Titov et al. *Cell Death and Disease* (2018)9:897
DOI 10.1038/s41419-018-0918-x

Cell Death & Disease

REVIEW ARTICLE Open Access

The biological basis and clinical symptoms of CAR-T therapy-associated toxicites

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Abstract

Currently, immunotherapy is attracting a lot of attention and may potentially become a leading approach in the treatment of cancer. One emerging therapeutic, the chimeric-antigen receptor T-cell adoptive immunotherapy (CAR-T) is showing remarkable efficacy in the treatment of several B-cell malignancies. The popularity of CAR-T has been founded on two CAR T-cell products recently approved by FDA (during 2017) in the treatment of relapsed/refractory B-cell acute lymphoblastic leukemia and B-cell lymphoma. However, their toxicities observed in clinical trials were extremely significant and in some cases even fatal with no approved algorithms for toxicity prediction being available to date. A deeper understanding of the biological basis of such complications is the key to prompt and comprehensive clinical management. Here we review the wide spectrum of effects associated with CAR T cell therapy with a major focus on the pathogenesis of cytokine release syndrome and neurotoxicity as the most common, potentially life-threatening effects of this treatment. We discuss the basis of clinical management and the existing models that predict the severity of toxicity, as well as the key factors that modulate this event. Finally, we will summarize the literature detailing universal allogenic CAR T-cells and their toxicity profile.

Facts

1. The chimeric-antigen receptor T-cell adoptive immunotherapy (CAR-T) is a potent instrument for treating several hematological malignancies, not only those expressing the CD19 receptor.
2. There is a pressing need to make this therapy available to a wider spectrum of patients.
3. However, although the safety levels of CAR-T therapy are generally acceptable, several fatal outcomes due to severe cytotoxicity have been reported in clinical trials of CAR-T therapies.
4. Therefore, better understanding of the spectrum of toxicities, their etiology and pathogenesis as well as the knowledge of toxicity-promoting factors may help develop and validate the predictive scales and define better prophylactic strategies for high-risk patients.

Open questions

It is known that some of the factors that worsen the toxicity of CAR-T therapy (higher CAR T-cell dose, intensive lymphodepletion) also positively affect its efficacy. How can one achieve the proper balance between these?

What kind of predictive model one should use for the toxicity risk assessment and which group of patients should be given the treatment for prophylaxis of such toxicity?

Would universal allogenic CAR T-cells be as safe and effective as the autologous CAR T-cells?

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