POSTER 19: Pediatric B-Acute lymphoblastic leukemia mesenchymal stem cells display abnormal functional characteristics disrupting normal hematopoiesis

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Background: The 5-years event free survival of children with B-acute lymphoblastic leukemia (B-ALL) is now 85% with contemporary therapies. However, the disease relapse causes poor survival rates ("'50%). In fact, our previous work showed divergences in the differentiation of hematopoietic stem and progenitor cells (HSPC) derived from B-ALL patient bone marrows at initial diagnosis or at relapse. This analysis demonstrated that at initial diagnosis HSPC presented a weak residual hematopoiesis, while a return to a functional state was observed when relapse occurs. Yet, the understanding of B-ALL microenvironment interactions, including mesenchymal stromal cells (MSC), with residual HSPCs and leukemic cells is limited. In that respect, deciphering MSC functionality and potential alterations during leukemogenesis could improve our knowledge of pediatric B-ALL relapse mechanisms.

Aims: This study aims to characterize B-ALL MSC phenotypically and functionally to further analyze their roles in the disease.

Methods: After getting informed consent (Clinicaltrials.gov NCT03278145), MSCs were sorted from marrow samples of healthy children (n=7), children with B-ALL at initial diagnosis before any chemotherapy administration (n=l4), or at relapse (n=5). MSC immunophenotyping, colony forming unit capacity and growth rate were evaluated. Osteoblastic and adipocytic differentiation were measured. Evaluation of MSC ability to support hematopoiesis was performed in long-term co-culture with CD34+CD38· HSPCs sorted from cord blood units and analyzed after 28 days by flow cytometry. Mann Whitney or Kruskal-Wallis tests were performed using GraphPad Prism.

Results: Pediatric B-ALL derived MSC presented expected immunophenotype, revealed variable speed growths but altered functional abilities. Indeed, we found a decrease in osteoblastic and adipocytic differentiation and in colony forming unit capacities, with a high variability between B-ALL subsets compared to healthy MSC. B-ALL MSCs also showed a significant reduced ability to support hematopoiesis ($p<0,05$) which was even worse for relapsed MSCs ($p=0,013$).

Conclusion: Our characterization ofB-ALL MSC demonstrate alterations in their functionality and their ability to support normal hematopoiesis. Ongoing molecular characterization of these MSCs as well as investigations on the molecular dialogue between MSC, HSPC and leukemic cells will provide new clues to find innovative microenvironment therapeutic targets.