VIEWPOINT

CAR T Therapies: Game Changer or Culprit in Cancer Treatment?

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Abstract

The FDA alerts to potential T cell malignancy risks linked to CAR T therapies targeting CD19/BCMA, recognizing their advantages but advocating vigilant monitoring. Influential factors in secondary T cell malignancy encompass viral vectors, CAR design, and patient genetics. Analytical findings highlight instances of T cell cancer, stressing the necessity for prolonged safety studies and refined CAR T strategies. Global collaboration is crucial for consistent reporting and adherence to treatments. Recommendations include extended safety assessments, refined CAR T strategies, enhanced data reporting, and global cooperation. This viewpoint addresses safety concerns regarding CAR T therapies and proposes measures to enhance their safety and effectiveness. The discussion emphasizes the importance of optimizing CAR T strategies to minimize risks and elevate treatment outcomes.

Keywords: *Chimeric antigen therapy, T cell malignancy, CD19/BCMA targeting, Safety assessments, Global collaboration*

Background

Chimeric Antigen Receptor (CAR) T cell therapy introduces potential challenges, including fratricide, where the engineered cells intended for targeting malignant T cells may inadvertently harm non-malignant T cells, hindering their necessary expansion for effective tumor eradication (Cinquina et al., 2022). Additionally, concerns arise regarding T-cell deficiency, as CAR T cells directed towards T-cell markers may compromise both malignant and non-malignant cells, increasing the risk of opportunistic infections (Khawar et al., 2023a). Another complication involves potential contamination of collected T-cells with malignant counterparts, heightening the risk of T cell malignancy (Stewart & Henden, 2021). In response to these challenges, strategies such as utilizing nanobody-derived CAR T cells, exploring allogeneic CAR T products, and integrating CAR natural killer (NK) cells aim to address these concerns and minimize the risks associated with fratricide and tumor contamination (Khawar et al., 2023b). Navigating the complexities of CAR T cell therapy and the disclosed risks underscores the importance of finding a balance between advancing therapeutic strategies, such as using specialized CAR T cells, and maintaining vigilant monitoring to minimize potential adverse outcomes. Formerly, we have discussed the potential of nanoengineered formulations in clinical trials (Khawar et al., 2023c) and CAR associated toxicities (Khawar, et al., 2023a).

FDA Alert on Secondary T Cell Malignancies Following CAR T Therapy

The US Food and Drug Administration (FDA) discloses on November 28, 2023, that patients receiving autologous CAR T cell immunotherapies targeting CD19 or BCMA develop T cell malignancies, including CAR-positive lymphoma. The FDA also determines that all FDA-approved genetically engineered autologous CAR T cell immunotherapies, such as axicabtagene ciloleucel (Breyanzi), tisagenlecleucel (Kymriah), and ciltacabtagene autoleucel (Carvykti), which target CD19 and BCMA, carry a risk of T cell malignancies (Furlow, 2024). Despite these findings, the FDA asserts that the overall advantages of these therapies surpass the potential risks. Nevertheless, the agency is vigilantly monitoring the established risk of T cell cancer, which may

result in severe consequences, including hospitalization. Contemplating the necessity for supplementary regulations, the authorization of CAR T products depends on initiating safety studies lasting 15 years to evaluate prolonged safety and the probability of post-treatment tumor development. Therefore, FDA advocates for continuous cancer screenings for individuals in clinical trials and patients undergoing treatment with these medications (Levine et al., 2024). Expected in early 2024, upcoming FDA updates aim to provide additional information to the public.

Limited Evidence and Potential Factors

More than 34,400 patients have undergone CAR T cell therapy produced by different organizations. However, comprehensive data pertaining to patients afflicted with T cell malignancies who have undergone CAR T therapy, as well as the specific products utilized in their treatment, remain notably scarce. Although theoretical possibilities exist, research conducted so far has failed to establish a conclusive connection between CAR T cell therapy and secondary T cell cancers. Several preclinical studies involving rodents and clinical trials have not provided substantial evidence supporting such associations. Notably, in experiments where the TET2 gene was deliberately excised from CAR T cells, observations revealed only instances of clonal T-cell expansions (Furlow, 2024; Harrison et al., 2023). Furthermore, it's noteworthy that some individuals with B-cell malignancies may naturally progress to develop T-cell malignancies over time, irrespective of CAR T therapy administration. Factors contributing to the genesis of secondary malignancies may include the type of viral vector employed (lentiviral or retroviral), the specific design of the CAR (such as incorporating CD28 or 4-1BB costimulatory domains), or inherent genetic predispositions within the patient, such as a pre-existing TET2 mutation (Jain et al., 2023).

It is imperative to acknowledge the inherent resilience of T cells to genotoxic insults, with clonal competition regulating T cell homeostasis in vivo, specifically concerning the T cell receptor. Nonetheless, in infrequent cases, conditions conducive to the onset of T cell lymphomas may manifest. These include retroviral activation of JAK kinase3 and exceptionally high insertion copy numbers associated with certain methodologies employed in CAR gene delivery, such as the transposon method (Banerjee et al., 2024; Heinrich et al., 2013; Micklethwaite et al., 2021).

FDA Monitoring and Risk Comparison

As of early January 2024, the Center for International Blood and Marrow Transplant Research (CIBMTR) has identified over 11,000 individuals who received CAR T cell therapy products commercially. Among them, approximately 8,000 are actively participating in safety studies after authorization to detect occurrences of secondary tumors. Reports from patients receiving commercial CAR T cell products indicate 565 instances of such neoplasms among 485 individuals, while those involved in post-authorization studies reported 420 cases affecting 357 patients. The median follow-up period for these individuals spans 13 months, ranging from 0 to 69 months. Remarkably, as of December 14, 2023, the CIBMTR documented three cases of T cell cancers, comprising one instance each of large granular lymphocyte leukemia, anaplastic large cell lymphoma, and T cell lymphoma. It is noteworthy that routine clinical immunophenotyping has not identified any abnormal CD19 expression in tumors (Albelda, 2024; Ji et al., 2024; Levine et al., 2024; Savoldo et al., 2024).

Within the FDA Adverse Events Reporting System (FAERS) database, encompassing 8,000 cases, the total number of T cell cancer cases stands at 20. It is essential to emphasize the relative rarity of T cell malignancies in comparison to certain alternative therapeutic approaches, considering the collective exposure of around 34,400 individuals to commercially available CAR T cell products. Occasional reports of T lymphocyte cancer associated with immune checkpoint inhibition exist, although such occurrences are infrequent. Furthermore, an analysis of the FAERS database conducted by the authors unveiled the occurrence of T cell cancer subsequent to pembrolizumab checkpoint inhibitor therapy. However, the linkage to pembrolizumab, nivolumab, or ipilimumab administration constituted only a minimal 0.02% of T cell lymphoma cases (Anand et al., 2020).

Despite the requirement for a 15-year monitoring period for the FDA-approved products, there is a possibility that some patients may not adhere to recommended follow-up protocols, potentially resulting in missed or unidentified early warning symptoms. Patients are required to complete an informed consent form as part of the post-authorization safety study framework to participate in follow-up research. Although the responsibility for reporting lies with the CAR T treatment center, the optional nature of reporting to systems such as FAERS and CIBMTR hampers the ability to accurately assess both the denominator and numerator of adverse events. While the global number of patients treated with commercial FDA-approved products by the is estimated to exceed 34,400, data from only around 8,000 patients are present in the FDA FAERS database, despite the FDA mandating follow-ups every 15 years.

Comparing the risks linked with CAR T cell treatment to alternative therapeutic methods facilitates a comprehensive understanding of these risks. Traditional chemotherapy and radiation therapy are extensively documented to lead to the development of secondary malignancy (Meadows et al., 2009). These widely employed treatments are associated with considerable prolonged adverse effects, including genotoxicity, and a notably higher probability of secondary tumors when juxtaposed with the reported incidences of post-therapy T cell cancer.

Potential Research Directions

When considered the most suitable approach, patients are advised to continue with the use of commercially available CAR T products. Adherence to the FDA guidelines for prolonged follow-up is crucial, ensuring that providers of CAR T cell therapy access current and validated safety data in addition to some essential measures for future inquiries as given below.

Long-term Safety Assessment

Conduct comprehensive, long-term safety studies spanning beyond the FDA-mandated 15-year period to further evaluate the occurrence of post-treatment malignant neoplasms and T cell malignancies in subjects undergoing CAR T cell therapy.

Optimizing CAR T cell Strategies:

Investigate and refine strategies to minimize the risk of fratricide, T-cell deficiency, and potential contamination during CAR T cell therapy. Explore innovative approaches, such as nanobody-derived or naturally selected CAR T cells, allogeneic CAR T products, and CAR NK cells, to enhance therapeutic efficacy and reduce adverse outcomes.

Improved Data Reporting and Monitoring:
Enhance reporting mechanisms and monitoring systems to overcome the optional nature of reporting adverse events. Explore strategies to ensure accurate assessment of both the numerator and denominator of adverse events, addressing potential gaps in data representation, especially considering the estimated global number of patients treated versus the data available in regulatory databases.

Global Collaboration on Treatment Adherence:
Establish international collaborations to address challenges related to patient adherence to recommended follow-up protocols. Develop standardized protocols for informed consent and reporting, ensuring consistent and comprehensive data collection across CAR T treatment centers worldwide.

Conclusion/Future Prospects

In summary, patients are advised to persist with the use of commercially available CAR T products, emphasizing adherence to FDA guidelines for prolonged follow-up. Research directions include conducting comprehensive, long-term safety studies, optimizing CAR T cell strategies to minimize risks, improving data reporting and monitoring mechanisms, and establishing global collaborations for consistent treatment adherence and data collection across CAR T treatment centers worldwide.

Author contributions

MBK: Conceptualization; Data curation; Supervision. **AA:** Writing - original draft; Investigation; Writing - review & editing; Project Administration.

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