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Development of a unique anti-AML immune therapy consisting of cord blood HSCT and cord blood stem cell-derived dendritic cell (CB-DC) vaccination

Colin de Haar*, Maud Plantinga, Nina Blokland, Lotte Spel, Marianne Boes, Stefan Nierkens, Jaap Jan Boelens

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Background

Development of novel (immune) therapies is of utmost importance to improve survival in relapsed pediatric-AML (acute myeloid leukemia). We aim to develop a powerful and safe therapy consisting of 2 synergistic components: Cord Blood (CB) HSCT and vaccination with CB-derived Wilms Tumor-1 (WT1) mRNA-electroporated dendritic cells (DCs).

Materials & methods

After isolation, the CD34+ CB stem cells were cultured using a two-step protocol. First, they were expanded using a combination of (growth) factors (Flt3L, SCF, IL-3 and IL-6). Next, the cells were differentiated towards DCs for one week using medium containing Flt3L, SCF, GM-CSF, IL-4 and human serum followed by a CYTOMIX (IL-1β, IL-6, TNF-α and PGE2)-induced maturation for the last 24 hours. Finally, the CB-DC culture was electroporated with WT1-mRNA and their phenotype (cell surface markers) and function (migration and antigen presentation) were assessed.

Results

Using the two-step protocol a total cell expansion of 300-500 fold was achieved. Based on surface marker expression, at least 5 different DC subsets could be distinguished in our CB-DC cultures. Since no differences in antigen presentation capacity between the DC subsets were detected, the whole CB-DC culture was used in all phenotypic and functional assays. The maturation using CYTOMIX induced upregulation of costimulatory molecules and CCR7. These cells were also functional, showing enhanced CCR7-dependent migration towards CCL21 in a trans-well migration assay. Finally, the stimulation of WT1-specific T cells by the CB-DCs, matured using CYTOMIX and electroporated with WT1 mRNA, confirmed presentation of WT1 antigens.

Conclusion

We have developed and tested an in vitro system for culturing large amounts of DCs from the CD34+ CB stem cells. Both the phenotypic and functional data support the use of the whole CB-DC culture as vaccine. The next step will be to translate the preclinical protocol to GMP production of a clinical grade vaccine.

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U-DANCE, Tumor Immunology Section, Laboratory of Translational Immunology, UMC Utrecht, Utrecht, the Netherlands