International Research Journal of Oncology

5(1): 30-34, 2021; Article no.IRJO.70653

Outlook on Genetically Engineered CAR T-Cell Therapies for Solid Tumours

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Authors' contributions

This work was carried out in collaboration among all authors. Author LM and YP conceptualized the paper. Other authors reviewed the literature, reviewed the manuscript, and provided useful inputs. All authors read and approved the final manuscript.

Article Information

Editor(s):
(1) Dr. Prabakaran Nagarajan, The Ohio State University, USA.
Reviewers:
(1) Xiao-san ZHU, Xiamen University, China.
(2) Maite Lopez Deogracias, University of Basque Country, Spain.
Complete Peer review History: https://www.sdiarticle4.com/review-history/70653

Short Communication

Received 20 May 2021
Accepted 24 July 2021
Published 29 July 2021

ABSTRACT

T-cell-based methods using genetic engineering technology are considered the most advanced treatments in cancer therapy. Chimeric antigen receptor (CAR) T-cell therapy is an innovative immunotherapy wherein autologous T-cells are genetically modified to recognize and destroy cancer cells more effectively. CAR T-cell therapy has shown remarkable success in the treatment of CD19-expressing hematologic malignancies. However, such extraordinary experience has not been translated to treatment of solid tumors, where its efficacy remains limited. This article gives an overview of these obstacles that CAR T-cells research needs to overcome to achieve efficient next-generation T-cell therapy for solid malignancies.

Keywords: CAR T-cell therapy; solid tumours; clinical trials; T-cells.

1. INTRODUCTION

One of the latest immunotherapy innovations in cancer treatment is to genetically modify T-cells to express a chimeric antigen receptor (CAR) that redirects patients' T-cells to specifically target and destroy tumour cells. CAR is an engineered fusion protein composed of an

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antigen recognition domain derived from a monoclonal antibody and intracellular T-cell signalling and costimulatory domains [1]. CAR recognizes the specific surface of peptide antigens on tumour cells in a major histocompatibility complex (MHC)-unrestricted manner [2]. The generation of CAR T-cells is complex. In brief, the enriched lymphocyte cells are taken from patients after being collected and sent to a specialized laboratory, where they are engineered to produce specific CARs on their surface. Before returning these cells to the patient, they are multiplied in a laboratory to obtain millions of modified cells [3]. A CAR sequence is introduced to T-cells using a plasmid or viral vector (e.g., adenovirus, retrovirus, or lentivirus) of which lentivirus has become the most common method of transducing human T-cells [4]. Protocols for manufacturing large-scale CAR T-cells for medical use have now been established. Four clusters of differentiation 19 (CD19) CAR T-cell therapies have been approved in the United States and other territories. The efficacy of the approved CAR T-cells has been exceptional, with a remarkable impact on the survival of high-risk, bad-prognosis hematological malignancies, which has resulted in a significant expansion of clinical trials of CAR T-cells directed against multiple hematological antigens, such as CD19, CD20, and CD22 [5].

CAR T-cells are in continuous development, with efforts being made to increase their efficacy. The first-generation CARs contain only one intracellular signalling domain, the zeta chain (CD3ζ), but this was insufficient to trigger CAR T-cell expansion and engender continuous antitumor activity *in vivo* [5]. Therefore, better-armed CARs containing additional costimulatory molecules, such as 4-1BB, CD28, CD27, OX40, ICOS, or RIAD, and some third or fourth-generation CARs with two or more signalling domains have been developed [6].

The associated toxicity must be taken into account when considering treatment with CAR T-cells. CAR T-cell toxicities after treatment of hematological malignancy may positively correlate with infusion dosage. While mild or moderate adverse events (AEs) are easily medically managed, approximately 45%–50% of patients enrolled in the early CAR T-cell trials required intensive care management. A correlation also exists between the presence of cytokine release syndrome (CRS) and CAR T-cell efficacy. The range of severity of CRS can range from flu-like constitutional symptoms, such as myalgia, headache, nausea, and anorexia, to capillary leak with hypoxia, hypotension, disseminated intravascular coagulation, and ultimately multi-organ failure [7].

The second most clinically significant AE following CAR T-cells infusion is Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS), which typically occurs following CRS's peak (often ≥ three days later) and rarely happens without antecedent CRS. Patients most commonly present with encephalopathy, with pertinent symptoms including aphasia, delirium, and confusion. Deaths due to CRS and ICANS have been reported, highlighting the gravity of these syndromes and the critical nature of appropriate early interventions [8]. The toxicities and optimum therapeutic dosage remain a topic for further research.

Several clinical CAR T-cell therapy trials have been carried out in solid tumours after the great success in treating hematological malignancies. However, the results have been disappointing and varied, from "none" to "unsatisfactory" responses among different solid tumours. The study with the best outcomes reported that four of 19 patients with neuroblastoma achieved objective clinical responses, and three of them achieved complete remission after CAR-T cells treatment [9]. Another study reported modest response in ten recurrent glioblastoma adult patients treated with anti-EGFRvIII CAR-T cells. Nine patients achieved stable diseases and one reported progressive disease [10]. A meta-analysis from 22 studies with 262 patients with different solid tumours was carried out to analyse the response rate of the CAR T-cell therapy. The solid tumours included in the study were neurological tumors, hepatobiliary, pancreatic, melanoma, sarcoma, gastrointestinal malignancies, prostate cancer, breast cancer and non-small-cell lung cancer. The overall response rate among the solid tumours scarcely reached 9% (95% CI:4–16%) [11]. It is noteworthy that the route of administration appears to be essential for the efficacy of CNS tumours. A patient with recurrent multifocal glioblastoma received multiple infusions of CAR-engineered T-cells targeting the tumour-associated antigen interleukin-13 receptor alpha 2 (IL13Rα2) through two intracranial delivery routes. After CAR T-cell treatment, regression of all intracranial and spinal tumours was observed, along with toxic effects of grade 3 or higher [12].

Three main hurdles that may explain the lack of efficacy of CAR T-cell therapies in solid tumours include:

1. The presence of tumour-specific antigen and heterogenicity;
2. The limited trafficking of CAR T-cells to tumour sites; and
3. The immunosuppressive effect of tumour antigen density and the tumour microenvironment (TME).

Concerning the first hurdle, the ideal target should be the tumour-specific antigens (TAA) expressed only on tumour cells. Unfortunately, they are rarely used as targets for CAR T-cells because of their scarcity. The TAA enriched in tumour cells and expressed at low levels in normal tissues, such as HER2, CEA, GD2, and mesothelin, are the first choice for CAR T-cell targets. However, the on-target/off-tumour toxicity has been an issue since low-expressed antigens in normal tissues can also be attacked by CAR T-cells [13]. Targeting neoantigens – the somatic mutations expressed only by tumour cells – might enable tumour destruction without causing undue damage to healthy tissues. However, there are significant challenges to targeting neoantigens with CAR T-cells, such as the heterogenicity and variability in antigen processing as well as the presentation of tumour targets and constant mutant evolution [14]. Another aspect to consider is that only very few neoantigens are immunogenic, and the driver mutations often exhibit early immune evasion mechanisms [15].

Trafficking to the tumour does not seem to be a significant issue for hematologic tumours but is an issue for CAR T-cells targeting solid tumours. Most solid tumours present with a fibrotic stroma, which may make it more difficult for engineered T-cells to infiltrate. Also, T-cells will have to cross the tumour vasculature to access the target tissue. Several factors are involved in this step, including critical players in several aspects of the tumour progression, such as angiogenesis, metastasis, leukocyte migration into tumour sites, and chemokines. Some studies have shown that modifying CAR T-cells to express a chemokine receptor (e.g., CCR2, CCR4, or CXCR2) matching the chemokine secretion by the target tumour cells leads to improved T-cell homing into the tumour and enhanced antitumor efficacy *In vivo* [16]. Hypoxia, a feature of growing tumours of metabolic stress, suppresses T-cell responses, including lymphocyte abilities to migrate. Apart from hypoxic conditions, altered metabolic factors (e.g., reduced glucose, increased lactate) are likely to affect the T-cell motility within tumours [17].

Once CAR T-cells have passed the stromal obstacles described above, they need to have productive contacts with malignant cells. Recent data has indicated that the density of the target antigen plays a critical role in CAR T-cell efficacy [18]. Logically, CAR T-cells would not establish productive immunologic synapses with malignant cells that have lost their target antigens. There is also an observation that tumour cells with decreased target antigen expression are not efficiently eliminated; CAR T-cell efficacy may require a higher antigen density at the cancer cell surface.

CAR T-cells are insufficient to overcome all TME obstacles; therefore, it will be necessary to combine CAR T-cell treatments with various modifications aimed at overcoming the challenges posed by solid tumours. A new generation of CAR T-cell therapies targeting fibroblasts, T- regulatory cells, M2 macrophages, myeloid-derived suppressor cells, or CAR T-cells expressing pro-inflammatory cytokines are being investigated. Furthermore, the overexpression of chemokine receptors on CAR T-cells overcomes the obstacles of poor trafficking to tumour sites and may also present another therapy option [19].

2. CONCLUSION

To date, CAR T-cell therapy has proven a great success in treating hematological malignancies; however, its therapeutic effect in solid malignancies remained unsatisfactory. It is expected that CAR T-cell therapy would achieve significant advances and sustainable success in the field of solid tumours via the genetically-manipulated infused CAR T-cells, thought to provide limitless opportunities for changes and improvements to overcome main obstacles limiting CAR T-cell effectiveness. However, the modification of CAR T-cells to obtain better efficacy but may be associated with more toxicities. Therefore, the continuous development of CART T-cell therapies mandates a detailed rationale and refinement of preclinical models to predict efficacy and toxicity before their use in clinical trials.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our

area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

CONSENT AND ETHICAL APPROVAL

As per university standard guideline, participant consent and ethical approval have been collected and preserved by the authors

DISCLOSURE STATEMENT

Authors Luis Mendoza, Yana Pautova, Yuri Tolkunov and Brian Mark Churchill are employees of IQVIA, a leading global provider of advanced analytics, technology solutions, and clinical research services to the life sciences industry but the views in the article are the authors' own.

Other than this, the authors declare no professional, academic, competitive, or financial conflicts of interest related to this article. No funding was used in the preparation of this article.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Lipowska-Bhalla G, Gilham DE, Hawkins RE, Rothwell DG. Targeted immunotherapy of cancer with CAR T cells: achievements and challenges. Cancer Immunol Immunother. 2012;61(7): 953–962.
   DOI: 10.1007/s00262-012-1254-0
2. Labanieh L, Majzner RG, Mackall CL. Programming CAR-T cells to kill cancer. Nat Biomed Eng. 2018;2(6):377–91.
3. Levine BL, Miskin J, Wonnacott K, Keir C. Global manufacturing of car t cell therapy. Mol Ther Methods Clin Dev. 2016;4:92-101. Published 2016 Dec 31.
   DOI:10.1016/j.omtm.2016.12.006
4. Dufait I, Liechtenstein T, Lanna A, Bricogne C, Laranga P, Padella A, et al. Retroviral and lentiviral vectors for the induction of immunological tolerance. Scientifica. 2012;2012:694137.
   DOI: 10.6064/2012/694137
5. Fousek K, Watanabe J, Joseph SK. et al. CAR T-cells that target acute B-lineage leukemia irrespective of CD19 expression. Leukemia. 2021;35:75–89.
   Available: https://doi.org/10.1038/s41375-020-0792-2
6. Li J, Li W, Huang K, Zhang Y, Kupfer G, Zhao Q. Chimeric antigen receptor T cell (CAR-T) immunotherapy for solid tumors: lessons learned and strategies for moving forward. J Hematol Oncol. 2018;11(1):22.
7. Kawalekar O, O'Connor R, Fraietta J, Guo L, McGettican S, Posey A, et al. Distinct signaling of coreceptors regulates specific metabolism pathways and impacts memory development in CAR T cells. Immunity. 2016;44:380–90.
   DOI: 10.1016/j.immuni.2016.01.021
8. Vorozheikina E, Ruiz M, Solari ML, Ostasevich D, Mendoza L. Overview of Adverse Events Associated With Anti-CD19 Chimeric Antigen Receptor T-Cell Therapy. Preprints 2021; 2021040517.
   DOI: 10.20944/preprints.202104.0517.v1.
9. Louis CU, Savoldo B, Dotti G, et al. Antitumor activity and long-term fate of chimeric antigen receptor-positive T cells in patients with neuroblastoma. Blood. 2011;118(23):6050–6056.
10. O'Rourke DM, Nasrallah MLP, Desai A, et al. A single dose of peripherally infused EGFRvIII-directed CAR T cells mediates antigen loss and induces adaptive resistance in patients with recurrent glioblastoma," Science Translational Medicine. 2017;9(399), article eaaa 0984.
11. Bin Hou, Yao Tang, Wenhan Li, et al. Efficiency of CAR-T Therapy for Treatment of Solid Tumor in Clinical Trials: A Meta-Analysis. Disease Markers;2019;11. Article ID 3425291.
    Available:https://doi.org/10.1155/2019/3425291
12. Brown CE, Alizadeh D, Starr R, et al. Regression of Glioblastoma after Chimeric Antigen Receptor T-Cell Therapy. N Engl J Med. 2016;375(26):2561-2569.
    DOI:10.1056/NEJMoa1610497
13. Feifei Guo, Jiuwei Cui. CAR-T in solid tumors: Blazing a new trail through the brambles. Life Sciences 260 (2020).
    Available:https://doi.org/10.1016/j.lfs.2020.118300

14. Morotti M, Albukhari A, Alsaadi A. et al. Promises and challenges of adoptive T-cell therapies for solid tumours. Br J Cancer. 2021;124:1759–1776.
Available: https://doi.org/10.1038/s41416-021-01353-6
15. Marty R, Kaabinejadian S, Rossell D, Slifker M. J, van de Haar J, Engin H. B. et al. MHC-I genotype restricts the oncogenic mutational landscape. Cell. 2017;171:1272–1283.e1215.
16. Tian Y, Li, Y, Shao Y. *et al.* Gene modification strategies for next-generation CAR T cells against solid cancers. J Hematol Oncol. 2020;13:54.
Available: https://doi.org/10.1186/s13045-020-00890-6
17. Ohta A. Oxygen-dependent regulation of immune checkpoint mechanisms. International Immunology. 2018;30(8):335–343.
Available:https://doi.org/10.1093/intimm/dxy038
18. Wing A, Fajardo CA, Posey AD, Shaw C, Da T, Young RM, Alemany R, June CH, Guedan S. Improving CART-cell therapy of solid tumors with oncolytic virus-driven production of a bispecific T-cell Engager. Cancer Immunol Res. 2018;6(5):605–16.
19. Rodriguez-Garcia A, Palazon A, Noguera-Ortega E, Powell DJ Jr, Guedan S. CAR-T Cells Hit the Tumor Microenvironment: Strategies to Overcome Tumor Escape. Front Immunol. 2020;11:1109. Published 2020 Jun 17.
DOI:10.3389/fimmu.2020.01109

Peer-review history:
The peer review history for this paper can be accessed here:
https://www.sdiarticle4.com/review-history/70653