CAR-T cells as an Anticancer Therapy: current challenges and emerging opportunities

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Introduction

Infusion of chimeric antigen receptor-genetically modified T cells (CAR-T cells) have shown outstanding results in clinical trials with patients suffering from relapsed or refractory B-cell malignancies. However, besides the clinical benefit established for these therapies, CAR-T cells are associated with unique acute toxicities, mainly Cytokine Release Syndrome and Neurotoxicity. The aim of this work is to present some of the key points that are currently related to CAR-T cell therapies, such as the major risk factors related to the life-threatening toxicities (cytokine release syndrome and neurotoxicity), the emerging applications from both large pharmaceutical companies and small-medium biotechnology industries and the progresses made so far in CAR-T cells-based therapies including the latest innovations in CAR design.

CAR-T cells

Genetically engineered autologous or allogenic T cells to express a chimeric antigen receptor (CAR). The CAR enables the redirection of T-cells’ cytotoxic activity to a specific tumor antigen. CAR-T cells are targeted to cancer cells independently of MHC expression and HLA haplotypes.

CANCER CELL

Acute Lymphoblastic Leukemia (r/B-ALL), Non Hodgkin’s Lymphoma (r/B-NHL), Chronic Lymphocytic Leukemia (r/B-CLL)

Prior Lymphodepletion Regimen promotes peak expansion and persistence of CAR-T cells in vivo.

2nd generation CAR

Endothelial activation (in increased in serum levels of ANG2 and Von Willebrand factor) → blood brain barrier (BBB) permeability increased → Blood brain barrier (BBB) 

transit into the CNS of serum cytokines and CAR-T cells → Secretion of TNFα and IL1β induces pericyte stress → Loss of cerebral vascular integrity and disruption of BBB

Figure 1

Figure 2: CAR expressing with the antigen CD19

High response rates in the treatment of relapsed or refractory CD19+ B-cell malignancies with CD19 specific CAR-T cells.

First-in-class Products

KYMRIAH (tisagenlecleucel)

Approved for the treatment of r/B-ALL on 10/08/2017.

Second indication r/r DLBCL approved on 01/05/ 2018.

YESCARTA (axicabtagene ciloleucel)

Approved for the treatment of r/B-NHL on 03/10/2017.

The Future of CAR-T cells

The SUPRA CAR

The SUPRA CAR combines four distinct domains that provide unique features to the CAR.

EndTime

in vivo

Neurotoxicity (NTX)

Systemic inflammatory response.

Risk Factors: tumor burden, antigen expression level, in vivo peak expansion promoted by prior lymphodepletion, IL-6 and effectiveness of anti-IL-6R receptor monoclonal antibody tocilizumab.

New data from study conducted by Norell et al. (2018) revealed that monocytes are the major sources of IL-6 (and IL-1) during CRS, rather than CAR-T cells. According to a time-course analysis, the release of IL-1 preceded IL-6. As IL-1 is capable of inducing the secretion of IL-6, is IL-1 the primary cause of CRS?

Severe CRS leads to severe NTX.

Risk Factors: infused dose of CAR-T cells, tumor burden and progressing neurologic comorbidities.

Key role of IL-6 - early plasmatic peak leads to NTX severe.

Study conducted by Gust et al. (2017) provides evidence for cytokine-mediated endothelial activation.

Conclusion

CAR-T cell-based therapy as a new valuable option for the treatment of relapsed or refractory B-cell malignancies.

First products approved in 2017 and new candidates are emerging.

Safety challenges yet to be overcome - focus on the management of life-threatening toxicities.

Emerging Pipeline

Allogenic T cells genetically edited by TALEN® technology

Autologous and Allogenic delta gama (δy) T cells

Approved for the treatment of r/B-NHL on 03/10/2017.

Disclosures

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