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CAR T cells reside in the bone marrow and inhibits healthy hematopoiesis

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Background

Cytokine release syndrome and neurotoxicity are well-described side effects of CAR T cell therapy. A third initially neglected side effect, hematological toxicity (hemato-tox) occurring more than 30 days after CAR T cell infusion, is reported in most patients regardless of the specificity of CAR T cell used (CD19, BCMA, GD2 or claudin18.2). However, the pathophysiology of hemato-tox remains unclear. Our study aims to understand Hemato-tox onset in B cell malignancies patients treated with CD19 CAR T cells to improve their management.

Methods

Bone marrow (BM) were obtained from B cell malignancies patients before (BASELINE, n=4) and 2-3 months after (POST CART, n=10) CAR T cell injection. BM mononuclear cells (BMMC) were collected for subsequent spectral flow cytometry. Bulk and scRNAseq analysis were performed respectively on sorted BMMC (CD34+, CD3+ and CAR T+) and total BMMC. BM plasma was analyzed for 65 analytes using multiplex ELISA assay. Sorted cells (CD3+ and CD14+) derived from peripheral blood mononuclear cell were collected after CAR T cell treatment and NGS technology was performed.

Results

Retrospectively, 43% of CAR-T treated patients (n=79) exhibited hemato-tox. Low hemoglobin and platelet counts at day -7 were the only clinical factors associated with hemato-tox occurrence. We observed CAR T infiltration in all BM examined; which correlated with hemato-tox severity. CXCR4 expression was detected on CAR-T cells in PBMC confirming their ability to reach the BM. BM secretome analysis showed an inflammatory cytokine profile in POST CART samples inversely related to platelet count. Interestingly, scRNAseq analysis revealed a drastic reduction of HSC following CAR T injection with an hematopoiesis biased at the expense of megakaryopoiesis. In parallel, we observed a significant expansion of mutated progenitors for CHIP associated genes (TET2, DNMT3A, ASXL1, PPM1D) following CAR T injection.

Conclusions

Our findings show that CAR T cells reside in the BM, and their infiltration correlates with hemato-tox severity suggesting a direct effect of CAR T cells on hematopoiesis through the secretion of multiple cytokines deleterious for the HSC compartment.

Legal entity responsible for the study

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