NICORD® EXPANDS HAEMATOPOIETIC STEM CELLS AND PROVIDES PROMPT AND DURABLE ENGRAFTMENT IN PATIENTS UNDERGOING CORD BLOOD TRANSPLANTATION FOR HAEMATOLOGICAL MALIGNANCIES AND SICKLE CELL DISEASE: RESULTS OF EARLY PHASE CLINICAL TRIALS USING FRESH AND CRYPRESERVED PRODUCT.

J Kurtzberg, Durham, M Horwitz, Durham, *G.* F. *Sanz, Valencia*, P. Montesinos , Valencia
E. Galamidi Cohen, Jerusalem, I. Peleg, Jerusalem, D Snyder, Jerusalem, T Peled, Jerusalem

Delayed or failed engraftment after unrelated donor cord blood transplantation (UCBT) is a major barrier to the overall success of the procedure. Strategies using ex vivo expansion have been developed to increase the progenitor cell dose delivered by a single umbilical cord blood unit (UCBU) and to abrogate the engraftment barrier associated with UCBT. NiCord® is an ex vivo-expanded cell product derived from a single UCBU that uses nicotinamide as the active agent to inhibit differentiation and enhance the functionality of hematopoietic progenitor cells expanded in culture. NiCord® has been tested in adults with hematological malignancies (HM) and children with sickle cell anemia as a strategy to increase the probability and speed of engraftment after UCBT.

NiCord® is comprised of a cultured fraction (CF) and a non-cultured fraction (NF) and is manufactured from a single UCBU. After thaw and wash, CD133 cells are selected and placed in culture. The CD133- NF (T cells containing fraction) is re-cryopreserved until administration. The CD133 cells are cultured with cytokines and nicotinamide for 21(-3, +2) days. Initially, the CF was administered to the patient following an 11-hour hold period (median) from the time the product was harvested and packaged in transfusion buffer. More recently, the CF was developed in a cryopreserved formulation, a significant technological milestone in the development of NiCord® . This enables flexibility in the timing of transplantation, which can now be determined according to the clinical conditions of the patient. On the day of transplant, the CF and the NF are thawed and administered, intravenously, sequentially to the patient.

We are performing a series of phase I/II trials testing the safety and efficacy of NiCord® in both double and single UCBT platforms. In the first trial, NiCord® was transplanted with a second unmanipulated unit in 11 adults with HM undergoing myeloablative conditioning therapy with total body irradiation and fludarabine ± cyclophosphamide. This study was completed. Eight of 11 patients engrafted with the NiCord® unit and those patients engrafted neutrophils and platelets at a median of 11 and 30 days, respectively. These patients were discharged after a median 15 days duration of primary hospitalization. Based on the chimerism tests performed, all eight patients remain engrafted with NiCord® up to last follow-up or disease recurrence. Immune reconstitution was complete and the incidence of acute and chronic GvHD was low. 1-year overall and progression-free survival rates for the entire cohort were 82% and 73%, respectively,

A second trial, using NiCord® as the sole UCB graft for HM is currently enrolling patients in US and EU. Early results are encouraging: Seven patients have been transplanted and achieved neutrophil engraftment at a median of 8 days, with no evidence of primary or secondary graft failure thus far. Platelet engraftment was achieved at a median of 30 days. At a median follow-up of 197 days, all patients are alive and disease-free. Three patients are now one year post transplantation.

Two patients were transplanted at La Fe University Hospital, undergoing myeloablative preparative therapy with Thiotepa/Busulfan/Fludarabine (without ATG). These two patients, transplanted with the cryopreserved product, engrafted at days 7 and 8 with kinetics of engraftment similar to the fresh product.

NiCord® is also being tested in the double cord configuration in children with Sickle Cell Disease (SCD), a condition known to have a high incidence of graft failure and autologous reconstitution after standard cord blood transplantation. The children on the study undergo preparation for transplant with myeloablative chemotherapy (busulfan/cyclophosphamide/ATG or fludarabine/busulfan/cyclophosphamide). Thus far, 5 patients have been treated and 4/5 are engrafted and surviving for 15-27 months. Neutrophil recovery with NiCord® cells occurred in all patients between days 6-10 post transplant. Two patients engrafted with the NiCord® graft and two with the unmanipulated unit. One patient experienced graft failure, failed a second transplant and eventually died. All symptoms of SCD have resolved in the surviving patients. An additional study will be opened during 2015 in US and EU using NiCord® as a sole UCB graft for patients with SCD and Thalassemia.

NiCord® is a promising product for patients with HM and SCD. The expanded cells provide prompt and durable engraftment strongly suggesting that true hematopoietic stem cells are expanded without differentiation using this approach. If these results are confirmed in a phase III study, NiCord® has the potential to broaden accessibility and to improve the outcomes of UCBT.