

Title : ALL relapse after anti-CD19 CAR-T cells therapy in a young patient: which therapeutic options ?

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Abstract

Therapeutic options in B-acute lymphoblastic leukemia (ALL) relapses after anti-CD19 CAR-T cells are still debated. Here, we analysed leukemic cells of a young patient who had several CD19⁺ relapses of B-ALL after hematopoietic stem cells transplant (HSCT) and after anti-CD19 CAR-T cells (tisagenlecleucel). Extensive membrane immunophenotype revealed the appearance of new targets. Lysis sensibility analysis performed by ⁵¹Cr release and long term killing assays revealed the *in vitro* persistence of sensitivity to cytolytic activity of CAR-T cells. An immunosuppressive monocytic population was identified in the last relapse sample. Mechanisms leading to ALL resistance are analysed and therapeutic options are discussed.

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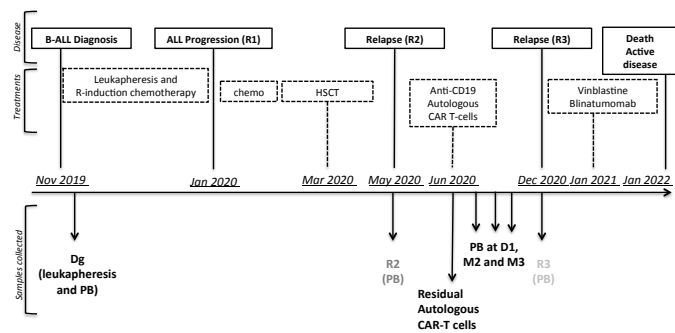


Figure 1 : Clinical case medical history : disease progressions, treatments received and samples collected (Dg ; R2 ; patient's CAR-T cells, blood samples and R3). ALL : Acute Lymphoblastic Leukemia ; R : Rituximab ; HSCT : hematopoietic Stem Cell Transplantation ; PB: peripheral blood; chemo: chemotherapy

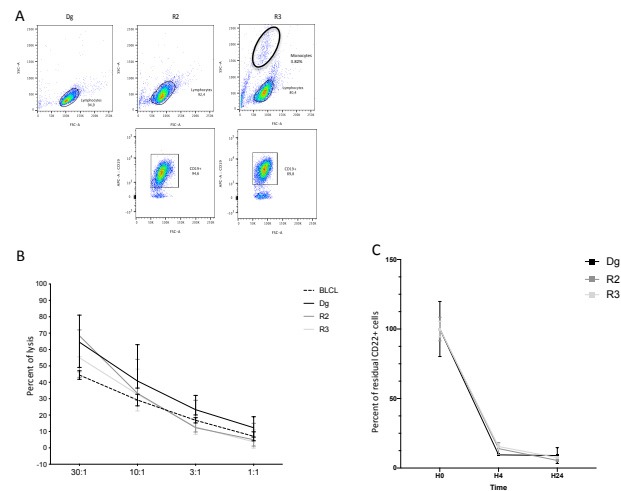


Figure 2: Flow cytometry analysis and results of cytotoxicity assays: A. Morphologic Dot plot of peripheral blood cells isolated at Dg, R2 and R3 relapses and used for phenotype analysis, showing on R3 sample appearance of monocytic population which was secondly analysed and was CD14⁺, HLA-DR^{neg}, CD33⁺, CD11b^{high}. B. ⁵¹Cr cytotoxic assays over 4h : Analyse of sensitivity of ALL to cytotoxic activity of a purified autologous anti-CD19 CAR-T cells preparation (BLCL : B cell lineage used as control) C. Co-culture assays over 24h: ALL viable residual cells at 3 time points of co-culture H0 (starting point), H4 after 4 hours of co-culture, H24 after 24 hours of co-culture (Diagnosis ALL in black curve ; R2 relapse in dark grey and R3 relapse in light grey) with a purified autologous anti-CD19 CAR-T cells preparation.