Review Article

A narrative review on the management of glioblastoma in China

Ming-Juan Zhao[1,2#], Taojunjing Lu[1#], Chao Ma[1], Ze-Fen Wang[3], Zhi-Qiang Li[1]

[1]Department of Neurosurgery, Zhongnan Hospital of Wuhan University, Wuhan, China; [2]Center for Evidence-Based and Translational Medicine, Zhongnan Hospital of Wuhan University, Wuhan, China; [3]Department of Physiology, Wuhan University School of Basic Medical Sciences, Wuhan, China

Contributions: (I) Conception and design: MJ Zhao, T Lu, ZQ Li; (II) Administrative support: None; (III) Provision of study materials or patients: None; (IV) Collection and assembly of data: MJ Zhao, T Lu, ZQ Li; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

[#]These authors contributed equally to this work.

Correspondence to: Zhi-Qiang Li. Department of Neurosurgery, Zhongnan Hospital of Wuhan University, Wuhan, China. Email: Lizhiqiang@whu.edu.cn.

Background and Objective: Glioma is the most common intracranial primary malignant tumor, and half of it is glioblastoma. Despite receiving the standard treatment, the prognosis of glioblastoma is still poor and its 5-year survival rate in China is only 9%. In addition, new targeted and immunotherapy therapy and tumor treating fields also have certain curative effects on glioblastoma. To help clinicians and patients make appropriate treatment based on current evidences, we summarize the Chinese guidelines on the management of glioma and review the recent management of glioblastoma.

Methods: We systematically searched PubMed, China National Knowledge Infrastructure (CNKI) and Wanfang databases to retrieve guidelines on glioma in China published from the establishment of the database to 24 January 2022. We performed a narrative review of current clinical study related to the management of glioblastoma, especially in the surgical, targeted and immunotherapy therapy and tumor treating fields.

Key Content and Findings: In this review, 19 guidelines were included, including 8 subclassified as the guideline, 8 subclassified as the consensus and 3 subclassified as the standard. Two guidelines reported the contents of the system search, 4 guidelines are updated, and 9 guidelines reported the source of funding. At present, most clinical trials on the immune and targeted therapy of glioblastoma are ongoing in China.

Conclusions: China's guidelines still need to be improved in terms of preciseness, applicability and editorial independence. In addition, the cooperation in clinical research of glioblastoma in multiple centers needs to be strengthened in China.

Keywords: Glioblastoma (GBM); management; China; guideline

Submitted Feb 23, 2022. Accepted for publication Aug 24, 2022.
doi: 10.21037/cco-22-18
View this article at: https://dx.doi.org/10.21037/cco-22-18

Introduction

Glioma is the most common intracranial primary malignant tumor, and half of it is glioblastoma (also named IDHwt-GBM). The incidence rate of GBM increases with age, with rates highest in patients aged 75 to 84 years (1). According to the report of Central Brain Tumor Registry of the United States (CBTRUS), GBM has the lowest 1-year survival rate (40.9%) and 5-year survival rate (6.6%) compared with other primary brain tumors (2). A single center retrospective study in China included 1,285 patients with glioma, of which 254 were GBM. The 1- and 5-year survival rates were 61% and 9% respectively, in line with what is observed in other countries (3). Standard of care management for GBM involves maximum safe surgical resection, radiation therapy, temozolomide (TMZ) chemotherapy, and consideration of alternating electrical fields. The degree

Table 1 The literature search strategy

Items	Specification
Date of search	24 Jan, 2022
Databases and other sources searched	PubMed, CNKI and Wan Fang databases
Search terms used	Search terms: "consensus" or "guideline" or "standard", and "glioma" or "glioblastoma" or "glial tumor", and "China"
	We have presented detailed search strategy of PubMed database in Table S1
Timeframe	From origin until 24 January, 2022
Inclusion and exclusion criteria	Clinical practice guideline or consensus study
	English or Chinese Language
	All guidelines focusing on diagnosis, treatment and or management of gliomas in China were included
	If guidelines were duplicated, we would select the one with most recent or complete guideline
	The abstract of guidelines and unpublished drafts of guidelines were excluded
Selection process	Two review authors independently collected the data and checked the relative standardized electronic form
	Any disagreements were settled by discussion or adjudication by other author
	Collected data items included the title, organization (institution or working group), publish time, and the topic of the target population of guidelines

CNKI, China National Knowledge Infrastructure.

of surgical resection is the most important factor affecting the effect of radiotherapy and chemotherapy and survival. Despite this prognosis remains poor, however, there are promising treatments actively under investigation (4-6).

Systematic guidance is very important to help clinicians make appropriate treatment decisions. Good clinical practice guidelines can improve the overall quality of diagnosis and treatment. In this review we have included Chinese guidelines on the management of glioma. In addition, we also summarized the current situation regarding the surgical, targeted and immunotherapy therapy and tumor treating fields (TTF) of GBM treatment in China, in order to help clinicians and patients make appropriate treatment based on current evidences. We present the following article in accordance with the Narrative Review reporting checklist (available at https://cco.amegroups.com/article/view/10.21037/cco-22-18/rc).

Guidelines for glioma management in China

Clinical practice guidelines play an important role in healthcare. Good clinical guidelines can improve the overall diagnosis and treatment level and limit unnecessary treatments and costs. Europe, America and other countries have successively formulated guidelines for glioma treatment (6,7). China has discussed the formulation of guidelines for glioma diagnosis and treatment since 2005 (8).

We systematically searched PubMed, China National Knowledge Infrastructure (CNKI) and Wanfang databases, with the terms "consensus" or "guideline" or "standard", and "glioma" or "glioblastoma" or "glial tumor", and "China". The retrieval time was from the establishment of the database to 24 January 2022. The detailed search strategy was reported in *Table 1*. Finally, 19 guidelines (8-26) were included, including 8 subclassified as the guideline (8,10,12-15,17,23), 8 subclassified as the consensus (9,11,16,18-20,22,26) and 3 subclassified as the standard (21,24,25). There is 1 guideline focused on low-grade glioma (15), 1 focused on brainstem glioma (16) and 2 focused on pediatric glioma (24,25). Two guidelines (10,14) reported the contents of the system search, 4 guidelines

Table 2 Characteristics of clinical practice guidelines for glioma

Title	Organization	Year	Topic	Evidence-related	Systematic search	Recommendation	Funding source	Update
Guidelines for diagnosis and treatment of single disease of gliomas (2005 discussion draft) (8)	Department of Neurosurgery, Affiliated Hospital of Sun Yat-sen University	2005	Gliomas	No	NR	NR	NR	NR
Chinese consensus for diagnosis and treatment in central nervous system malignant gliomas (simplified version) (9)	SNO-China	2009	Malignant gliomas	No	NR	Reported	NR	Updated in 2011
Chinese guidelines for diagnosis and treatment in central nervous system malignant gliomas (2012) (10)	CGGWC	2013	Gliomas	Yes	Reported	Reported	Society	NR
Expert consensus for the removal of functional brain during awake glioma surgery (11)	CGCG	2013	Gliomas	No	NR	Reported	NR	Updated in 2014
Guidelines for the removal of functional brain during awake glioma surgery (2014 version) (12)	CGCG	2014	Gliomas	Yes	NR	Reported	NR	Updated in 2018
Guidelines for molecular diagnosis and treatment of glioma in China (13)	CGCG	2014	Gliomas	No	NR	Reported	Government	NR
Guidelines for diagnosis and treatment of central nervous system glioma in China (2015) (14)	CGGWC	2016	Gliomas	Yes	Reported	Reported	Society	NR
Guidelines for surgical treatment of adult supratentorial low-grade gliomas (15)	CGCG	2016	Low-grade gliomas	Yes	NR	Reported	NR	NR
Expert consensus for the comprehensive management of brainstem glioma in China (16)	SNO-China, CGCWC	2017	Brainstem gliomas	No	NR	NR	Government	NR
Guidelines for the removal of functional brain during awake glioma surgery (2018 version) (17)	CGCG, GPCCMA	2018	Gliomas	Yes	NR	Reported	Government	NR
Expert consensus for the multidisciplinary diagnosis and treatment of glioma in China (18)	SNO-China	2018	Gliomas	No	NR	NR	Society	NR

Table 2 *(continued)*

Table 2 *(continued)*

Title	Organization	Year	Topic	Evidence-related	Systematic search	Recommendation	Funding source	Update
Expert consensus of China on radiation therapy for gliomas in 2017, (19)	China Society for Radiation Oncology	2018	Gliomas	Yes	NR	Reported	NR	NR
Expert consensus on immune and targeted therapy of central nervous system gliomas in China (20)	GPCCMA, Neuro-Oncology branch of Shanghai Anti-cancer Association	2018	Gliomas	Yes	NR	Reported	Government	Updated in 2020
Guidelines for diagnosis and treatment of glioma (2018 version) (21)	Bureau of Medical Administration of National Health Commission	2019	Gliomas	Yes	NR	Reported	NR	NR
Expert consensus on immune and targeted therapy of central nervous system gliomas in China (second edition) (22)	GPCCMA, Neuro-Oncology branch of Shanghai Anti-cancer Association	2020	Gliomas	Yes	NR	Reported	Government	NR
Clinical practice guidelines for the management of adult diffuse gliomas (23)	CGCG, SNO-China, CBCA, CGGA, AGGA	2021	Adult diffuse gliomas	Yes	NR	Reported	Government	NR
Guidelines for the management of pediatric brain gliomas in China (2021 version) (24)	National Health Commission of the People's Republic of China	2021	Pediatric gliomas	No	NR	NR	NR	NR
Guidelines for the management of pediatric ependymoma in China (2021 version) (25)	National Health Commission of the People's Republic of China	2021	Ependymoma	No	NR	NR	NR	NR
Expert consensus on tumor electric field therapy for glioblastoma in China (26)	Glioma Professional Committee of China Anti-Cancer Association, CGCWC	2021	Glioblastoma	No	NR	Reported	NR	NR

NR, not reported; SNO-China: Society for Neuro-Oncology of China; CGGWC, Chinese Glioma Guideline Working Committee; CGCG, Chinese Glioma Cooperative Group; CGCWC, Chinese Glioma Consensus Working Committee; GPCCMA, Glioma Professional Committee of Chinese Medical Association; CBCA, Chinese Brain Cancer Association; CGGA, Chinese Glioma Genome Atlas; AGGA, Asian Glioma Genome Atlas.

(9,11,12,20) are updated, and 9 guidelines (10,13,14,16-18,20,22,23) reported the source of funding (*Table 2*). Up to now, the year with the largest number of published guidelines is 2018, with a total of 4 guidelines (17-20) published (*Figure 1*). Overall, China's guidelines and expert consensus still need to be improved in terms of preciseness, applicability and editorial independence.

Surgical resection

Surgical treatment is the first choice for patients with GBM. On the premise of fully protecting the patient's brain function, the tumor tissue can be removed to the greatest extent (27,28). Several assistive technologies, including intraoperative magnetic resonance imaging (MRI) scanning,

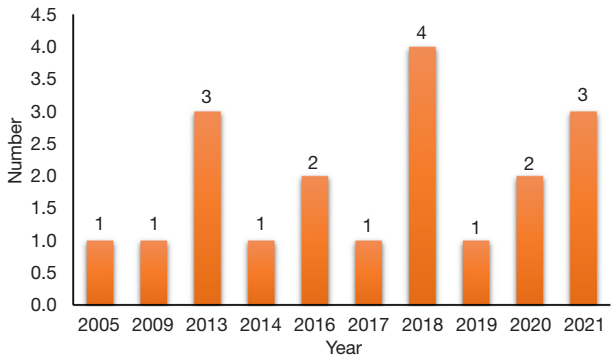

Figure 1 Number of glioma management guidelines published annually in China.

intraoperative ultrasound, fluorescence contrast and neuro-navigation, can be used to observe and confirm whether there is residual tumor (7,29).

Neuro-navigation integrates the structural and functional image information obtained before operation into neuro-navigation, registers reference points and reference frames, and determines important anatomical structures, so as to shorten the time of intraoperative functional positioning. Neuro-navigation device have been equipped by many large academic hospitals in urban centers, for example Beijing, Shanghai, Guangzhou, Wuhan, and so on.

At present, the main problem of intraoperative neuro-navigation is brain displacement, but intraoperative MRI can correct brain displacement and update navigation in real time, which is helpful to improve the resection degree of glioma (30). In addition, intraoperative ultrasound can guide the operator to judge the lesion location and resection degree in real time through the bone window, which is easy to popularize, but its image is easy to be affected by section, air, edema, etc. (31). Because of the high price and high requirements for surgical instruments, only a few academic hospitals have equipped the intraoperative MRI, such as Beijing Tiantan Hospital, Huashan Hospital in Shanghai and so on.

The surgical technique of resection of gliomas in brain functional areas in wake-up state is regarded as an important technique to safely remove gliomas in brain functional areas to the greatest extent. At present, it is still a hot and difficult issue in the field of surgery. In 2013, China first published the expert consensus on the surgical technology of removing gliomas in brain functional areas in wake-up state (11). Based on the release of new research results, the Chinese brain glioma group updated the guidelines in 2014 (12) and 2018 (17) respectively to further improve the standardization and standards of surgery. At present, the key to resection of gliomas in brain functional areas under wake-up anesthesia lies in the detection and protection of important functional structures. Although Chinese hospitals carried out wake-up surgery in the 1990s, considering the technical requirements of anesthesiologists, the cooperation of patients and the extension of operation time, this technology has not been well promoted at present. Only few neurosurgeons in the academic hospitals, such as Beijing Tiantan Hospital, Huashan Hospital in Shanghai, Zhongnan Hospital of Wuhan university, and so on, regularly performed the wake-up craniotomy for patients with GBM located in brain functional areas.

Although China's guidelines recommend image technology to assist surgical treatment, it is difficult to completely remove the real tumor boundary due to the diffuse, invasive and special location of GBM. Further research is still needed to overcome this problem.

Targeted therapy and immunotherapy

The standard treatment of GBM includes maximum surgical resection, postoperative radiotherapy and TMZ chemotherapy, but these may have immunosuppressive effect. Coupled with the immune particularity of the central nervous system, GBM is a disease that is difficult to be treated by immune pathway. However, the new study found that the central nervous system has an appropriate immune response and is connected with the peripheral immune system (32). At the same time, GBM growth can destroy the blood-brain barrier and facilitate the entry and exit of lymphocytes into and out of brain tissue (33). These provide a theoretical basis for immunotherapy of GBM. In recent years, targeted therapy represented by bevacizumab (BEV) has been widely used in clinical treatment. New targeted therapy medicine for GBM, such as a MET kinase inhibitor PLB-1001, also demonstrated remarkable potency in selectively inhibiting MET-altered tumor cells in preclinical models in China (34). At present, a variety of GBM immunotherapy methods have entered the stage of clinical trials, mainly including immune checkpoint inhibitors, chimeric antigen receptor T (CAR-T) cells and vaccines.

Bevacizumab

BEV is a human clonal antibody that blocks tumor angiogenesis by inhibiting vascular endothelial growth

factor. It can prevent epithelial growth factor receptor (EGFR) from binding to its receptor and reduce tumor cardiovascular formation, so as to inhibit tumor growth. The US Food and Drug Administration (FDA) first approved BEV for the treatment of recurrent GBM in 2009 (35). A systematic review included 5 randomized controlled trials (RCTs) with 834 patients provided clear proof of the beneficial effects of BEV treatment in recurrent GBM patients (36). However, two phase III randomized controlled trial of BEV combined with standard first-line radiotherapy and chemotherapy in the treatment of newly diagnosed GBM showed that BEV could not prolong the overall survival (OS), only could improve the progression free survival (PFS) (37-39). The study of BEV combined with TMZ in the treatment of recurrent GBM in China showed that the effect is better in the short term, but there was no significant difference in the long-term curative effect between China and foreign countries (40). Based on the current evidence, China's guidelines (22) reported that BEV was not recommended in combination with standard treatment for newly GBM patients, except for the guidance of clear molecular markers and other test results. BEV was recommended for patients with recurrent GBM. In addition, clinical trials on BEV are combination therapy in China. For recurrent GBM, BEV combined with hypofractionated re-radiation, Camrelizumab, ASC40 tablets, Irinotecan plus re-radiotherapy, and Nimustine (ChiCTR2000035881, NCT04952571, NCT05201326, NCT05118776, NCT02698280). Most trials are in the recruitment stage. One ongoing clinical trial to explore the potential image biomarkers in newly GBM with BEV (NCT01939574) (*Table 3*)

CAR-T cell therapy

CAR-T cell therapy, namely chimeric antigen receptor T cell therapy. By using the patient's own T lymphocytes, they are remodeled in the laboratory, loaded with receptors and costimulatory molecules that recognize tumor antigens, amplified *in vitro* and then reinfused into the patient's body, so as to identify and attack their own tumor cells. CAR-T therapy solves the problem of tumor heterogeneity. The transformed T cells can target tumor cells, but the toxic reactions of treatment need to be closely monitored and treated. The common targets of CAR-T therapy in GBM are EGFR variant type III (EGFRvIII), human epithelial growth factor receptor 2 (HER2) and interleukin 13 receptor alpha 2 (IL-13R α 2), etc. (41). In addition, there are some promising antigens characterized by high expression of GBM, such as B7-H3 and CSPG4 (42,43). The first CAR-T clinical trial directed to EGFRvIII in 10 recurrent GBM patients showed that the median OS time was 8 months, and the clinical benefit was not significant (44). Another CAR-T clinical trial with HER2 as the target indicated that the median OS after the first infusion of T-cell and diagnosis in 17 patients with progressive GBM were 11.1 and 24.5 months respectively, and 8 patients had clinical benefits (45). Besides, there are also some encouraging results in the research of CAR-T in the treatment of GBM, but further research is needed to achieve stable clinical benefits (46,47). Treatment of GBM with CAR-T is plagued by the lack of ideal tumor antigens as targets and serious side effects. There are six ongoing clinical trials of CAR-T therapy for recurrent GBM in China (NCT04385173, NCT02844062, NCT04045847, NCT04077866, NCT05241392, NCT02937844), of which 3 trials were treated with anti-B7-H3 CAR-T and 1 was treated with CD147 CAR-T (*Table 3*).

Dendritic cells (DC) vaccine

DC are derived from bone marrow hematopoietic progenitor cells or monocytes. They are the most powerful antigen-presenting cells known at present. They can activate the body's specific immunity by efficiently ingesting, processing and presenting antigens to T and B lymphocytes. DC vaccine is to use DC to present antigen and activate immunity. DC that can specifically recognize tumors induced or constructed *in vitro*, can be imported back into tumor patients to activate the immune response of T cells to tumors. A multicenter phase III clinical trial showed that the addition of an autologous tumor lysate-pulsed dendritic cell vaccine (DCVax®-L) to standard treatment may improve the median survival of GBM (48). One phase II clinical trial in China reported that DC vaccine may significantly prolong the OS of GBM patients. GBM patients with IDH1 wild-type, TERT mutation and low expression of B7-H4 are more sensitive to specific active immunotherapy activated by Glioblastoma stem-like cell antigens-primed DC vaccines (GSC-DCV) (49). Based on the current research, China's latest guidelines recommend that DC vaccine can be used in the relevant clinical trials of recurrent GBM. In recent years, the "personalized DC vaccine" was proposed according to tumor heterogeneity, which can provide more accurate treatment for different tumor patients. At present, there are two ongoing clinical trials (NCT02709616, NCT02808364) on personalized

Table 3 Summary of clinical trials on the management of GBM in China

Title	NCT number	Study type	Institution	Date of registration	Trial phase	Patients (N)	Treatment		Primary outcomes
							Experimental group	Control group	
Bevacizumab									
Efficacy and safety of hypofractionated re-radiation therapy plus bevacizumab versus bevacizumab alone in the treatment of recurrent glioblastoma: a prospective, single-center, phase II, parallel, randomized, controlled trial	ChiCTR2000035881	RCT	Fudan University Huashan Hospital	Aug-2020	Phase 2	Recurrent GBM (N=86)	Bevacizumab + HFRT	Bevacizumab	PFS
An exploratory study on camrelizumab combined with bevacizumab for adult patients with recurrent GBM	NCT04952571	Interventional study	Beijing Sanbo Brain Hospital	Jul-2021	Phase 2	Recurrent GBM (N=94)	Bevacizumab + Camrelizumab	Bevacizumab	PFS at 6 months
A phase III randomized, double-blind, placebo-controlled, multi-center trial to evaluate safety and efficacy pf ASC40 tablets combined with bevacizumab in subjects with recurrent glioblastoma	NCT05118776	RCT	Beijing Tiantan Hospital, Capital Medical University	Nov-2021	Phase 3	Recurrent GBM (N=180)	Bevacizumab + ASC40 tablets	Bevacizumab + placebo	PFS and OS
An open-label, single arm study to explore whether potential image biomarkers correlate with efficacy of bevacizumab combined with conventional therapy in newly diagnosed glioblastoma	NCT01939574	Single arm study	Shandong Cancer Hospital and Institute	Aug-2013	NA	Newly diagnosed GBM (N=20)	Bevacizumab + standard treatment		PFS and image biomarker change
Phase II study of bevacizumab and Nimustine in patients with recurrent high-grade glioma	NCT02698280	Single arm study	Huashan Hospital, Fudan University	Mar-2016	Phase 2 (completed)	Recurrent GBM (N=23)	Bevacizumab + Nimustine		All cause response within 3 weeks
An open and single-arm prospective clinical study of the safety and efficacy of irinotecan and bevacizumab combined with re-radiotherapy in the treatment of recurrent glioblastoma	NCT05201326	Single arm Study	Ruijin Hospital, Shanghai Jiao Tong University School of Medicine	Jan-2022	Phase 1	Recurrent GBM (N=20)	Bevacizumab + Irinotecan + re-radiotherapy		SAE at 28 days

Table 3 *(continued)*

Table 3 *(continued)*

Title	NCT number	Study type	Institution	Date of registration	Trial phase	Patients (N)	Treatment		Primary outcomes
							Experimental group	Control group	
CAR-T									
B7-H3-targeted CAR-T cells in treating patients with recurrent or refractory glioblastoma	NCT04077866	RCT	Second Affiliated Hospital, School of Medicine, Zhejiang University	Sep-2019	Phase 2	Recurrent and refractory GBM (N=40)	Anti-B7-H3 CAR-T + TMZ	TMZ	OS
A safety and efficacy study of autologous chimeric antigen receptor engineered T cells redirected to EGFRvIII in patients with recurrent glioblastoma multiforme	NCT02844062	Single arm study	Beijing Sanbo Brain Hospital	Jul-2016	Phase 1	Recurrent GBM (N=20)	Anti-EGFRvIII CAR-T + Cyclophosphamide + Fludarabine		IAE
A safety and efficacy study of autologous chimeric switch receptor engineered T cells redirected to PD-L1 in patients with recurrent glioblastoma multiforme	NCT02937844	Single arm study	Sanbo Brain Hospital, Capital Medical University	Oct-2016	Phase 1	Recurrent GBM (N=20)	Anti-PD-L1 CSR-T + Cyclophosphamide + Fludarabine		NAE
A clinical study to investigate the safety, tolerance and efficacy evaluation of single-centre, open-label of local treatment of CD147-CAR-T in recurrent glioblastoma	NCT04045847	Single arm study	National Translational Science Center for Molecular Medicine & Department of Cell Biology	Aug-2019	Early Phase 1	Recurrent GBM (N=31)	CD147-CAR-T		Incidence and type of AE
A pilot study of CAR-T cells targeting B7-H3 antigen in treating patients with recurrent and refractory glioblastoma	NCT04385173	Single arm study	Second Affiliated Hospital, School of Medicine, Zhejiang University	May-2020	Phase 1	Recurrent and refractory GBM (N=12)	Anti-B7-H3 CAR-T + TMZ		AE; MTD; OS and PFS
An open, single-arm, phase 1 study to evaluate the safety/preliminary effectiveness and determine the maximal tolerated dose of B7-H3-targeting CAR-T cell therapy in treating recurrent glioblastomas	NCT05241392	Single arm study	Beijing Tiantan Hospital	Feb-2022	Phase 1	Recurrent GBM (N=30)	Anti-B7-H3 CAR-T		DLT; Incidence and severity of AE

Table 3 *(continued)*

Table 3 *(continued)*

Title	NCT number	Study type	Institution	Date of registration	Trial phase	Patients (N)	Treatment		Primary outcomes
							Experimental group	Control group	
DC vaccine									
A triple-blind randomized clinical study of vaccination with dendritic cells loaded with glioma stem-like cells associated antigens against brain glioblastoma multiform	NCT01567202	RCT	Huashan Hospital, Fudan University	Mar-2012	Phase 2	GBM (N=100)	DC vaccination + standard treatment	Blank placebo + standard treatment	ORR
Clinical study of a dendritic cell vaccine combined with immune checkpoint inhibitors for treatment of glioblastoma	ChiCTR1900025835	Observational study	Chinese People's Liberation Army General Hospital	Sep-2019	Phase 0	GBM (N=30)	DC vaccine + standard treatment DC vaccine + standard treatment + immune checkpoint blocker	Standard treatment	MRI results; PFS; OS; Quality of life score
Neoadjuvant PD-1 antibody alone or combined with autologous glioblastoma stem-like cell antigens-primed DC vaccines (GSC-DCV) for patients with recurrent glioblastoma: A phase II, randomized controlled, double blind clinical trial	NCT04888611	RCT	Huashan Hospital, Fudan University	May-2021	Phase 2	Recurrent GBM (N=40)	DC vaccine + Camrelizumab	Placebo + Camrelizumab	OS and PFS
Personalized cellular vaccine therapy in treating patients with newly diagnosed glioblastoma (PerCellVac)	NCT02709616	Single arm study	Guangdong 999 Brain Hospital	Mar-2016	Phase 1	Newly diagnosed GBM (N=10)	Personalized DC-based vaccine + standard treatment		Incidence of AE and SAE
Personalized cellular vaccine therapy in treating patients with recurrent glioblastoma (PerCellVac2)	NCT02808364	Single arm study	Guangdong 999 Brain Hospital	Jun-2016	Phase 1	Recurrent GBM (N=10)	Autologous DC		Incidence of AE and SAE
Clinical study of a dendritic and glioma cells fusion vaccine with IL-12 for treatment-naïve GBM patients	NCT04388033	Single arm study	Second Affiliated Hospital, School of Medicine, Zhejiang University	May-2020	Phase 2	Treatment-naïve GBM (N=10)	DC vaccine + IL-12 + standard treatment		AE; SAE; PFS at 6 months
Phase I clinical study of safety & efficacy of DC vaccine and TMZ for the treatment of newly-diagnosed glioblastoma after surgery	NCT04968366	Single arm study	Beijing Tiantan Hospital	Jul-2021	Phase 1	Newly diagnosed GBM (N=10)	DC vaccine + TMZ		IAE

Table 3 *(continued)*

Table 3 *(continued)*

Title	NCT number	Study type	Institution	Date of registration	Trial phase	Patients (N)	Treatment		Primary outcomes
							Experimental group	Control group	
TTF									
To evaluate the safety and efficacy of wearable glioma electric field therapy combined with temozolomide in the treatment of recurrent GBM: a randomized, controlled, open-label, multicenter trial	ChiCTR2000034285	RCT	Beijing Tiantan Hospital, Capital Medical University	Jun-2020	Phase 0	Recurrent GBM (N=300)	TTF + TMZ	TMZ	OS
Prospective, multicenter, open, randomized, parallel controlled trial for tumor treating fields (EFE-G100) combined with temozolomide versus temozolomide alone in patients with newly diagnosed glioblastoma	ChiCTR2000034706	RCT	Huashan Hospital Affiliated to Fudan University	Jul-2020	NA	Newly diagnosed GBM (N=330)	TTF + TMZ	TMZ	PFS
The clinical effect and safety of radiotherapy Concurrent of TTF in the treatment of post-operation patients with glioblastoma	NCT04902586	RCT	Zhongnan Hospital, Wuhan	May-2021	NA	GBM (N=30)	TTF + radiotherapy + TMZ	Radiotherapy +TMZ	Disease-free survival time
Evaluate the efficacy and safety of tumor electric field therapy system in the treatment of newly diagnosed supratentorial glioblastoma	ChiCTR2100047049	Interventional study	Beijing Tiantan Hospital, Capital Medical University	Jun-2021	NA	Newly diagnosed supratentorial GBM (N=411)	TTF + TMZ	TMZ	PFS
A prospective, single-center, single-arm, exploratory study on the treatment of recurrent glioblastoma with Tumor Electric Fields Treatment System	ChiCTR2000032655	Single arm study	Xiangya Hospital Central South University	May-2020	Phase 0	Recurrent GBM (N=5)	TTF		Frequency of AE and SAE
A prospective, single-center, single-arm, exploratory study on the treatment of recurrent glioblastoma with Tumor Electric Fields Treatment System	NCT04417933	Single arm study	Xiangya Hospital of Central South University	Jun-2020	Early Phase 1	Recurrent GBM (N=5)	TTF		AE; time to Progression; OS at 12 months
A prospective, open-label, single-arm clinical Study evaluating TTF in combination with chemotherapy for recurrent glioblastoma	NCT04689087	Single arm study	Sun Yat-sen University Cancer Center	Dec-2020	NA	Recurrent GBM (N=40)	TTF + second-line chemotherapy		OS at 6 months
A single-arm, open, single-center exploratory clinical study of the safety and efficacy of concurrent postoperative radiotherapy and adjuvant temozolomide combined with tumor treating fields/ apatinib in patients newly diagnosed with glioblastoma	ChiCTR2100041969	Single arm study	West China Hospital	Jan-2021	Phase 2	Newly diagnosed GBM (N=30)	TTF		PFS at 12 months

Standard treatment: including surgery, TMZ-chemotherapy and radiotherapy. AE, adverse events; CAR-T, chimeric antigen receptor T; CSR-T, chimeric switch receptor T; DC, dendritic cells; DLT, incidence of dose limiting toxicity; EGFRvIII, epithelial growth factor receptor variant type III; GBM, glioblastoma; HFRT, hypofractionated re-radiation therapy; IAE, incident of adverse events; IL-12, interleukin 12; MRI, magnetic resonance imaging; MTD, maximum tolerated dose; NA, not applicable; NAE, number of adverse events; NCT, National Clinical Trial; ORR, objective response rate; OS, overall survival; PD-L1, programmed cell death 1 ligand 1; PFS, progression-free survival; RCT, randomized controlled trial; SAE, serious adverse events; TMZ, temozolomide; TTF, tumor treating fields.

DC vaccine for the treatment of newly GBM and recurrent GBM in China, and five studies on DC vaccine combined with TMZ, programmed cell death 1 (PD-1) and interleukin 12 (IL-12) for the treatment of GBM (ChiCTR1900025835, NCT01567202, NCT04968366, NCT04888611, NCT04388033) (*Table 3*).

Tumor treating fields

TTF is a new type of physical therapy. It interferes with the mitosis of tumor cells by acting on the tubulin of proliferating cancer cells, causes the apoptosis of affected cancer cells and inhibits tumor growth. The Food and Drug Administration approved TTF product Optune® to treat adult patients with recurrent and newly diagnosed GBM in 2011 and 2015 respectively, based on the positive clinical trial results (4,50,51). In 2015, TTF technology was incorporated into the guidelines for the diagnosis and treatment of glioma of the nervous system in China (14). In 2018, the National Health Commission of China published the standard for the diagnosis and treatment of glioma (2018 version) (21), and TTF was recommended for the treatment of new GBM (level I evidence) and recurrent high-grade glioma (Level II evidence). In May 2020, China's Drug Administration approved the combination of TTF and TMZ for the treatment of newly diagnosed GBM patients and as a monotherapy for recurrent GBM patients. In 2021, experts such as the glioma Professional Committee of China Anti-Cancer Association prepared an expert consensus on electric field treatment of GBM, and made a detailed report on the action mechanism, influencing factors, clinical evaluation, use scheme and patient management of TTF in the treatment of GBM (26). However, the application research of TTF in China is limited. At present, clinical trials are promoting the combination of TTF with radiotherapy and chemotherapy, targeted therapy, immunotherapy and so on. In addition, six ongoing clinical trials in China are trying to determine the safety and efficacy of TTF combined with radiotherapy and chemotherapy (ChiCTR2100047049, ChiCTR2100041969, ChiCTR2000034706, ChiCTR2000034285, NCT04689087, NCT04902586). Two ongoing clinical trials in China explore the recurrent GBM with TTF treatment system (ChiCTR2000032655, NCT04417933) (*Table 3*).

Conclusions

In summary, glioma guidelines in China are increasing year by year, and the quality of guidelines is also gradually improving, but the preciseness, applicability and independence of guidelines still need to be further improved. At present, emerging immune and targeted therapy are under research in China. However, the cooperation in clinical research of GBM in multiple centers needs to be strengthened in China.

Acknowledgments

We express our gratitude to Xian-Tao Zeng from Zhongnan Hospital of Wuhan University for his support and help in database system search.
Funding: None.

Footnote

Reporting Checklist: The authors have completed the Narrative Review reporting checklist. Available at https://cco.amegroups.com/article/view/10.21037/cco-22-18/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (https://cco.amegroups.com/article/view/10.21037/cco-22-18/coif).The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. Miller KD, Ostrom QT, Kruchko C, et al. Brain and other central nervous system tumor statistics, 2021. CA Cancer J Clin 2021;71:381-406.
2. Ostrom QT, Cioffi G, Waite K, et al. CBTRUS Statistical Report: Primary Brain and Other Central Nervous System

Tumors Diagnosed in the United States in 2014-2018. Neuro Oncol 2021;23:iii1-iii105.
3. Yang P, Wang Y, Peng X, et al. Management and survival rates in patients with glioma in China (2004-2010): a retrospective study from a single-institution. J Neurooncol 2013;113:259-66.
4. Stupp R, Taillibert S, Kanner A, et al. Effect of Tumor-Treating Fields Plus Maintenance Temozolomide vs Maintenance Temozolomide Alone on Survival in Patients With Glioblastoma: A Randomized Clinical Trial. JAMA 2017;318:2306-16.
5. Lukas RV, Wainwright DA, Ladomersky E, et al. Newly Diagnosed Glioblastoma: A Review on Clinical Management. Oncology (Williston Park) 2019;33:91-100.
6. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) Central Nervous System Cancers, version 2. 2021-November 29, 2021. Available online: https://www.nccn.org/professionals/physician_gls/pdf/cns-poland.pdf
7. Weller M, van den Bent M, Preusser M, et al. EANO guidelines on the diagnosis and treatment of diffuse gliomas of adulthood. Nat Rev Clin Oncol 2021;18:170-86.
8. Chen ZP, Zhou WN. Guidelines for diagnosis and treatment of single disease of gliomas (2005 discussion draft). Proceedings of the 4th annual meeting of Neuro Oncology Committee of Guangzhou Anti-cancer Association; 2005 July 8; Guangdong: Sun Yat sen University; 2005:9-18.
9. Society for Neuro-Oncology of China. Chinese consensus for diagnosis and treatment in central nervous system malignant gliomas (simplified version). National Medical Journal of China 2009;89:3028-30.
10. Chinese Glioma Guideline Working Committee, Zhou L, Wang R. Chinese guidelines for diagnosis and treatment in central nervous system malignant gliomas (2012). National Medical Journal of China 2013;93:2418-49.
11. Chinese Glioma Cooperative Group, Wang W, Bai H, et al. Expert consensus for the removal of functional brain during awake glioma surgery. Chinese Journal of Minimally Invasive Neurosurgery 2013;18:143-9.
12. Chinese Glioma Cooperative Group. Guidelines for the removal of functional brain during awake glioma surgery (2014 version). Chinese Journal of Minimally Invasive Neurosurgery 2014;19:479-85.
13. Chinese Glioma Cooperative Group. Guidelines for molecular diagnosis and treatment of glioma in China. Chinese Journal of Neurosurgery 2014;30:435-44.
14. Chinese Glioma Guideline Working Committee. Guidelines for diagnosis and treatment of central nervous system glioma in China (2015). National Medical Journal of China 2016;96:485-509.
15. Chinese Glioma Cooperative Group. Guidelines for surgical treatment of adult supratentorial low-grade gliomas. Chinese Journal of Neurosurgery 2016;32:652-8.
16. Society for Neuro-Oncology of China. Expert consensus for the comprehensive management of brainstem glioma in China. National Medical Journal of China 2017;97:964-75.
17. Chinese Glioma Cooperative Group. Expert consensus for the removal of functional brain during awake glioma surgery (2018 version). Chinese Journal of Minimally Invasive Neurosurgery 2018;23:383-8.
18. Society for Neuro-Oncology of China. Expert consensus for the multidisciplinary diagnosis and treatment of glioma in China. Chinese Journal of Neurosurgery 2018;34:113-8.
19. China Society for Radiation Oncology. Expert consensus of China on radiation therapy for gliomas in 2017. Chinese Journal of Radiation Oncology 2018;27:123-31.
20. Glioma Professional Committee of Chinese Medical Association. Expert consensus on immune and targeted therapy of central nervous system gliomas in China. National Medical Journal of China 2018;98:324-31.
21. Bureau of Medical Administration of National Health Commission. Guidelines for diagnosis and treatment of glioma (2018 version). Chinese Journal of Neurosurgery 2019;35:217-39.
22. Glioma Professional Committee of Chinese Medical Association. Expert consensus on immune and targeted therapy of central nervous system gliomas in China (Second Edition). National Medical Journal of China 2020;100:3388-96.
23. Jiang T, Nam DH, Ram Z, et al. Clinical practice guidelines for the management of adult diffuse gliomas. Cancer Lett 2021;499:60-72.
24. National Health Commission of the People's Republic of China. Guidelines for the management of pediatric brain gliomas in China (2021 version). Journal of Multidisciplinary Cancer Management (Electronic Version) 2021;7:22-31.
25. National Health Commission of the People's Republic of China. Guidelines for the management of pediatric ependymoma in China (2021 version). Clinical Education of General Practice 2021;19:773-6.
26. Glioma Professional Committee of China Anti-Cancer Association. Expert consensus on tumor electric field therapy for glioblastoma in China. Chinese Journal of

Neurosurgery 2021;37:1081-9.
27. Sanai N, Berger MS. Glioma extent of resection and its impact on patient outcome. Neurosurgery 2008;62:753-64; discussion 264-6.
28. Sanai N, Berger MS. Operative techniques for gliomas and the value of extent of resection. Neurotherapeutics 2009;6:478-86.
29. Stummer W, Pichlmeier U, Meinel T, et al. Fluorescence-guided surgery with 5-aminolevulinic acid for resection of malignant glioma: a randomised controlled multicentre phase III trial. Lancet Oncol 2006;7:392-401.
30. Senft C, Bink A, Franz K, et al. Intraoperative MRI guidance and extent of resection in glioma surgery: a randomised, controlled trial. Lancet Oncol 2011;12:997-1003.
31. Bai HM, Wang WM, Li TD, et al. Three core techniques in surgery of neuroepithelial tumors in eloquent areas: awake anaesthesia, intraoperative direct electrical stimulation and ultrasonography. Chin Med J (Engl) 2011;124:3035-41.
32. Keskin DB, Anandappa AJ, Sun J, et al. Neoantigen vaccine generates intratumoral T cell responses in phase Ib glioblastoma trial. Nature 2019;565:234-9.
33. Hilf N, Kuttruff-Coqui S, Frenzel K, et al. Actively personalized vaccination trial for newly diagnosed glioblastoma. Nature 2019;565:240-5.
34. Hu H, Mu Q, Bao Z, et al. Mutational Landscape of Secondary Glioblastoma Guides MET-Targeted Trial in Brain Tumor. Cell 2018;175:1665-1678.e18.
35. Moen MD. Bevacizumab: in previously treated glioblastoma. Drugs 2010;70:181-9.
36. Zhang T, Xin Q, Kang JM. Bevacizumab for recurrent glioblastoma: a systematic review and meta-analysis. Eur Rev Med Pharmacol Sci 2021;25:6480-91.
37. Gilbert MR, Dignam JJ, Armstrong TS, et al. A randomized trial of bevacizumab for newly diagnosed glioblastoma. N Engl J Med 2014;370:699-708.
38. Chinot OL, de La Motte Rouge T, Moore N, et al. AVAglio: Phase 3 trial of bevacizumab plus temozolomide and radiotherapy in newly diagnosed glioblastoma multiforme. Adv Ther 2011;28:334-40.
39. Weller M, Yung WK. Angiogenesis inhibition for glioblastoma at the edge: beyond AVAGlio and RTOG 0825. Neuro Oncol 2013;15:971.
40. Lu Y, Qi S, Ouyang H, et al. Preliminary clinical evaluations of bevacizumab for recurrent malignant glioma in Chinese patients. Zhonghua Yi Xue Za Zhi 2014;94:1165-8.
41. McGranahan T, Therkelsen KE, Ahmad S, et al. Current State of Immunotherapy for Treatment of Glioblastoma. Curr Treat Options Oncol 2019;20:24.
42. Nehama D, Di Ianni N, Musio S, et al. B7-H3-redirected chimeric antigen receptor T cells target glioblastoma and neurospheres. EBioMedicine 2019;47:33-43.
43. Pellegatta S, Savoldo B, Di Ianni N, et al. Constitutive and TNFα-inducible expression of chondroitin sulfate proteoglycan 4 in glioblastoma and neurospheres: Implications for CAR-T cell therapy. Sci Transl Med 2018;10:eaao2731.
44. O'Rourke DM, Nasrallah MP, Desai A, et al. A single dose of peripherally infused EGFRvIII-directed CAR T cells mediates antigen loss and induces adaptive resistance in patients with recurrent glioblastoma. Sci Transl Med 2017;9:eaaa0984.
45. Ahmed N, Brawley V, Hegde M, et al. HER2-Specific Chimeric Antigen Receptor-Modified Virus-Specific T Cells for Progressive Glioblastoma: A Phase 1 Dose-Escalation Trial. JAMA Oncol 2017;3:1094-101.
46. Brown CE, Alizadeh D, Starr R, et al. Regression of Glioblastoma after Chimeric Antigen Receptor T-Cell Therapy. N Engl J Med 2016;375:2561-9.
47. Choe JH, Watchmaker PB, Simic MS, et al. SynNotch-CAR T cells overcome challenges of specificity, heterogeneity, and persistence in treating glioblastoma. Sci Transl Med 2021;13:eabe7378.
48. Liau LM, Ashkan K, Tran DD, et al. First results on survival from a large Phase 3 clinical trial of an autologous dendritic cell vaccine in newly diagnosed glioblastoma. J Transl Med 2018;16:142.
49. Yao Y, Luo F, Tang C, et al. Molecular subgroups and B7-H4 expression levels predict responses to dendritic cell vaccines in glioblastoma: an exploratory randomized phase II clinical trial. Cancer Immunol Immunother 2018;67:1777-88.
50. Stupp R, Wong ET, Kanner AA, et al. NovoTTF-100A versus physician's choice chemotherapy in recurrent glioblastoma: a randomised phase III trial of a novel treatment modality. Eur J Cancer 2012;48:2192-202.
51. Stupp R, Taillibert S, Kanner AA, et al. Maintenance Therapy With Tumor-Treating Fields Plus Temozolomide vs Temozolomide Alone for Glioblastoma: A Randomized Clinical Trial. JAMA 2015;314:2535-43.

Cite this article as: Zhao MJ, Lu T, Ma C, Wang ZF, Li ZQ. A narrative review on the management of glioblastoma in China. Chin Clin Oncol 2022;11(4):29. doi: 10.21037/cco-22-18