**VEGF inhibitor-induced hypertension is ameliorated by DMSC-EVs in male rats**

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**Introduction:** Vascular endothelial growth factor (VEGF) inhibitors are effective cancer therapies, but are associated with significant cardiotoxicity, particularly hypertension, and kidney injury. These adverse effects are driven by activation of the endothelin (ET) system, endothelial dysfunction and oxidative stress. Decidual mesenchymal stromal cells (DMSCs) and their extracellular vesicles (EVs) are highly resistant to oxidative stress and can restore endothelial function. We hypothesised that DMSC-EVs can mitigate VEGF inhibitor-induced hypertension and kidney injury.

**Aims**: To assess the effects of DMSC-EVs on VEGF inhibitor-induced hypertension and kidney injury, and to determine whether these effects are sex-dependent.

**Methods**: Twelve-week-old male and female Sprague Dawley rats were treated with the VEGF inhibitor, sunitinib (14 mg/kg/day o.p.) or vehicle (Nutella) for 7 days. On days 4 and 6, rats received either DMSC-EVs (50 μg in 200 μl saline, i.v.) or vehicle. Mean arterial pressure (MAP) was measured via radiotelemetry on days 1-6. On day 7, 24h urine was collected to determine proteinuria. Plasma ET-1, PGI2 and PGF2α levels were measured via ELISA. Endothelial function was assessed in mesenteric and kidney vessels.

**Results:** Sunitinib induced a rapid and sustained increase in MAP in both males (24±2 versus 1±1 mmHg in vehicle on day 6; P<0.001) and females (22±2 versus 1±1 mmHg in vehicle on day 6; P<0.001). Co-treatment with DMSC-EVs reduced the pressor response to SU by 50% in males (11±3 mmHg on day 6; P<0.05 versus SU), but not in females. Sunitinib significantly impaired endothelial nitric-oxide (NO)-dependent vasodilator function in mesenteric and kidney arteries in males but not in females. Sunitinib also increased the sensitivity to ET in these arteries in males. DMSC-EVs restored NO function and ET sensitivity in both arterial beds in males. In addition, DSMC-EVs alone had no effect on MAP or vascular function.

**Discussion:** These findings suggest sex-specific mechanisms in VEGF inhibitor-induced hypertension and that DMSC-EVs may be a novel intervention to allow male cancer patients to gain the full benefit of VEGF inhibitor therapy without adverse cardiovascular and kidney effects.