

**TCS/16/31 - Cancer Chemotherapeutics and the Vasculature: *Endothelial Effects of VEGF Inhibitors In Vivo in Man***

Recent developments in chemotherapy, particularly VEGF-inhibitor (VEGFI) drugs, have markedly improved the prognosis of patients with cancer. However, these drugs frequently cause high blood pressure (hypertension) which can lead to heart attacks, heart failure and stroke and can limit their use for cancer treatment.

Endothelin-1 is a hormone that causes blood vessels to tighten and may contribute to high blood pressure associated with VEGFI drugs. Blocking the effects of endothelin-1 may therefore reduce or prevent VEGFI-associated blood pressure changes, although this has never been tested in humans.

Our long-term goal is to assess the protective effects of endothelin-1 blocker drugs in patients treated with VEGFI. Before doing so, we must better explore whether VEGFIs cause blood vessel narrowing and if endothelin-1 blockers prevent this. We will assess this in healthy volunteers using a special technique called 'forearm plethysmography'. We will examine the effect of VEGFI on blood flow and also the effect of simultaneous administration of endothelin-1 blockers. These will be given at doses that produce local effects in the arm without affecting the rest of the body.

These studies will show whether endothelin-1 blockers may help treat VEGFI-associated hypertension to enable more patients safely to receive vital cancer treatments.