MOUSE MODEL OF CAR-RELATED ICANS DEVELOPMENT AFTER TREATMENT WITH HUMAN CD19 CAR-T CELLS

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Background Immune effector cell-associated neurotoxicity syndrome (ICANS) is an adverse event commonly observed in cancer patients receiving CAR-T cell therapies. Despite the clinical features of ICANS being recognizable, its pathophysiology remains poorly understood, current hypothesis are mainly based on findings in autopsies performed on individuals who suffered fatal neurotoxicity after CAR-T cell therapy and preclinical models are limited. Recently, a syngeneic mouse model of CAR-related neurotoxicity has been described; unfortunately, it does not allow to study ICANS that develops upon interaction of human CAR-T cells with human immune and tumor cells.

Methods Here we proposed a humanized mouse model, previously characterized for its ability to recapitulate CAR-related cytokine release syndrome (CRS) toxicity, in which we observed the development of multifocal brain haemorrhages, reminiscent of neurotoxic manifestations observed in patients with high-grade ICANS.

Results Interestingly, we found that microhaemorrhages did not occur in mice treated with untransduced T cells, while they were observed in about the 45% of mice treated with human CD19 CAR-T cells. Moreover, we observed that this event is associated with CRS severity, as it occurs in patients, and by assessing the number and dimensions of microhaemorrhages by brain tissue area we found them to be greater in terms of extension and incidence in the cerebellum.

By magnetic resonance imaging we observed the onset of hypointense lesions in deep brain structures and noteworthy an extravasation event of the injected contrast agent occurred, suggesting changes in blood vessels permeability. Moreover, according to the most affected mentioned brain areas, we find changes in locomotor abilities likely providing a clinical relevance to the phenomena occurring in the brain.

Conclusions These findings suggest that our humanized mouse model is promisingly able to recapitulate ICANS-related complications, thus providing us with a preclinical tool to deepen ICANS pathophysiology studying.

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