CAR-T cell therapy: The state-of-the-art of evidence and barriers in a real-world setting

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Introduction

- Chimeric Antigen receptor T cells are T- cells engineered to express synthetic receptors directed primarily against lymphomas and advanced leukemias, redirecting patients T cells to identify and eradicate cells expressing a target antigen. (Figure1)
- This unique and complex therapy has revolutionized the treatment of hematological malignancies such as B cell lymphomas and leukemias with patients achieving complete remission and survival rates. Encouraging results have culminated in 2017 with the first FDA approval of a CAR-T cell therapy, for the treatment of pediatric and young adult patients with ALL .
- Although advanced genetic engineering and synthetic biology have enhanced functionality of this novel therapy, there are numerous challenges to adoption in the real-world (RW).

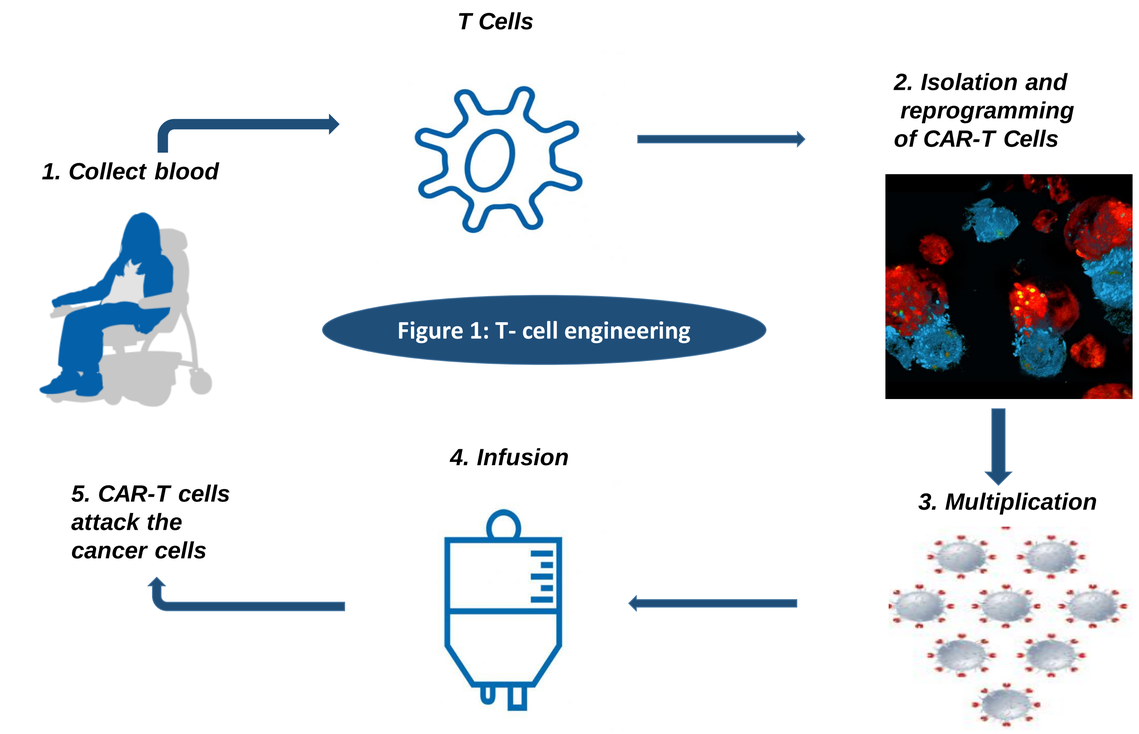

Figure 1: T- cell engineering

Objective

- The objective of this review is to evaluate research findings of RW use of commercial CAR-T therapy to date with emphasis on barriers to CAR-T Real World adoption and to identify evidence gaps informing future RWE generation efforts

Methods

- For this pragmatic literature review study publications were collected by searching the following key words selected from Mesh: “Car-t cell therapy” “Hematological tumors” “Solid tumors” “Real world evidence”.
- The following databases were searched “PubMed”, “Google Scholar”
- Information on RW effectiveness, safety, recent developments, gaps in existing knowledge, and barriers to utilization of CAR-T therapies in the RW were extracted.
- After extracting data from each study those findings were organized under four competencies Data on RW CAR-T use, Safety and effectiveness, RW Logistics, Healthcare utilization

Figure 2. Flowchart of literature survey

Results

- Since the approval of the first CAR-T therapy in 2017 majority have been focused on therapeutic aspects from clinical trials with a paucity of data on RW CAR-T use.
- To date the majority of studies in the RW examined effectiveness and safety but there is a lack of data on RW quality of life and patient reported outcomes

Figure 3: Identified key competencies:

RW Effectiveness and Safety :

- Most of the literature focused on RW effectiveness and safety of anti-CD19 CAR-T therapies for treatment of relapsed or refractory (RR) diffuse B-cell lymphoma (DLBL) and B-cell acute lymphoblastic leukemia (B-ALL) with comparators including commercially available CAR-Ts or non-CAR-T standard of care (SoC).
- Patients treated with CAR-T in RW show comparable responses to those reported for clinical trials with superior efficacy of CAR-T therapy over non-CAR-T SoC as evidenced by longer progression free and overall survival.
- RW effectiveness of CD-19 CAR-T in patient subgroups is not usually well represented in clinical trials including older patients, patients with underlying comorbidities, such as active CNS disease or high-risk disease subtypes including double and triple hit lymphoma.
- RWE available on outcomes after non-response or relapse after CAR-T with worse outcomes reported in patients with earlier relapse after CAR-T treatment.
- The effect of treatment and patient level characteristics such as type of bridging therapy used, CAR-T cell dose and tumor burden on RW outcomes such as OS have also been investigated in RW.
- RWE plays a significant role for conducting indirect treatment comparisons to CAR-T single arm trial efficacy data for indications in LBCL, FL, B-ALL.

RW Access

- As for clinical trials, disparities reported in RW with respect to CAR-T access in African American and Hispanic populations.
- Socioeconomic disparities reported in patients with lower income, uninsured and publically insured patients less likely to receive CAR-T and more likely to incur costs.
- Research conducted on barriers to hematopoietic cell transplantation (HCT) access in RW can inform approaches to address barriers to CAR-T use in RW.

RW Manufacturing and Logistics

- Manufacturing of CAR-T cells is a complex process with RW experience in clinical settings used to gain understanding of factors impacting manufacturing quality such as recommendations to ensure optimal leukapheresis product.
- Cumbersome logistics of administering therapy.
- RW ethical challenges posed by manufacturing ‘bottle-necks’ related to supply chain issues with demand for CAR T-cell therapy outpacing manufacturing capacity.
- Regional variation in RW CAR-T turnaround times (e.g. USA vs Europe).
- Manufacturing, transportation, cell-banking solutions, and lack of standardization.
- Operational logistics- A complex workforce is required to develop and implement these treatments.

Conclusions

- Importance of RWE on CAR-T as randomized clinical trials are not sufficient to address effectiveness every subset of patient or answer every clinical query concerning CAR T-cell use.
- RWE generation through use of registries, surrogate endpoints, external control arms and tokenization can help us in understanding the long-term effectiveness of CAR-T use.
- Whole genome sequencing, next generation sequencing, and liquid biopsies have provided an understanding of genomic instability and other biomarkers relative to patient response. Such techniques complemented with traditional imaging and treatment outcomes can be used to understand RW patient responses to CAR-T.
- RWE through comparative effectiveness, cost-effectiveness, and drug utilization studies, has provided evidence to influence payers’ perspective bridging the gap between development and use in the RW. Therefore, RWE will help us in surmounting the existing barriers and play a key role in navigating future treatment decisions addressing the unmet needs (RW treatment after relapse, access, RW outpatient use and optimal sequencing of subsequent therapies).

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Disclosures

This study was funded by Novartis Pharma AG, Basel, Switzerland. Asees Bajwa, Sikha Sinha, Prakriti Kalra, Oonagh Dowling, Amritanshu Kumar are employees of Novartis.

Poster presented at the ISPOR Europe 2022,Vienna, Austria and Virtual

6-9 November 2022

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