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Efficacy and safety of gene therapy approaches for malignant gliomas: A systematic review and meta-analysis: ConNRNRNRNR22.5NRNR1011.413.511.9NRNRNR

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Highlights

- Gene therapy is a novel treatment method applied for management of high-grade gliomas which are known as the most invasive brain tumors.
- The present meta-analysis shows the efficacy of gene therapy for increasing overall survival of glioblastoma patients in the included phase I clinical trial.

- Progression free survival improvement was also observed using retroviral vector, Toca genes as compartments of gene therapy.

Abstract

Background

Malignant gliomas are the most aggressive brain tumors with no certain therapeutic methods. Nowadays, novel treatment methods are introduced for gliomas among which gene therapy is known as a promising and robust method. In this method, genes with key roles in the prevention of cell cycle or induction of cell suicide are transferred to the tumor site using vectors. Viral vectors are the most popular transfer methods, while the liposomes are also used for gene therapy.

Methods

This meta-analysis and systematic review was performed based on PRISMA guidelines. We performed a comprehensive search in databases including PubMed, Embase, and clinicaltrial.gov. After processing and filtering the articles, phase 1 clinical trials were chosen for the evaluation of the efficacy and safety of gene therapy for malignant gliomas.

Results

The obtained results showed that gene therapy increases overall survival (OS) and progression-free survival (PFS) in two years of follow-up. Subgroup analysis also showed that cytokines exhibit the highest effectiveness compared to suicide genes and oncolytic genes. It was found that gene therapy is more efficient for recurrent gliomas than primary gliomas. The subgroup analysis for vectors revealed that Adenovirus is the most effective for increasing the OS in malignant glioma patients.

Conclusion

Gene therapy is an immunotherapy method for malignant gliomas following the standard treatment approach. Considering the effectiveness of gene therapy on the survival of patients, it is hoped that solving related issues with gene therapy will help to increase the OS rate in this malignant disease.

Introduction

Gene therapy is a type of immunotherapy composed of nucleic acid (DNA or RNA) and a vector for delivering the targeted gene. Gene therapy was introduced in 1990 as a treatment method for patients with adenosine deaminase (ADA) deletion as an immunodeficiency. In the mentioned study, T-cells inserted with the ADA gene were infused into the blood flow of patients.[1] Gene

therapy was noticed as a therapeutic method for cancers a few years ago while it mainly relied on the induction of T-cell immunity to recognize cancer cells as antigens and attack them.[2] A large number of clinical trials have been performed for evaluation of the efficacy of different genes and delivery approaches in various cancer types among which some have been introduced to the market.[3] Malignant gliomas are known for aggressiveness, diffusion into the parenchymal brain tissue, and frustrating prognosis. The standard treatment approach for gliomas includes surgery followed by chemotherapy and radiotherapy, which has shown an increase in the survival rate of patients, while the prognosis of glioma is still between 2 and 4 years.[4] Accordingly, immunotherapy was applied as a promising approach to induce immune response in T-cells and lysate tumor cells in the glioma microenvironment. Gene therapy was used for glioma treatment in the early 1990s, for the first time, using a suicide gene and viral vector that showed high efficacy in patient prognosis.[5] Several genes and vectors have been suggested and used for treating malignant glioma since then.

Suicide (Herpes Simplex Virus tyrosine kinase and cytosine deaminase), oncolytic (HSV, Adenovirus, measles virus, and Poliovirus), cytokines (interferon-ɣ (IFNɣ), IFNβ, IL-2, IL-4, and IL-12), and tumor suppressor (p53, p16, and PTEN) genes are known as the most frequent gene therapy targets. However, each group has advantages and disadvantages which have been mentioned by Okura and colleagues.[6] In addition, different vector types have been suggested for glioma from viral vectors to chimeric T-antigen receptor (CAR) T-cell and liposomes. Meanwhile, viral-based vectors are considered by researchers and clinicians because of their safety and low adverse effects. These vectors are divided into the replication-incompetent and the replication-competent viruses.[7] Tobias and colleagues reviewed different types of vectors for malignant gliomas and found similar results for two types of viral vectors ranging from no efficacy in prognosis to increase in survival duration to two-fold compared to the standard treatment approach.[8] Noteworthy, the implemented clinical trials have shown a wide range of results, while no consistent results are found among them to be used as preclinical models for improvements in glioma gene therapy.[9]

Accordingly, there are still lots of challenges in gene therapy for malignant gliomas, though several review studies are available that have evaluated genes, vectors, and approaches from different viewpoints. In addition, no meta-analysis has been implemented on the evaluation of the results of gene therapy in comparison with the standard treatment approach (STA) including surgery followed by chemotherapy and/or radiotherapy. In this regard, we aimed to collect published clinical trials and perform a comprehensive systematic review and meta-analysis to describe the advantages and disadvantages of gene therapy for gliomas.

Section snippets

Search strategy and selection criteria

We performed the present meta-analysis using the guidelines of Preferred Reporting Items for

Systematic Review and Meta-analysis.[10] The search process was performed in public databases including Embase, PubMed, Cochrane Library, and clioncaltrial.gov, to find the published articles with the methodology of clinical trials. The keywords were used in three groups, including group one (gene therapy, glioma, glioblastoma, and malignant glioma), group two (HSV-TK, Adenovirus, and Retrovirus), and …

Study selection

The primary search yielded 1451 studies from databases and registered clinical trials, among which 216 duplicates were found and excluded. At the next step, abstracts of the studies were reviewed, and screening led to the exclusion of 1155 studies because they didn't use gene therapy, the population hadn't malignant gliomas, they were not clinical trials, pediatric gliomas studies, and not available full-text articles. The remaining 233 publications were screened using full texts and those …

Discussion

According to the results of the present meta-analysis, GT leads to an increase in OS rate within two years of follow-up in malignant glioma patients rather than the STA. Based on our knowledge, this is the first meta-analysis conducted to evaluate the efficacy and safety of GT compared to the standard treatments. According to our results, GT not only increased the number of patients who survived within two years compared to patients who underwent only STA, but also led to an increase in overall …

Conclusion

Gene therapy is known as a novel and promising method for treatment of patients with malignant glioma. This method is usually used after STA as an adjuvant treatment to improve the OS rate and duration and recurrence of this aggressive brain tumor. We showed the efficacy of GT for glioma, and based on the obtained results, we suggest conducting more clinical trials with large populations for assessment of methods that have been assessed more frequently and implementing more preclinical and …

Declaration of competing interest

The authors whose names are listed below certify that they have NO with or involvement in any organization or entity with any financial interest or non-financial interest in the subject matter of materials in this manuscript. …

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