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REVIEW ARTICLE

Advanced treatment in high-grade gliomas

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Summary

Gliomas are tumors with high incidence and poor prognosis among primary brain tumors and they present difficulties in surgical removal, having also high recurrence rate. The efficacy of various treatments on high-grade gliomas is not satisfactory. Some studies have found that age, surgery, radiotherapy, chemotherapy and other factors, such as tumor molecular pathology, have a certain impact on the recurrence of high-grade gliomas, and a common concern in the studies of high-grade gliomas is that one single treatment often has low efficacy. However, with the development of molecular biology, there is a deeper understanding of the pathogenesis of these tumors, and molecular targeted therapy has attracked impressive attention. The treatment of recurrent high-grade gliomas is also more abundant , with a diversity of treatment options than before. Oncolytic virus therapy, stem cell therapy, immunotherapy and electric field therapy are now available. These emerging treatments are expected to improve the prospect of treating recurrent high-grade gliomas.

Key words: *high-grade glioma, immunotherapy, molecular targeted therapy, recurrence, treatment*

Introduction

Glioma is a tumor originating from the glial cells differentiated from neuroectoderm, which accounts for about 60% of the primary tumors in the brain. Among them, high-grade gliomas (WHO grade III-IV) show strong invasive capability without obvious boundaries and poor prognosis, making it difficult to completely remove by operation. The median overall survival (OS) of patients with glioblastomas is about 14-16 months [1]. Currently, the standard diagnostic method for glioma recurrence remains histopathology. Modern methods for treating gliomas include surgery, chemotherapy, radiation therapy and immunotherapy. Recurrence of gliomas depends on a variety of factors such as location of recurrence, Karnofski performance score (KPS), and first-treatment effects. In recent years, the treatment of recurrent high-grade gliomas has made some progress, and is summarized as follows:

Related factors of prognosis

Age is considered an important factor influencing the prognosis of patients with gliomas. A study has shown that the prognosis of the elder people is relatively poor [2]. The reason may be that the older the patient, the higher the pathological grade of the tumor may be, and even if the pathological grade is low, the invasiveness is still higher compared with younger patients. As for symptoms, elderly patients are more responsive than younger ones during treatment. However, treatment of el-

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derly patients is less effective compared to younger ones. Moreover, the metabolism and immune functions of older patients are decreased compared to younger patients, and their tolerance to surgery, postoperative radiotherapy and chemotherapy is reduced. Various complications are likely to occur after the operation.

Because of the invasive growth of high-grade gliomas, it is difficult to completely remove the tumor. Residual tumor cells after surgery will be the source of recurrence. Radiotherapy has become an important treatment for postoperative patients with high-grade gliomas. For these neoplasms, it is currently recommended to safely maximize the removal of tumors, followed by chemoradiotherapy and adjuvant temozolomide (TMZ) therapy. Three-dimensional conformal radiotherapy (3DCRT) is gradually being applied to glioma radiation therapy. The technique can reduce normal tissue damage, while accurately positioning the tumor resulting in less complications than other treatments. In 11 randomized controlled trials including a total of 2062 patients, the results showed that patients with high-grade gliomas receiving postoperative radiotherapy and supportive care achieved better OS [3]. On the other hand, chemotherapy as an adjuvant treatment for gliomas has become an indispensable partner. Postoperative chemotherapy can further kill residual cells and help improve the survival of patients. Alkylating agents are part of the effective drugs for the treatment of glioma. TMZ is a new alkylating agent that penetrates the blood-brain barrier and has high bioavailability after oral administration, which has become a recommended first-line drug for the therapy in patients with glioma in NCCN guidelines. Hart et al. have found that TMZ prolonged the OS and progression-free survival (PFS) of patients with high-grade gliomas [4]. Phase III clinical trials by the European Cancer Research and Treatment Organization (EORTC) and the National Cancer Institute of Canada (NCIC) have shown that 6 cycles of adjuvant TMZ after TMZ combined with radiotherapy significantly prolonged patients' survival [5]. Although TMZ is generally more effective in treating gliomas than previous chemotherapeutic drugs with mild adverse effects, clinical practice has found that TMZ still cannot solve the problem fundamentally because of the intrinsic and induced resistance of the tumor, of which MGMT (O6-methylguanine-DNA methyltransferase) promoter methylation is particularly eye-catching. The study on MGMT promoter methylation found that MGMT promoter methylation reduced the expression of MGMT activity, which can improve the anti-tumor effect of TMZ and prolong the patient survival [6]. Kato et al. used liposome-mediated transduction of MGMT-SiRNA into glioblastoma cells, which resulted in decreased expression of MGMT in tumor cells, thereby increasing the killing effect of TMZ on tumor cells [7].

Following the advancements of molecular biology technology, great progress has been made in the research of molecular markers for the diagnosis, differential diagnosis and targeted drug therapy of glioma. Mutations in the TERT promoter region have important clinical implications for classification and prognosis. The mutation hotspots of the TERT promoter are C228T and C250T, which can increase the mRNA, protein and enzyme activities of TERT, thereby gaining the length of telomere [8-10]. The Eckelpassow's et al. study showed that patients with both TERT promoter and IDH mutations had the longest OS in grade II and III gliomas, while the OS of patients whose TERT, IDH and 1p19q were all negative was significantly shorter than that of the TERT and IDH double or triple positive groups. Meanwhile, patients with mutations in the TERT promoter alone had the worst prognosis, and the TERT promoter mutation accounted for 74% in grade IV gliomas [11].

BRAF is a member of the RAF gene family, which is mainly found in neuronal and testicular tissue and regulates cell growth, proliferation and apoptosis. Tanaka et al. believe that BRAF V600E mutation is closely related to the clinical grade of epithelioid glioblastoma, which can change epithelial glioblastoma from low to high level, indicating that BRAFV600E mutation can predict potential risks of tumor malignancy [12]. Studying BRAF gene mutations not only helps understand the pathogenesis of glioma, but also provides new targets for the treatment of these tumors.

MGMT can repair damaged DNA of tumor cells making it an important factor of resistance to TZM [13]. Methylation of the MGMT promoter silences the gene and inhibits protein synthesis, thereby decreasing the expression of MGMT protein. Hegi et al. reported that in 206 patients with glioblastoma treated with TMZ, the incidence of MGMT promoter methylation was about 40% [14]. In glioma patients of the report taking radiotherapy and therapy with TMZ the survival of methylated patients was significantly longer than that of non-methylated patients, suggesting that patients with MGMT promoter methylation are sensitive to TMZ.

Isocitrate dehydrogenase 1 and 2 (IDH1/2) gene mutations mainly occur in astrocytoma, anaplastic astrocytoma, oligodendroglioma, anaplastic oligodendroglioma and secondary glioblastoma. Mutations in the IDH1/2 gene predict a better prognosis. Another report [15] showed that the

median survival (about 65 months) of anaplastic astrocytoma patients with IDH1/2 mutation was significantly longer than that without IDH1/2 mutation (20 months), while the median survival (31 months) in glioblastoma patients was also significantly longer than those without gene mutations (15 months) [15].

Progress in treatments

The conventional treatments of recurrent high-grade glioma recommended by the NCCN guidelines include secondary surgery, re-radiation, chemotherapy, and combination of radiotherapy with chemotherapy. However, the traditional standard treatment has limited effect on recurrent high-grade glioma. Other new adjuvant treatment methods including immunotherapy, molecular targeted therapy, oncolytic virus therapy, stem cell therapy and electric field therapy have gradually become research hotspots.

Secondary surgery

When the patient is generally in good condition with the recurrent tumor producing an acute mass effect or the imaging indicating a change in tumor properties, surgical treatment is recommended. Whether re-operations for patients with relapsed high-grade glioma can benefit them is currently lacking evidence. It is generally believed that patients with a significant tumor-occupying effect and general good condition may be considered for surgical treatment, since surgery may further confirm the pathological and molecular pathological diagnosis of tumor after recurrence, alleviate the effect of occupancy, and facilitate subsequent chemotherapy.

Re-radiotherapy

Radiation therapy for gliomas generally includes conventional radiotherapy, three-dimensional conformal radiotherapy and stereotactic radiotherapy. Currently, there is no prospective study of re-radiation for recurrent high-grade gliomas. Modern high-precision radiotherapy (such as stereotactic segmentation radiotherapy) can be used as a palliative treatment option for cases with small recurrent lesions and high KPS scores. According to a retrospective study in patients with partial recurrence, re-radiation after application of bevacizumab could prolong post-relapse survival (PRS) and post-relapse progression-free survival (PR-PFS) [16]. Emerging radioimmunotherapy includes glioma-specific antibodies or ligands as carriers to transport, for example, I_{125} radionuclides getting into the interior of cells to better eliminate residual tumor cells. Clinical studies have shown that this method has a small dose (Radiation I_{125} small dose of radiation) of close-range exposure with higher patients' tolerance, which may become a new method of radiotherapy in the future [17].

Chemotherapy

There is a need for recurrent high-grade gliomas to reassess the amount of TMZ (temozolomide capsules) used and the course of administration. For patients with recurrent high-grade gliomas who have not undergone TMZ concurrent treatment with chemoradiotherapy during the first treatment, standardized TMZ concurrent with chemoradiotherapy and adjuvant chemotherapy regimens can be used. After failure of both radiotherapy and TMZ treatment, there is no well-recognized effective chemotherapy regimen but a recommendation for the TMZ dose density regimen. A meta-analysis with 15 phase II clinical studies included a total of 902 patients with recurrent glioblastoma multiforme (GBM). Five hundred patients of 7 studies were treated with standard regimens (150-200 mg/m^2 temozolomide capsules d1-5, q28), and 402 of the other 8 studies were treated with a dose-dose (Different drug dosing) regimen low TMZ dose density regimen: ≤100 mg/m^2; high dose density: >100mg/m^2). The analysis indicated that the TMZ dose density protocol could significantly improve patient survival compared to the TMZ standard treatment regimen [18]. A prospective, non-randomized, phase II clinical trial enrolled 90 patients with recurrent gliomas taking TMZ therapy: 1-7 days, 15-21 days, 150 mg/m^2 per day, one cycle every 28 days for a total of 12 cycles. The primary end point was 6-month DFS (DFS-6) in GBM patients and toxicity in the general population. The results claimed that the 6-month DFS rate was 44% with good tolerance, and the incidence of lymphopenia was low (12%), suggesting that this low-dose TMZ (d 1-7, d 15-21, q28 days) in patients with relapsed glioma is a feasible, safe and effective therapy [19].

Immunotherapy

Dendritic cells (DC) sensitized by various glioma antigens can induce tumor antigen-specific immune responses. Preparation of a vaccine by sensitizing DCs using a protein peptide derived from the surface of an autologous tumor cell or a tumor cell lysate can induce the production of tumor antigen-specific T cells. Currently, DCs are considered to be the most promising tumor vac-

cines. The individualized dendritic vaccine on the other hand makes DCs activate and direct the immune system to attack cancer cells, which present the antigen information to the immune system, allowing the immune cells to find the cancer cells and then to clear them. In a phase I clinical trial of DC-glioma fusion cell immunotherapy, interferon (IFN) secretion levels from peripheral blood lymphocyte increased and tumor volume decreased [20]. However, DC-mediated immunotherapy has certain drawbacks: in addition to the autoimmune response, the use of a single glioma antigen-related peptide vaccine treatment may not improve the prognosis of patients due to the heterogeneity of glioma cells.

A wide range of immune system defects in glioma patients include a decrease in the number and effect of T cells. Therefore, it is difficult to stimulate a strong and effective anti-tumor immune response. Adoptive immunotherapy is a viable option. Some immune effector cells including natural killer (NK) cells, lymphokine-activated killer cells (LAK cells), natural killer T cells (NKT cells), cytotoxic T lymphocytes (CTL cells), and tumor infiltrating lymphocytes (TILs) have been used in the treatment of glioma. However, the clinical application of LAK cells and NK cells does not produce the desired results considering their non-specificity, limited number, low killing activity or short effect time. In addition, as more tumor-associated antigens are segregated and identified, a large number of activated CD4+ and CD8+ T cells can be infused into glioma patients for treatment in an *in vitro* environment (experimental environment). It is believed that the therapeutic effects of the combined use of CD4+ cells, CD8+ cells and NK cells will be enhanced in the future. The most widely used high-grade glioma-specific immunotherapy is cytotoxic T lymphocytes (CTLs) or chimeric antigen receptor (CAR)-modified T cells (CAR-T therapy), which depends on the corresponding tumor-associated antigens (TAAs), and CD133 expressed on the surface of glioma stem cells is one of the most popular TAAs . In addition, some immunological adjuvants such as interleukin-2 (IL-2), interleukin-4 (IL4), interleukin-12 (IL-12), IFN, and granulocyte-macrophage colony stimulating factor (GM-CSF)) can activate cytotoxic T lymphocytes and NK cells, and enhance the expression of the major histocompatibility complex (MHC) antigen in tumor cells. Costimulatory molecules such as Th1 cytokines (IL-2, IL12, IFN) can provide a secondary signal for T cell activation to promote cell-mediated immune responses.

However, cytokines (CKs) present the following disadvantages in glioma immunotherapy: their toxic side effects and the difficulties of determining their dose. Therefore, how to combine multiple CKs and whether to give intracranial or intratumoral topical drugs are good ideas to perform further studies. Although glioma active immunization showed a good therapeutic effect in previous clinical studies, tumor heterogeneity, immune microenvironment, blood-brain barrier and other factors make glioma immunotherapy to face many challenges in practice [21].

Molecular targeted therapy

High vascularization is the essence of glioblastoma and bevacizumab is a monoclonal antibody against vascular endothelial growth factor. The VEGFR-targeted drug bevacizumab is currently a drug approved by the FDA for gliomas, which was based on the results of two independent studies conducted in the United States [22]. Bevacizumab monotherapy for patients with relapsed high-grade gliomas showed no improvement in median survival (4 to 15 months) compared with post-relapse chemotherapy. However, the patient's 6-month PFS (8 to 36%) was prolonged and the response rate was improved [22]. On the other hand, recent data from randomized trials of European Organization for Research and Treatment of Cancer (EORTC) trial has shown that semustine with administration of bevacizumab improves OS better than semustine alone. Whether it is administered alone or in combination with radiation therapy, its efficacy in recurrent glioma is significant. Studies have found that bevacizumab cannot prolong the PFS of patients with glioma, but it significantly improves the patient quality of life and the reduction of peritumoral edema in imaging, thus relieving symptoms [23]. Now, a clinical phase III trial of bevacizumab in combination with chemotherapeutic drugs, viral vectors, radiation therapy and immunological drugs is underway. In addition, vatalanib is a VEGF receptor inhibitor that blocks VEGF tyrosine kinase receptor activity and the VEGF signaling pathway. Goldbrunner et al. found that vatalanib has significantly inhibited the growth of VEGF-mediated C6 glioma cells by inhibiting angiogenesis and proliferation of tumor cells [24].

EGFR-based inhibitors such as afatinib, cetuximab, ABT-414, Sym004, PF-299804, Tesevatinib, are currently in phase II trials. Overexpression of EGFRvIII in glioblastoma without expression in normal brain tissue make it an ideal target for immunotherapy. Rindopepimut (an immunotherapeutic vaccine targeting the tumor-specific molecule EGFRvIII) showed clinical benefit and significant efficacy in phase II clinical trials [25]. However,

one of its Phase III clinical trials was terminated early due to failure to achieve the expected results [25]. The immunological efficacy of Rindopepimut in patients with glioblastoma may be achieved by a combination of drugs. In addition, the immunocrosslinker AMG595 is a cross-linking agent of anti-human EGFRv-III antibodies combined with cytotoxic factors, and it is currently in clinical phase I study. This monoclonal antibody binds to EGFRv-III on the surface of the tumor and then destroys the microtubule structure of the cell by cytotoxic factors, thereby inhibiting tumor cells' proliferation. Erlotinib is also a small molecule tyrosine kinase inhibitor, and the combination of this kind of tyrosine kinase inhibitor and a monoclonal antibody such as cetuximab may improve the preclinical antitumor activity. However, whether EGFR-targeted drugs can gain certain application effects in the treatment of recurrent high-grade glioma still requires a large number of experiments *in vitro* and *in vivo* and clinical trial observations.

IL-13Rα2 and IL-4R are ideal glioma ligand-mediated therapeutic targets. Some researchers have designed a cytotoxic drug targeting IL-13Rα2 on the surface of malignant glioma cells. This drug has good anti-glioma activity *in vivo* and *in vitro* [26]. In addition to the important researches in the above signal pathways, other valuable potential targets have gradually attracted attention. For example, BCL6 is a prognostic marker of glioblastoma and a promoter of tumor development. BCL6 gene silencing inhibits the growth of GBM cells, making it a potential therapeutic target for glioblastoma.

Molecular markers for glioma are diverse. With an increasing number of relevant researches, new relevant markers have been discovered. However, so far, no single molecule has been found to have a breakthrough activity in the treatment of glioma. It is often necessary to use a combination of multiple molecules, but this again plays a very limited role in prolonging the survival of glioma patients. In addition, different molecular targets and molecular variants of the same type of tumor or even different parts of the same tumor result in different sensitivities and specificities for molecular targeted therapy. Therefore, how to correctly apply molecular targeted therapy and evaluate its efficacy paves the way for future researches.

Oncolytic virus therapy

Oncolytic viruses usually refer to a type of viruses that selectively infect and kill tumor cells without causing harm to normal cells and tissues. Mutant strains of certain viruses lose pathogenicity due to the deletion of certain pathogenic genes, but retain the characteristics of specific oncolytic effects. Applying the oncolytic virus to treat glioma may have a certain development in the near future. The oncolytic virus can effectively infect and lyse the glioma stem cells after removing the ICP47 gene, and then the virus replicates in the target cells in a large amount, which causes the target cells to rupture and stimulate the immune response and finally to change the tumor microenvironment to cause cell death. In a phase I clinical trial in 2004 [27], 12 newly diagnosed and relapsed high-grade glioma patients were injected with a certain amount of HSV-1716 in the brain tissue surrounding the tumor after total surgical resection. The results showed no adverse reactions due to the injection of HSV-1716. Three patients survived 14 to 22 months after surgery, and one patient showed a reduction in tumor volume after 22 months. This study confirmed the safety and efficacy of HSV-1716 peritumoral injection [27].

Stem cell therapy

Aboody et al. believe that factors that may be released by tumor cells themselves or by tumor cell destruction tissues have the ability to attract neural stem cells (NSCs) [28]. In addition, they found in experiments that NSCs can stably express exogenous gene products *in vivo*, precisely because of their tendency and the stable expression of exogenous gene products, making it an ideal carrier for treatment [29]. Moreover, NSCs have the potential to differentiate into neurons and glia. The use of NSCs carrying exogenous genes for therapeutic purposes is expected to have the dual effect of cell transplantation and gene therapy. Stem cell vectors may target invasive tumor cells through their ability to migrate to tumors, providing a powerful adjunctive treatment model for the treatment of gliomas. However, there are still many problems, including biosafety, the selection of therapeutic transgenes, the optimal route of administration, and how to pick good cell carriers.

Electric field therapy

TTFields therapy is a new way to treat newly diagnosed or recurrent glioblastoma. It provides low-intensity, intermediate-frequency and alternating electric fields that produce selective antimitotic toxic effects against rapidly dividing tumor cells and it is harmless for healthy cells, while kills cancer cells. However, patients' survival and quality of life need further studies of TTFields therapy compared with systemic therapy. In 2011, the FDA

approved this method for the treatment of recurrent gliomas, which has been written into the NCCN guidelines. Recently, more than 10 countries in North America, Europe and Asia have begun to use TTFields therapy for the treatment of recurrent high-grade gliomas.

Conclusion and perspectives

Recurrent high-grade gliomas are a class of most challenging cancers. Traditional standard treatments such as reoperation, radiotherapy and chemotherapy have limited results. Many factors such as the invasive growth of tumors, the recurrence and the sites of recurrence and the complex biological characteristics influence the treatment effects. Any single way cannot achieve satisfactory results for recurrent high-grade gliomas. At present, surgery combined with radiotherapy and chemotherapy are still regarded as the first-choice option. Furthermore, some new adjuvant treatments should be combined organically to achieve prolongation of survival of patients and improvement of their quality of life. With the continuous development of research and the improvement of diagnostic and treatment technologies, we believe that a new model for the treatment of recurrent high-grade gliomas will bring hope to many patients.

Authors' contributions

Conception and design: Feng Wang and Xiao Qi Xie; collection and assembly of data: Lai Xiong; Manuscript writing: all authors. All authors approved the final version.

Conflict of interests

The authors declare no conflict of interests.

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