


BMJ Open Efficacy of cell-based immunotherapies on patients with glioma: an umbrella review of systematic reviews and meta-analysis protocol

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ABSTRACT

Introduction Glial brain tumours are highly mortal and are noted as major neurosurgical challenges due to frequent recurrence or progression. Despite standard-of-care treatment for gliomas, the prognosis of patients with higher-grade glial tumours is still poor, and hence empowering antitumour immunity against glioma is a potential future oncological prospect. This review is designed to improve our understanding of the efficacy of cell-based immunotherapies for glioma.

Methods and analysis This systematic review will be performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. A comprehensive search of main electronic databases: PubMed/MEDLINE, Scopus, ISI Web of Science EMBASE and ProQuest will be done on original articles, followed by a manual review of review articles. Only records in English and only clinical trials will be encountered for full-text review. All the appropriate studies that encountered the inclusion criteria will be screened, selected and then will undergo data extraction step by two independent authors. For meta-analyses, data heterogeneity for each parameter will be first evaluated by Cochran's Q and I² statistics. In case of possible heterogeneity, a random-effects meta-analysis will be performed and for homogenous data, fixed-effects models will be selected for reporting the results of the proportional meta-analysis. Bias risk will be assessed through Begg's and Egger's tests and will also be visualised by Funnel plots.

Ethics and dissemination As this study will be a systematic review without human participants' involvement, no ethical registration is required and meta-analysis will be presented at a peer-reviewed journal.

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INTRODUCTION

Gliomas are among highly mortal neoplastic lesions that remain a major neuro-oncological concern due to their frequent recurrence/progression despite standard treatments.¹ Up to the present, numerous attempts have

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ This review is the first umbrella review of systematic reviews and meta-analyses evaluating the efficacy of cell-based immunotherapies on patients with glioma.
- ⇒ Meta-analysis of studies according to Preferred Reporting Items for Systematic Reviews and Meta-analysis guidelines.
- ⇒ A comprehensive literature search from multiple databases was conducted.
- ⇒ The search was restricted to English-language articles only.
- ⇒ A limited number of studies will meet the inclusion criteria.

been devoted to improving the efficacy of the current standard-of-care treatment for gliomas that comprise concurrent chemoradiation and surgical interventions.² The major challenges limiting the efficacy of the standard-of-care treatments for gliomas comprise the infiltrative nature of high-grade gliomas, which limits the efficacy of total aggressive surgery due to residues remaining and also tumour heterogeneity. Another main concern is the mesenchymal-transformed cells referred to as cancer stem cells in the glioma tumour microenvironment (TME), which are resistant to chemoradiation. This piece of evidence proves the ultimate need for designing treatment strategies with precision to individual characteristics of the tumour in each patient.

A key feature in the glioma pathogenesis is its immune-suppressed microenvironment due to the pauci nature of the brain as an immune-privileged site and also the overproduction of angiogenic signals in the glioma TME produced in the hypoxic central niche of highly proliferating glioma cells, which

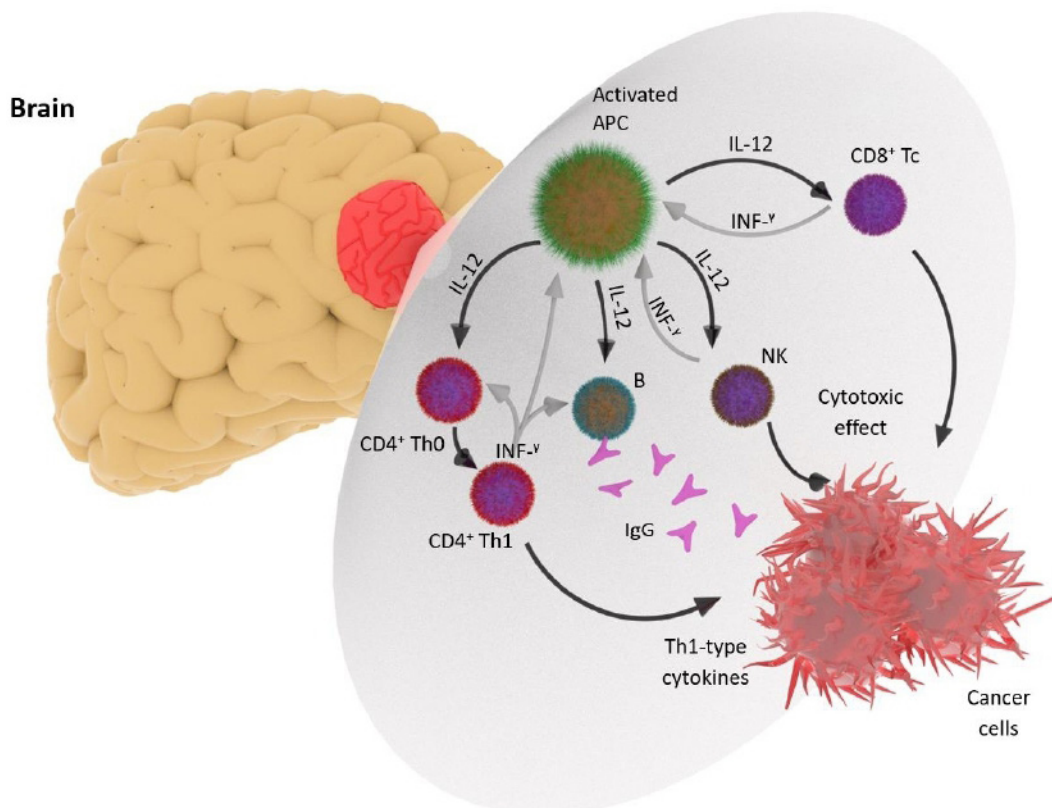


Figure 1 A schema of different cell-based immunotherapy strategies to combat glioma growth.

induces generation of tolerogenic dendritic cells (DCs) and impairs the antigen presentation process.³ The glioma TME comprises a low density of immune cells making it a ‘cold tumour’ with limited immune contexture. Hence, re-empowering the immune system components (ie, NK cells, cytotoxic T cells and DC cells) against gliomas in a coordinated fashion and also transferring autologous/allogeneic immune cells (ie, adoptive immunotherapy) to the tumour site to combat tumorous cells has been of particular interest as a highly precise therapy in the past decades.⁴ Standing at the first and foremost stages of interest for such attempts in the previous literature are cellular immunotherapies (eg, CAR T cells, DC cells, adoptive T cells, CIK cells and NK cells).

Cellular immunotherapies can comprise both innate and adoptive immune cells (figure 1). NK cells, granulocytic lymphocytes acting as powerful armamentaria of the innate immune system, are capable of eliminating abnormally transformed cells without any need for prior sensitisation. NK cells recruit to their action site in a chemokine-mediated manner. Some NK cells act as empowered soldiers able to kill numerous and diverse cells named ‘serial killers’, which are noted as potent antitumour cells.⁵ Moreover, the introduction of chimeric antigen receptor (CAR) NK cells also represented a step forward towards more efficient NK products⁶ and efforts are underway to further clinically translate such immune products from benches to bedsides.

DCs are also key players in the immune system referred to as linkers of adaptive and innate immune responses.

DCs enhance NK cell migration and recruitment to the tumour site by the production of numerous chemokines (eg, CXCL8, CXCL9 and CXCL11).⁷ Furthermore, DCs act as regulators of adaptive/cellular immune responses against tumorous cells mediated by CD8+cytotoxic T cells by cross-presenting the tumorous antigens via major histocompatibility complex II (MHCII)-antigen complexes.⁸ DCs are also responsible for coordinating the immune contexture in the TME by producing chemokines and cytokines responsible for an orchestrated migration of immune cells to the tumour site. DC therapy for gliomas has long been studied in clinical settings, yielding acceptable results⁹ and has introduced a paradigm shift toward more precise glioma management.

Furthermore, the advent of adaptive T-cell generation and clinical testing of such immune cell products has yielded promises towards glioma therapy. Early reports have suggested alloreactive T cells for glioma therapy.¹⁰ Testing the autologous lymphocyte transfer has also opened a new avenue toward more precision.¹¹ Such T cells were activated by several strategies against tumorous cells *ex vivo* such as total tumour RNA pulsing. Furthermore, mounting the previous literature, earlier attempts generating antigen-specific T cells have been of particular interest (eg, CMV-specific T cells).¹² Recently, the advent of CAR T cells has revolutionised the advent of T-cell therapy for gliomas as well as other neoplastic lesions.^{13–15} Genetically engineered T cells that express CARs can recognise tumour-associated antigens (TAAs) or tumour-specific antigens (TSAs) presented by the MHCs resulting

in a powerful antitumour immune response. Despite the potential limitations of CAR T cells for solid tumours, in gliomas, promises have been obtained in early attempts possibly due to the cold nature of the glioma immune context.¹⁶ CARs can be engineered to target various highly expressed tumour antigens and can serve as next-generation adoptive cell therapies for gliomas¹⁷ (online supplemental table 1). As future prospects, using combination therapy regimens may yield substantial improvements in the field of glioma immunotherapy. Furthermore, using adjuvants is also a potential proposed strategy to improve the efficacy of adoptive immune cell therapy for gliomas.^{18–21}

Summarising the results of the efficacy and limitations of the previous attempts on glioma immunotherapies opens the door to the discovery of novel techniques and yields insight into the treatment failure causes and ways to overcome them. Here, we aimed to discuss the main methods that will be applied in a comprehensive meta-analysis for assessing the response efficacy and survival of cell-based immunotherapies (eg, CAR T cells, DC cells, adoptive T cells, CIK cells and NK cells) for glioma. The meta-analysis on cell-based immunotherapies aims to provide a hierarchical summary on the road to clinical translation of adoptive immunotherapies for gliomas and also discusses the technical limitations introducing variability in generating GMP-grade immune cell products. The review will also highlight the potential need for standardised protocols for more reproducible and scalable production techniques. Furthermore, the review will discuss the potential strategies to enhance the efficacy of adoptive immunotherapies for gliomas. For instance, using adjuvants and also combination therapy.

Objectives

This systematic review and meta-analysis aims to summarise the results of previous clinical trials on (eg, CAR T cells, DC cells, adoptive T cells, CIK cells and NK cells) for glioma patients regarding the number of patients, administered doses, adjuvants, antigens/targets, phases, submission dates, completion dates and allocation. Furthermore, this study aims to investigate the immunological efficacy of cell-based immunotherapies (eg, CAR T cells, DC cells, adoptive T cells, CIK cells and NK cells) for glioma. Also, this compares the administered dose of each therapy (eg, CAR T cells, DC cells, adoptive T cells, CIK cells and NK cells) and the survival outcome of the patients enrolled in treatment groups or control groups for each treatment. Moreover, the survival of the patients enrolled in different treatment groups will also be compared. Furthermore, the immunological response will be compared among the patients receiving each treatment and control groups for each therapy. Furthermore, standardisation of the protocols used to harvest cells and produce and scale up the manufacturing process will hugely revolutionise the results obtained from each trial. There is a substantial need to improve guidelines for the GMP-level products moving from benches to bedside to

let the process be more reproducible and reliable. Additionally, standardising the strategies to assess treatment efficacy will also hugely impact the results of trial pipelines (eg, immunological response assessment, radiological response assessment criteria such as AVA Glio, RESICT, RANO or iRANO). In the current meta-analyses, we will discuss the limitations on the way of clinical translation of the GMP-level products in the trial pipelines for better outcome management and standardised results reporting.

METHODS AND ANALYSIS

Eligibility criteria

This study follows the Population, Intervention, Comparison, Outcomes and Study (PICOS)-type format for conducting systematic reviews and meta-analyses.²² According to PICO parts, the eligibility criteria will be as follows.

Participants/population

Inclusion criteria

This umbrella review will consider systematic reviews that include the population for the current work consisting of adult patients and controls enrolled in clinical trials for glioma cell-based immunotherapies (eg, CAR T cells, DC cells, adoptive T cells, CIK cells and NK cells).

Exclusion criteria

Studies reporting patients with other cancers will be excluded.

Intervention(s), exposure(s)

The intervention (exposure) of this study will be cell-based immunotherapies (eg, CAR T cells, DC cells, adoptive T cells, CIK cells and NK cells).

Comparator(s)/control

Administered doses, percentage of clinical trials targeting each tumorous antigen, immunological efficacy and survival.

Main outcome(s)

The standardised mean difference for administered doses, the pooled effect size for each antigen for glioma immunotherapy, the pooled effect size of significant immunological responses for each therapy and the overall survival benefit for each immunotherapy as an indicator of treatment efficacy.

Studies design

Inclusion criteria

Only systematic reviews and systematic review and meta-analysis studies will be included.

Exclusion criteria

Narrative reviews, commentaries, letters, case reports, case series, experimental studies and research works in any other language rather than English are excluded

from this review. Furthermore, studies suggesting a controversial result will be excluded with no time limits. Controversies are among the unavoidable issues while collecting huge clinical data from diverse clinical centres worldwide testing a specific therapy in trial pipelines. To cope with this issue in the systematic reviews, several strategies have been proposed such as removing the controversial reports. Here, when meeting a controversy, the two independent authors reviewing the selected manuscripts will discuss the potential differences and diversities in the cell production process or obtain the efficacy results and will draw a certain conclusion by getting in touch with the corresponding authors. If the conflicting answer is due to inappropriate methodology, it will not be considered in the meta-analysis stage. For instance, if the lack of adequate cell count to start the treatment is the reason for the trial failure, that study will not be considered in the meta-analysis stage but will be discussed in a separate section. For instance, if the lack of adequate cell count to start the treatment is the reason for the trial failure, that study will not be considered in the meta-analysis stage but will be discussed in a separate section summarising the failure reasons for each cell-based therapy and solutions to overcome will further be discussed.

Information sources

The current work includes a comprehensive search of main electronic databases (PubMed, Scopus, ISI Web of Science, EMBASE and Clinicaltrial.gov) and is also followed by a manual search of the reference lists of the previously published review articles.

Search strategy

Search syntax for each main electronic database (PubMed, Scopus, ISI Web of Science, EMBASE and Clinicaltrial.gov) will be generated according to their rules and Mesh terms.^{23–25} An example of the PubMed/MEDLINE search strategy is presented in [table 1](#). A filter for study type, review and clinical trial will be used to minimise the presence of unrelated articles in the recovery search. All the retrieved references will be deposited in a single Endnote file, and after duplicate removal they will undergo a title review for relevance.

Selection process

After retrieval of relevant articles and duplicate removal, two individual authors, PS and MN, will go through the title and abstracts of the relevant article to select the relevant qualified articles for the data mining process. In case of any disagreement between the two authors, it will be fixed via consensus and then will be checked by two other authors (SMMZ and AR). Irrelevant studies and studies with controversial results will be excluded at this stage. DA and MA will be asked to build a consensus in cases where discrepant opinions exist.

Data collection process

Relevant qualified articles will undergo a full-text review in order to extract data from them. Two individual

Table 1 Representative example of the search syntaxes generated for the comprehensive search

Search syntax for PubMed	
#1	((Glioma[tiab]) OR (Gliomas[tiab]) OR “Glial Cell Tumor”[tiab] OR (Tumor*[tiab] AND Glial Cell[tiab]) OR “Mixed Glioma” [tiab] OR (Glioma*[tiab] AND Mixed[tiab]) OR “Mixed Glioma”*[tiab] OR “Malignant Glioma”[tiab] OR (Glioma*[tiab] AND Malignant[tiab]) OR (glioblastoma[tiab]) OR “anaplastic astrocytoma” [tiab] OR “diffuse astrocytoma”[tiab] OR “anaplastic oligodendroglioma”[tiab] OR (oligodendroglioma[tiab]))
#2	((Immunotherapy[tiab] AND Adoptive[tiab]) OR “Cytokine-Induced Killer Cells”[tiab] OR “Dendritic Cells”[tiab] OR (Killer Cells AND Natural[tiab]) OR “cytokine induced killer”[tiab] OR “tumor infiltrating lymphocytes”[tiab] OR “lymphokine activated killer” [tiab] OR (autolymphocyte[tiab]) OR “activated T cells”[tiab] OR “activated killer cells” [tiab] OR “gamma delta T cells”[tiab] OR “γδ T cells” [tiab] OR “NKT cells” [tiab] OR “natural killer”[tiab] OR “NK cells” [tiab] OR “Adoptive Immunotherapy” [tiab] OR “Adoptive Immunotherapies”[tiab] OR (Immunotherapies[tiab] AND Adoptive[tiab]) OR (“Cellular Immunotherapy”[tiab] AND Adoptive[tiab]))
#3	(1992/01/01:2022/11/02[dp])
#1 AND #2 AND #3	

authors, PS and FHA, will extract data according to the checklist summarised in Excel from each study individually regarding the immunological responses and survival rates. AM and VFR will do so for radiological response rates. In case of any disagreement between the two authors, it will be fixed via consensus and then will be checked by two other authors (SMMZ and AR). At last, DA and MA will build consensus for discrepant reports.

The reports of data mining will be presented in tables for each cell-based immunotherapy (eg, CAR T cells, DC cells, adoptive T cells, CIK cells and NK cells) summarising in detail the aforementioned parameters. The radiological responses reported according to the guidelines Response Assessment in Neuro-Oncology Criteria (RANO), immunotherapy response assessment for Neuro-oncology (iRANO), Response evaluation criteria in solid tumors (RESICT), WHO oncology response criteria, Macdonald and AVAglio^{26–30} will be summarised as depicted in [table 2](#).

Quality assessment

The Cochrane Collaboration’s tool will be used as the checklist of choice to assess the risk of bias among included studies, which comprises five major domains: selection bias (random sequence generation and allocation), performance bias, detection bias, attribution bias and reporting bias. Each domain will be scored as high, low or unclear as implemented in our previous work.^{31–34}

Statistical analysis

For the assessment of heterogeneity among included studies, the I² statistic defined as the fraction of variance

Table 2 Data extraction checklist for each study

Study features	Patients feature	Treatment strategy features	Immunological response parameters	Survival features	Radiological response parameters
First author's surname	Estimated/actual number of enrolled patients	Immunotherapy strategy (innate or acquired)	INF γ increase	Overall survival rate	Complete response%
Publication date	Tumour pathology and grade	Product type (eg, CAR T, DC)	Induction of delayed type hypersensitivity (DTH)	Progression-free survival rate	Partial response%
Study design, allocation and randomisation		Adjuvants	Blood flow cytometry tests	Progression/recurrent rate	Stable disease%
University/institute		doses	TIL* flow cytometry tests	Mean/median overall survival (months)	Progression%
Phase		boosters		Mean/median progression-free survival (months)	
Estimated/actual study completion date		Antigens/targeting moieties		HR for overall survival	
Trial submission date				HR for progression-free survival	
Country					
Completion status					
Clinical trial submission number					

TIL, Tumor-infiltrating lymphocyte.

that is due to heterogeneity will be used.³⁵ Heterogeneity will be categorised as negligible ($I^2=0\%–25\%$), low ($I^2=25\%–50\%$), moderate ($I^2=50\%–75\%$) or high ($I^2>75\%$). Cochran's Q will also be encountered as a complementary measure for heterogeneity.³⁶ If we face high heterogeneity, Random Effect Model will be applied by Dersimonian and Laird method and when the heterogeneity is low, the fixed effect model will be applied for meta-analysis.³⁷ Egger's and Begg's tests will be used to investigate the presence of publication bias.^{38 39} For dose estimation meta-analysis, as a continuous measure, the 'Hedges g' statistic, as a function for standardised mean difference (SMD) will be used at a significant threshold of <0.05 .⁴⁰ For proportional data meta-analysis (for radiological and immune response assessment), Freeman-Tukey Transformation (arcsine square root transformation) will be used as the method of choice.⁴¹ For survival meta-analysis of survival rates (overall or PFS) at specific time points, also Freeman-Tukey Transformation will be performed; however, for survival meta-analysis with hazard ratios from KM analysis, the generic inverse variance method will be used.⁴² Furthermore, in order to visualise the data for better interpretation, the pooled effect size will be depicted by forest plots for each study and also funnel plots will be used for depicting the publication bias status.⁴³ The asymmetry

of the funnel plot will show the presence of publication bias.⁴⁴

The results of the bias risk assessment through Cochrane Collaboration's tool and meta-analysis will be summarised in tables depicting each variable, heterogeneity parameters for (I^2 and Q) for the variable and overall effect size with 95% CIs, and also the forest and funnel plot for each variable will be included.

Patient and public involvement

Patients and the public are not involved in the preparation of this protocol and will not be directly involved in the final systematic review.

DISCUSSION

In the discussion and conclusion parts, the results of the survival analyses performed will be discussed in detail and also the impact of using adjuvants on improving survival outcomes will be further discussed. In the later sections, previous adjuvants will be summarised and discussed. Regarding the immunological response rates, also a detailed discussion on the overall validity of each parameter for assessing the efficacy of immunotherapy will first be discussed and then the results will be compared for each therapy group.

ETHICS AND DISSEMINATION

This review will retrieve published data, so it will not require ethical approval. The findings of this systematic review and meta-analysis will be disseminated via an international peer-reviewed journal publication and several scientific conference presentations.

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Contributors DA, MN, AM and MA developed the search strategy and participated in writing up the draft of the protocol and SMMZ reviewed the manuscript and edited the final manuscript. All the authors read and approved the final draft. Data screening and selecting phases of the systematic review and meta-analysis will be performed by SMMZ and PS. Quality assessment and meta-analysis will be executed by PS, MR, FH and AR. Data extraction and preparing the draft of the manuscript will be performed by SMMZ, VF and AM. Moreover, PS, MN and SMMZ will be responsible for reviewing the manuscript and editing the final manuscript. EN contributed to designing the schemas and also revising the protocol.

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval This review will retrieve published data, so it will not require ethical approval. The findings of this systematic review and meta-analysis will be disseminated via an international peer-reviewed journal publication and several scientific conference presentations.

Provenance and peer review Not commissioned; externally peer reviewed.

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