxation in response to DEANO was unaltered for both the RTKIs tested, indicating a preserved reactivity of VSMCs to NO and intact VSMCs function. The vasodilator response to ATP was significantly increased after treatment with axitinib and lenvatinib (*p<0.05, **p<0.01, ***p<0.001, ****p<0.0001, Figure 3D), suggesting a potential role of purinergic signalling in the vascular responses associated with these RTKIs.

REFERENCES

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