Pump-Priming Grant

Report – Tamsyn Clark

Title: Normothermic machine perfusion of the *in situ* isolated liver

Objective

To assess the feasibility of in situ isolated normothermic liver perfusion, using a chemotherapeutic agent as proof of principle.

Methods

Laparotomy and complete, vascular isolation of the liver was performed on 55-65 Kg pigs (n=9). The hepatic artery (HA), portal vein (PV) and inferior vena cava were cannulated and normothermic machine perfusion (NMP) of the liver established *in situ*. Systemic circulation was maintained with veno-venous bypass. High-dose doxorubicin was delivered via the HA, circulated for 1 hour, then the liver flushed and vascular reconnection performed. Biochemical and physiological parameters were measured and doxorubicin quantified in blood, bile and tissue by high performance liquid chromatography.

Results

A standardised, surgical protocol enabled connection of the OrganOx liver transplant perfusion device to the liver in situ, achieving physiological vascular flow rates (PV 0.6-0.9 L/min; HA 0.2-0.4 L/min, acid-base (pH 7.26-7.42) and lactate levels (0.4-1.3 mM). There was very limited liver cell injury (median peak AST 578U/L, ALT 40U/L). Two-compartmental analysis of plasma doxorubicin decay demonstrated a distribution half-life of 1.8 minutes and a C_{max} 9-times higher than tolerable by systemic delivery due to cardiotoxicity. Resulting mean hepatic tissue concentration (14.6+/-2.8 µg/g) was significantly higher than could safely be achieved with systemic delivery. Notably, there was no systemic leak of doxorubicin and its metabolites and no accumulation in heart or kidney.

Conclusion

These are the first steps towards patient connected therapy using NMP technology. This study has shown the feasibility of in situ isolated liver perfusion as a means of delivering therapy whilst maintaining stable liver and systemic physiology. This study has shown that it is possible to deliver a therapeutic agent without systemic leak or extra-hepatic tissue accumulation.

Outputs

British Association of Surgical Oncology meeting – oral presentation awarded the BASO-Raven prize, Nov 2021

1st International Workshop on Liver Machine perfusion, Turin, Italy – invited speaker June 2022

Association of Upper Gastrointestinal Surgeons of Great Britain – accepted for oral presentation in Sept 2022

Next Steps

The next steps are to bring together a multidisciplinary working group to consider clinical translation. Publication for the preclinical work is in process.