CO126

Axicabtagene Ciloleucel for the Treatment of B-Cell Lymphoma- Gaps, Opportunities and Future Perspectives

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Introduction

B-cell non-Hodgkin's lymphoma (NHLs) is an extremely heterogonous malignancy, with the most frequent subtypes being diffuse large B cell lymphoma (DLBCL) and follicular lymphoma (FL). The genetic diversity of DLBCL, i.e., the presence of mutations, translocations, and chromosomal aberrations, poses the greatest challenge to treatment. [1]

The currently available treatment option with phosphatidylinositol 3-kinase (Pi3K) inhibitors or other novel agents have achieved some degree of clinical activity. However, short remission with cure remain elusive. [2, 3]

Axicabtagene ciloleucel (axi-cel; KTE-C19) is an engineered autologous anti-CD19 chimeric antigen receptor T cell therapy (CAR T-cell therapy) being used for the treatment of relapsed or refractory B-cell lymphomas (BCLs). [4] (Fig. 1 & 2)

Axi-cell therapies are a significant advance in BCL treatment compared to earlier Standard of Care (SOC) approaches. However, there are obstacles in successful Axi-cel therapy. Therefore, it is necessary to discuss current limitations and recent advancements to enhance clinical efficacy.

Aim & Methods

We aim to discuss the gaps, recent advances in axi-cel therapy and suggest future considerations based on available evidence collated through a comprehensive literature search across various databases.

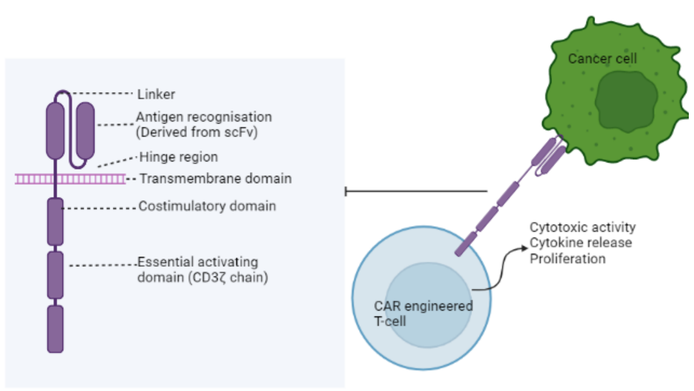


Figure 1. Structure of Axi-cell.

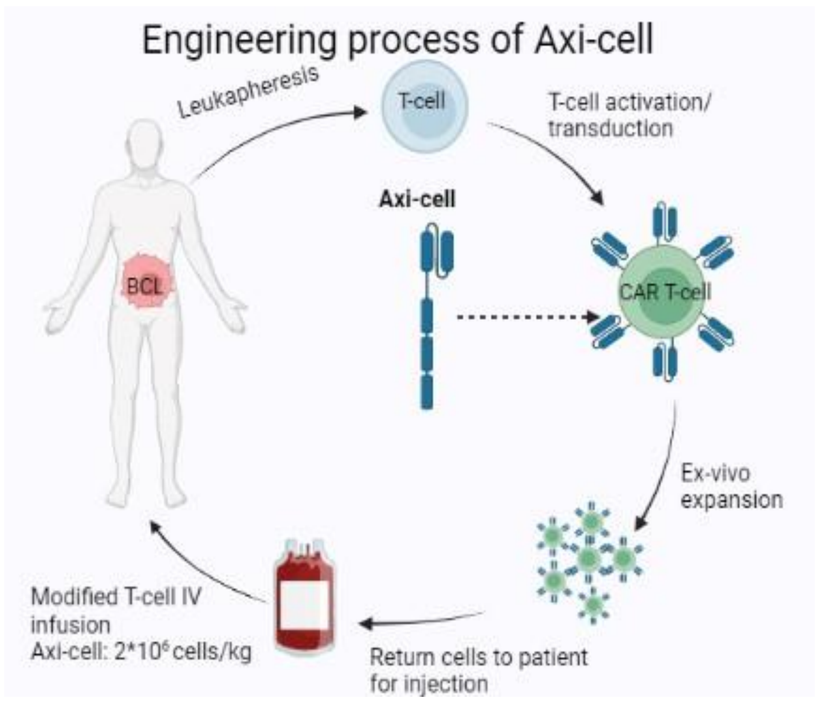


Figure 2. Engineering process of Axi-cel

Gaps

Two major **Axi-cel dysfunctions** that provide a significant obstacle to the development of successful axi-cel therapies are senescence and cell exhaustion. [5]

Manufacturing barriers include manufacturing errors, logistical complexity. [6]

Long waiting time- Each patient requires a fresh batch, which necessitates numerous procedures to collect, transport, manufacture, qualify, and eventually return the cells to the patients for infusion. The model is not scalable and is time consuming. Moreover, high cost of production is another challenge of this therapy. [6]

Opportunities & Future Perspectives

Increasing efficacy- Long-term maintenance of transferred cells is frequently required for Axi-cel therapy to be effective, which is dependent on the presence and persistence of memory T cells (TCM). The CCR71 CD45RA1 subset of CD8 product T cells is responsible for achieving durable response.[7]

Improving persistency- The JAK/STAT signaling activation is mediated by γc family cytokines, like IL-7, IL-15, and IL-21, which exert a significant impact on the expansion, differentiation, development, and survival of lymphocytes. Engineering less differentiated naïve (TN) and/or TCM cells, or culturing T cells in circumstances that preserve these phenotypes, results in CAR T cell products with greater persistence in vivo..[8]

Reducing resistance- Multi-target strategy construction of bispecific CARs, trivalent CARs, Universal CARs. [1](Fig 3.)

As a front-line therapy- Axi-cel when tested as a front-line therapy in ZUMA-12 trial has shown higher objective response and complete response compared to the ZUMA-1 trial. [9](Chart 1 & 2)

Improving the manufacturing process of Axi-cel therapy-

- **Long term sustainability-** Automation lowers labor expenses as well as production variations and batch failures which increases Cost of Goods (CoG).
- **Cost reduction-** Installation of automated closed systems, as well as the simplification of workflows and increased process resilience reduces the cost.
- **Addressing the production and supply chain complexity-** Turning from autologous to allogeneic cell sources. Allogeneic CAR-T cells with instant availability of off-the-shelf medications and the potential for product standardization, together with lower pricing, would considerably enhance accessibility. [10]
- **CRISPR/Cas9 Gene Editing Technology**: Generating CAR-T cells through genome editing with CRISPR/Cas9 can overcome several issues, including allogeneic response, tonic signaling, fatigue, poor Tumor Microenvironment (TME) function, and toxicity. Furthermore, the CRISPR/Cas9 system's large-scale genetic screens enable scalable methods for interrogating hundreds of genes in T cells with great efficiency and specificity. [11]

Chart 1. Axi-cel with higher Overall Survival than SOC.

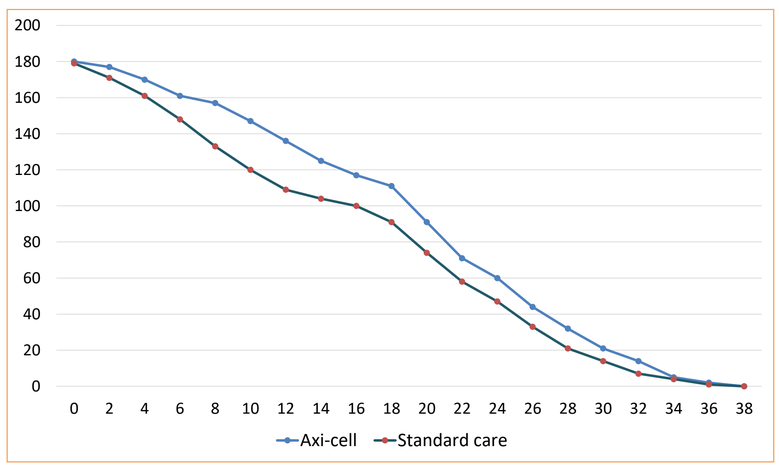
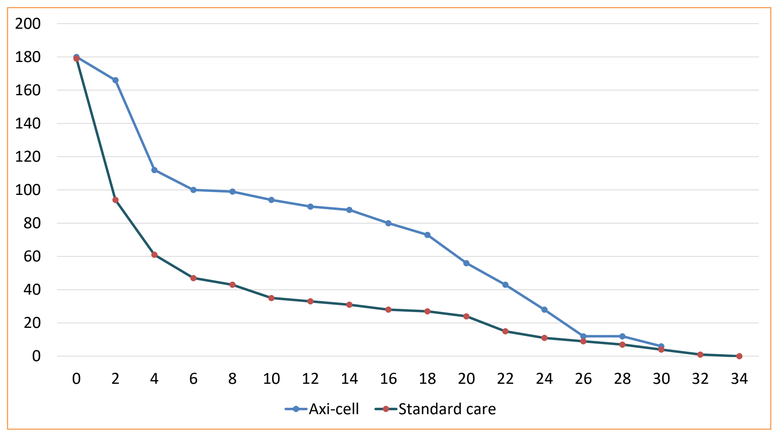


Chart 2. Axi-cel with higher Progression free Survival than SOC.



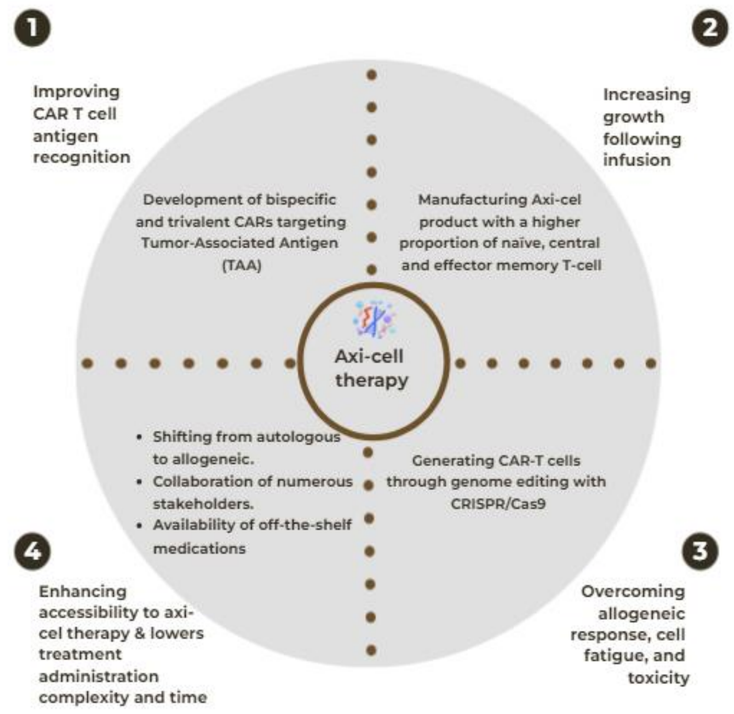


Figure 3. Opportunities & Future perspective in Axi-cel therapy.

Conclusion

Future long-term clinical trials and real-world data should be conducted to demonstrate T cells with optimal in vivo fitness, durable persistence and efficacy.

CAR T cell production is challenging yet extremely feasible for clinical and commercial uses. To tackle the manufacturing challenges, the development of innovative strategies such as automation, shifting from autologous to allogenic and CRISPER/ Cas9 gene editing technique could lead to the desired therapeutic outcomes in the clinic.

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