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Reimagining Clioblastoma Multiforme Treatment with the Emerging Role of CAR-T Cell Therapy

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ADMINISTRATIVE INFORMATION

Support - Nil.

Review Stage at time of this submission - Preliminary searches.

Conflicts of interest - None declared.

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 10 October 2024 and was last updated on 10 October 2024.

INTRODUCTION

Review question / Objective Applying the PICO methodology for this Systematic Editorial Review.

1. Population P : Individuals diagnosed with Glioblastoma Multiforme (GBM), a malignant tumour affecting the brain and spine.
2. Intervention I : Administration of Chimeric Antigen Receptor (CAR) T cell therapy against GBM.
3. Comparison C : None or the conventional treatments like chemotherapy with or without placebo.
4. Outcome O : Determination of efficacy of the CAR-T therapy and survival rate of the patients.

Research Question:
1. Does the use of Chimeric Immunoreceptors increase the chance of surviving GBM?
2. What is the therapeutic impact and safety profile of Chimeric Antigen CAR-T therapy in the management of GBM based on existing clinical studies?

Objectives:
1.To evaluate the clinical efficacy of CAR-T Immunotherapy against GBM diagnosed individuals.
2.To assess the safety, therapeutic response rates, and overall survival outcomes associated with CAR-T therapy in GBM.

Rationale GBM is a highly aggressive and malignant tumour that originates from astrocytes, a type of glial cell within the central nervous system (CNS). This tumour exhibits rapid growth and proliferation, often exerting pressure on surrounding healthy tissues and causing extensive damage. One of the notable advancements in targeted immunotherapy is the development of CAR-T therapy, wherein autologous cytotoxic T

cells are genetically engineered to express a specific receptor that targets GBM-associated antigens. This systematic review aims to synthesise the current evidence on the therapeutic efficacy and potential of CAR-T therapy in the treatment of GBM.

Condition being studied GBM is a brain tumour characterised by rapid growth, profound genomic instability, and poor treatment outcomes. Despite available therapies, survival rates remain low, with serious neurological symptoms such as cognitive decline and motor dysfunction, making it one of the most challenging malignancies to manage.

METHODS

Search strategy Methods of the extensive search strategy will be refined for each database, applying the combination of Medical Subject Headings (MeSH) terms and keywords related to GBM and CAR T therapy along with the boolean operators.
An example of search strategy for the pubmed is given below:
((("Glioblastoma/drug therapy"[Mesh] OR "Glioblastoma/immunology"[Mesh] OR "Glioblastoma/radiotherapy"[Mesh] OR "Glioblastoma/therapy"[Mesh])) AND ("Receptors, Chimeric Antigen/drug effects"[Mesh] OR "Receptors, Chimeric Antigen/immunology"[Mesh] OR "Receptors, Chimeric Antigen/therapeutic use"[Mesh])) AND "Immunotherapy, Adoptive"[Mesh].

Participant or population The review focuses on patients diagnosed with GBM, encompassing those undergoing treatment.

Intervention CAR-T therapy is gaining growing clinical relevance particularly in overcoming GBM's immune evasion and therapeutic resistance.

Comparator The comparator group consists of individuals receiving no intervention or those treated with conventional therapies like chemotherapy, which may be given independently or alongside a placebo.

Study designs to be included Randomised controlled trials (RCTs), clinical trials (CTs), cohort studies, case-control studies and observational studies.

Eligibility criteria Inclusion Criteria:
a. The review only consists of Randomised controlled trials (RCTs), Clinical trials (CTs), cohort studies, case-control studies, and observational studies.
b. Studies published between 2010 to 2024 are only included.
c. Only fully open-access studies are featured.
d. Studies relating to the therapeutic potential of CAR-T therapy against GBM.

Exclusion criteria:
a. Studies published in languages other than English are not considered.
b. Conference presentations are not taken into account.
c. Studies prior to 2010 have been excluded.

Information sources PubMed, Web of Science, and the Cochrane Central Register of Controlled Trials (CENTRAL) including reference lists with grey literature (e.g., clinical trial registries), and ongoing clinical trial data from platforms like ClinicalTrials.gov.

Main outcome(s) CAR-T therapy is being investigated for treating GBM, a highly malignant brain tumour known for its resistance to conventional therapies. CAR-T therapy, which involves engineering patient-derived T cells to specifically target tumour-associated antigens like EGFRvIII and IL13Rα2, represents a cutting-edge approach in immunotherapy for GBM. This revriew will systematically assess clinical outcomes, such as tumour regression, GBM-free survival, and overall survival, providing a deeper understanding of CAR-T therapy's potential to improve patient prognosis.
The review will, therefore, assess the effectiveness of CAR-T therapy in treating GBM, focusing on its ability to overcome the tumour's immunosuppressive environment. It will also evaluate the safety profile, including the incidence of other side effects and neurotoxicity. Additionally, the review will explore strategies to enhance CAR-T therapy's efficacy, such as combination therapies etc, aiming to improve clinical outcomes for GBM patients.

Additional outcome(s) Additional outcomes may include the assessment of biomarkers for treatment response and the evaluation of cognitive function, alongside monitoring for adverse events like cytokine release syndrome.

Data management Data management was conducted in accordance with standardised protocols, ensuring accurate collection, organization, and secure storage of relevant datasets throughout the review process.

Quality assessment / Risk of bias analysis Studies will be categorised as randomised

controlled trials (RCTs), observational studies, or animal studies and assessed using appropriate tools: the Cochrane Risk of Bias tool, the Newcastle-Ottawa Scale, and SYRCLE's risk of bias tool.

Strategy of data synthesis Data synthesis will involve narrative summary of all reviewed findings denoting the efficacy of CAR-T therapy against GBM. If appropriate, a meta-analysis may be conducted using a random-effects model to combine quantitative data, with heterogeneity assessed using the I7 statistic. This approach will provide a comprehensive understanding of the available evidence.

Subgroup analysis To assess the heterogeneity in outcomes, we will perform a subgroup analysis based on key variables that may influence the efficacy of CAR-T cell therapy in GBM.

A. Type of GBM Antigen Targeted:
1. EGFRvIII
2. IL-13Rα2
3. HER2
4. Other GBM-associated antigens

B. Mode of CAR-T Cell Administration:
1. Intracranial infusion
2. Intravenous infusion
3. Intrathecal infusion.

Sensitivity analysis Sensitivity analysis will evaluate the robustness of studies against GBM to make educated conclusions indicating the overall ability of CAR-T therapy. This will help determine the exclusion of potentially unreliable studies so as not to affect the synthesised evidence, ensuring a more reliable assessment of CAR-T therapy.

Language restriction The review is limited to studies published in English or fully available in English.

Country(ies) involved India (Department of Life Sciences, Kristu Jayanti College).

Other relevant information
Abbreviations:
1. CAR-T therapy: CAR T-Cell therapy
2. CNS: Central Nervous System
3. GBM: Glioblastoma Multiforme
4. MeSH: Medical Subject Headings

Keywords CAR-T cell therapy; glioblastoma multiforme; cancer therapy; brain tumours; oncology treatments; targeted therapy; chimeric antigen receptors.

Contributions of each author
Author 1 - Tarun Kumar - The first author was responsible for the overarching conceptualization of the study and the strategic oversight of the systematic review process, encompassing the formulation of research inquiries and methodological frameworks.
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Author 2 - Sauvit S Patil - The second author undertook the comprehensive literature review and data synthesis, facilitating an integrative evaluation of the prevailing research landscape.
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