Safety and Feasibility of Autologous Cord Blood Cell Therapy During the Norwood Operation

Objective: Phase I, open label safety and feasibility trial of autologous cord blood (CB) mononuclear cell (CBMNC) therapy via a novel blood cardioplegia-based intracoronary infusion technique during the Norwood procedure in neonates with antenatal diagnosis of hypoplastic left heart syndrome (HLHS). The interstage period between the Norwood and Stage 2 operation features high morbidity and mortality while the right ventricle (RV) is burdened with abnormally high loading condition. CBMNC therapy may support early cardiac remodeling with enhancement of RV function during the critical interstage period.

Methods: Recruitment was from February 2018 to June 2021. CB collection, testing and processing to clinical grade CBMNCs was done according to NetCord-FACT International Standards. CBMNCs were stored at 4°C without cryopreservation until the Norwood procedure at 2-3 days of life. CBMNC intracoronary delivery (4x15mL) was performed at the end of each cardioplegia dose. Patients were managed according to our standard post-Norwood care. Adverse events were monitored until completion of Stage 2 (? day 100 post-op).

Results: Of 16 patients with antenatal diagnosis, 13 were recruited, 3 were not treated due to unavailability of cells: placental abruption (n=1) or priority treatment delaying the Norwood more than 4 days (n=2). Ten patients received 644.9±424.6 x10⁶ (mean±SD) total nucleated cells. Interstage mortality was 30% occurring on post-op day 7, 25, and 62. There were 36 serious adverse events recorded (53% linked to 3 deaths), none were related to the CBMNC therapy. Cardiac magnetic resonance imaging before Stage 2 found RV mass index values in this series comparable to those of propensity matched patients from our historic Norwood cohort, while RV ejection fraction was 66.2±4.5% and indexed stroke volume was 47.4±6.2mL/m² versus 53.5±11.6% and 37.2±10.3mL/m², respectively (not powered). All 7 survivors have completed Stage 2 and are alive with good RV function as of Oct 17, 2022, with equal or less than mild tricuspid regurgitation n=6, or moderate n=1 (anterior leaflet prolapse).

Conclusions: This phase I trial demonstrated that autologous CBMNCs, delivered without prior cryopreservation, via a novel intracoronary infusion technique during cardioplegic arrest to HLHS patients during Norwood palliation on day 2-3 of life was feasible and safe. It allows delivery of a very large number of cells. A positive effect on systolic function is suggested.

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