Anti-CD19 chimeric antigen receptor T-cell therapy for B-cell acute lymphoid leukemia

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Historically the long-term survival of patients with relapsed and refractory B-cell acute lymphoblastic leukemia (ALL) has been poor despite the application of allogeneic stem cell transplants and especially after such transplants fail.[1] In the landmark paper by the group led by Stephan A. Grupp, Michael Kalos and Carl H. June at the University of

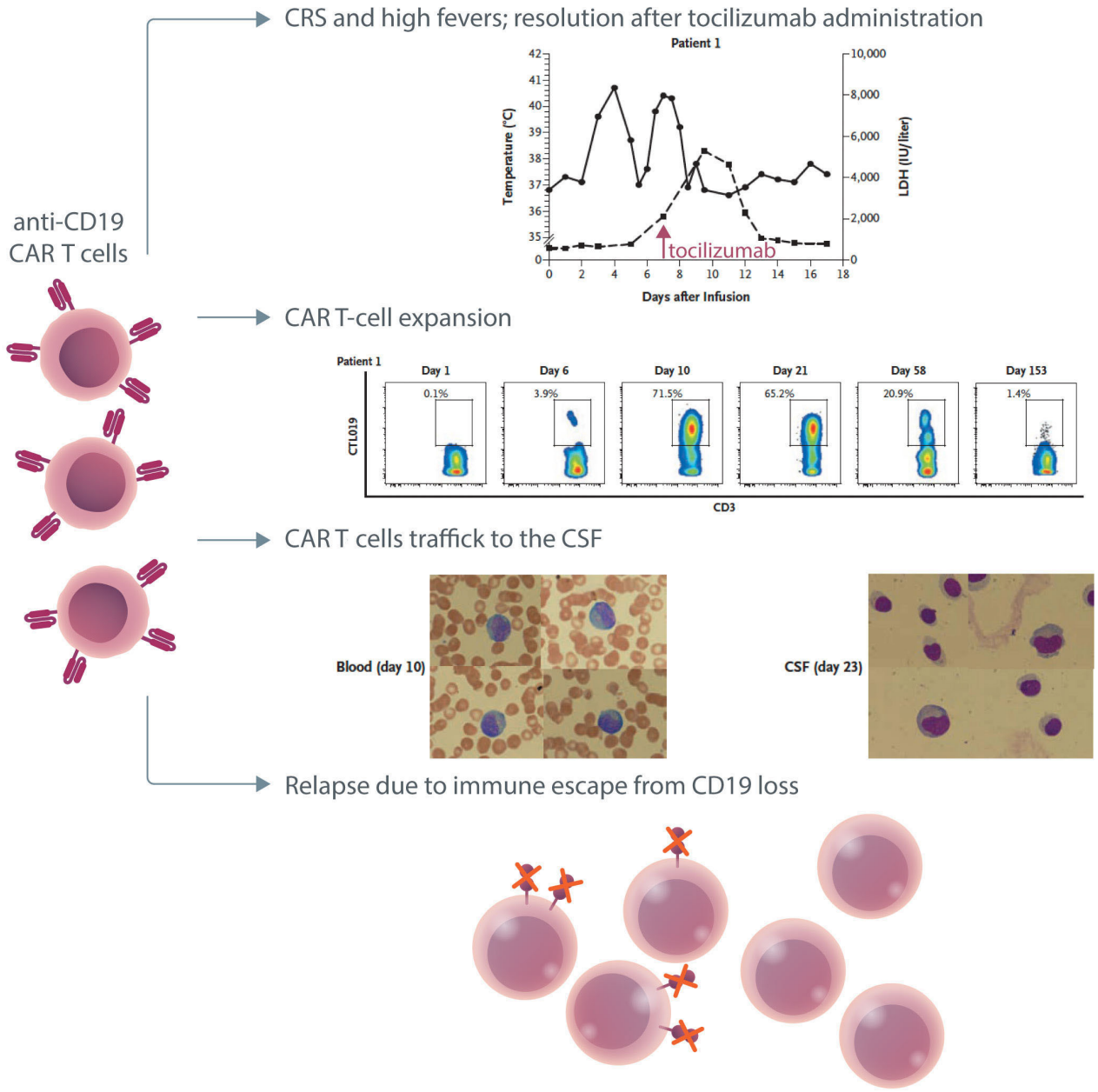

Figure 1. Essential principles of chimeric antigen receptor T-cell therapy. CAR; chimeric antigen receptor; CRS: cytokine release syndrome; LDH: lactate dehydrogenase; CSF: cerebrospinal fluid. *Figure adapted from Figures 1 and 2 in the original paper by Grupp et al.*[2]

Pennsylvania and the Children's Hospital of Philadelphia, two children received infusions of CD19-directed chimeric antigen receptor (CAR)-modified T cells (CTL019) for refractory pre-B-cell ALL (Figure 1).[2]

Both children experienced more than a 1,000-fold increase in CTL019 cells during the first 2 weeks after infusion, which comprised up to 72% and 34% of the total circulating T cells. Both children experienced high fevers starting a few days after the CTL019 infusion and lasting about 1 week; one of the children required blood pressure and ventilatory support while the other patient later developed encephalopathy. Both children had B-cell aplasia and total clearance of leukemia from their marrow by 1 month after treatment. One of the two children remained in remission for more than 12 years and recent studies suggest that anti-CD19 CAR T cells may persist, evolve into a $CD4^+$ predominant phenotype and remain functional for 10 years or more in long-surviving leukemia patients.[3]

In addition to first demonstrating that patients with advanced and refractory ALL could achieve complete and durable remissions after CAR T-cell therapy, this landmark paper highlighted several principles which have become integral to the care of all patients with aggressive B-cell (and other hematologic) malignancies who receive CAR T-cell therapies. These include: (i) the importance of prompt recognition of life-threatening cytokine-release syndrome with features of macrophage activation due to marked elevation of interleukin-6, interferon-γ and other cytokines and its successful management using the interleukin-6 receptor blocking antibody tocilizumab; (ii) potential trafficking of CAR T cells to the central nervous system and prolonged persistence leading to tumor clearance and perhaps contributing to neurological toxicity; and (iii) the risk of CAR T-cell target antigen loss (CD19) as a mechanism for treatment failure as one of the patients developed a CD19-negative relapse 2 months after treatment.

It is remarkable that so much was learned from a clinical research experience involving just two small patients. But, as Dr. Carl June and other wise clinical investigators have humbly said, "Every single patient can teach us important lessons".

Disclosure

No conflicts of interest to disclose.

References

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