Characteristics and trends of globally registered glioma clinical trials in the past 16 years

Xiaofang He* (ID), **Wenbin Zhao*, Jianwen Huang*, Jia Xu, Shaoqing Niu, Qun Zhang, Nu Zhang, Huawei Jin and Guoping Shen**

Abstract

Background: Advancement in the treatment of glioma has been vacant since temozolomide has proved its therapeutic value in glioblastoma in 2005.

Aim: To help investigators understand the landscape of glioma clinical research, we analyzed the characteristics and trends of globally registered glioma trials in the past decades.

Methods: This is a cross-sectional analysis of glioma trials registered on ClinicalTrials.gov between January 2006 and December 2021. Characteristics regarding phase, enrollment number, study design and type, funding source, tumor site, pathology, patient status, age of population, trial purpose, and participating country were abstracted, and chronological shifts were analyzed.

Results: There were 1531 registered glioma trials involved 58 participating countries. The trial purpose concerning surgery, radiotherapy, chemotherapy, targeted therapy, tumor-treating fields, immunotherapy, other antiglioma therapy and non-antiglioma research trial accounts for 3.5%, 6.5%, 9.5%, 28.9%, 2.0%, 16.4%, 12.5%, and 20.6%, respectively. In the past 16 years, the numbers of chemotherapy and targeted therapy trials declined; tumor-treating fields and immune checkpoint inhibitor application trials sprang at the latter half period; Immunotherapy, other antiglioma therapy and non-antiglioma research trials escalated (all above $p_{trend} < 0.005$). The trend also showed the phased trials registered diminishingly and that the trials which focused on glioblastoma registered incrementally (those two $p_{trend} < 0.05$). Among 784 drug therapy trials, it was included 45 cytotoxic drugs, 186 targeted drugs, 19 immune checkpoint inhibitors, 78 other drugs, and five immunomodulatory drugs. Two trials belonged to Bayesian adaptive randomized design. By the end of December 2021, 309 trials had publications. Only everolimus and tumor-treating fields exhibited meaningful survival benefit in specific glioma patients in phase 3 trials.

Conclusion: Meaningful effective treatments regarding drugs or methods for glioma were difficult to be found. Bayesian adaptive platform trials may accelerate clinical research in glioma. Development of novel treatment modalities for glioma is still challenged.

Keywords: characteristics, clinical trials, glioma, landscape analysis, trends

Correspondence to:
Huawei Jin
Department of Neurosurgery, The First Affiliated Hospital of Sun Yat-sen University, No.58, Zhongshan Road 2, Guangzhou 510080, Guangdong Province, P.R. China.
jinhw@mail.sysu.edu.cn

Guoping Shen
Department of Radiation Oncology, The First Affiliated Hospital of Sun Yat-sen University, No.58, Zhongshan Road 2, Guangzhou 510080, Guangdong Province, P.R. China.
shenguop@mail.sysu. edu.cn

Xiaofang He
Wenbin Zhao
Jianwen Huang
Shaoqing Niu
Qun Zhang
Department of Radiation Oncology, The First Affiliated Hospital of Sun Yat-sen University, Guangzhou, P.R. China

Jia Xu
Department of Emergency, The First Affiliated Hospital of Sun Yat-sen University, Guangzhou, P.R. China

Nu Zhang
Department of Neurosurgery, The First Affiliated Hospital of Sun Yat-sen University, Guangzhou, P.R. China

Guangdong Provincial Key Laboratory of Brain Function and Disease, Guangzhou, P.R. China

*These authors contributed equally.

Background

Glioma is the most common primary malignant tumor in the central nervous system.[1] This disease is difficult to treat because it is rather prone to recur after treatment. The 5-year survival rates of grades II, III, and IV glioma were 50–81%, 30–57%, and 5.5%, respectively.[2] And most of the patients with grade IV glioma survived less than 2 year. Despite tremendous efforts have been made over the past decade, the effective therapies for glioma are limited and unsatisfactory.[3] Therefore, how to improve the prognosis of patients with glioma still remains a severe challenge in the clinical practice.

Clinical trial has been proved to be a direct and effective way to discover and verify the efficacy of antitumor therapies, which connects the preclinical drug development to rigorous testing in the clinic.[4] The identification of the pivotal role of temozolomide as standard of care for glioma is based on its meaningful therapeutic effect for newly diagnosed glioblastoma by a randomized, open-label, phase 3 clinical trial in 2005.[5] A significantly improved 2-year survival rate was achieved from 10.4% to 26.5% *versus* radiotherapy alone, and the median survival was improved from 12.1 months to 14.6 months. Since then, the field of investigating innovative approaches for glioma has been rapidly expanding, which mainly focuses on advancing surgery, radiotherapy, chemotherapy, targeted therapy, and immunotherapy. However, it is disappointing that most of these therapies are plagued by mild or moderate improvements in survival. From 2006 to 2015, glioblastoma treatment has entered a plateau period as long as 10 years. Then in 2015, the interim analysis of a phase 3 trial reported significant survival benefit from the addition of alternating electric field therapy to the standard of care of glioblastoma.[6] Nevertheless, 6 years have passed, and the advancement in therapy of glioma is still limited. Thus, it is in urgent need for oncological physicians to develop effective treatments.

Many possible reasons accounting for this long-term lack of progress in glioma treatment have been indicated, including complex cell signaling and heterogeneous biological behavior,[2,7,8] however, clinical trial remains the most direct and final way to assess the efficacy of new drugs and treatments on patients.[4,9] Therefore, it is indispensable for clinical investigators to have a comprehensive understanding of the latest clinical trials landscape and to learn from the previous experience. Here, we described a landscape of all the glioma clinical trials registered on ClinicalTrial.gov from 2006 to 2021, summarizing their fundamental characteristics, chronological shifts and publication status, so as to address the critical challenges and help to improve prognosis of glioma.

Methods

Data source and study samples
We downloaded the records of all 338,881 clinical trials registered on ClinicalTrials.gov[10] from January 1, 2006, to December 31, 2021, and restricted our selection to trials with keywords of 'glioma', 'glioblastoma', 'GBM', 'gliosarcoma', 'astrocytoma', 'oligodendroglioma', 'oligoastrocytoma', 'xanthoastrocytoma', and 'astroblastoma' by reviewing titles or conditions. Of note, ependymoma was not included in this study. The whole reviewed work was done automatically by computer and checked by oncologists. Ultimately, there were 1531 trials involved with glioma. On the basis of different research purposes, we further classified these clinical trials into 8 categories: (I) surgery; (II) radiotherapy; (III) chemotherapy (cytotoxic drug); (IV) targeted therapy; (V) tumor-treating fields (TTF); (VI) immunotherapy; (VII) other antiglioma therapies; and (VIII) non-antiglioma research. Ethical approval for the study was waived by the Ethics Committee to the First Affiliated Hospital of Sun Yat-sen University in China.

Surgery trials included those (1) used navigation, imaging, ultrasound, or fluorescence guiding to improve surgical accuracy; (2) applied neoadjuvant therapy to reduce microinvasion and help with better surgical dissection; and (3) were stereotactic biopsy. Radiotherapy trials specifically referred to external radiation, while internal radiation and intraoperative radiation were included in other antiglioma treatments. Studies involved with radiotherapy sensitization drugs, hyperbaric oxygen sensitization radiotherapy, as well as radiographic or nuclear medicine helping to improve the rationality of the delineation of radiation target volume and the accuracy of radiation positioning also belonged to radiotherapy trials. Chemotherapy specifically referred to cytotoxic drugs, and chemosensitizers were included in chemotherapy as well, because they aimed at enhancing the curative effect of cytotoxic drugs. Targeted therapy was defined as drugs blocking the action of certain enzymes, proteins, or other molecules involved in the growth and spread of cancer cells. Immunotherapy was classified into six subgroups according the previous study,[11] including T-cell-targeted immunomodulatory [immune checkpoint inhibitors (ICI)], cancer vaccine, cellular immunotherapy, Chimeric antigen receptor T-cell therapy (CART), oncolytic virus, and immunomodulatory drugs. Other antiglioma treatment was divided into drugs and methods. These methods included virus (nononcolytic virus), diet therapy, internal radiation, blood–brain barrier disruption to increase drug
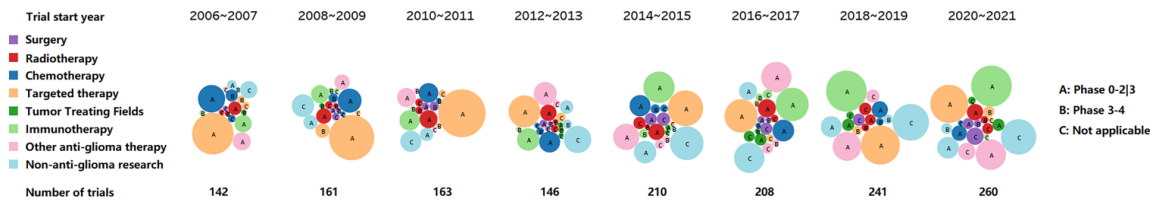
Figure 1. The landscape of glioma trials in the past 16 years. The size of the bubble correlated to the counts of trials. The end date of registered trial start year was December 31, 2021.

permeation into brain, thermal therapy, photodynamic therapy, intraoperative radiotherapy, radiofrequency therapy, immunotoxin, sonodynamic therapy, electrochemotherapy, and traditional Chinese medicine. Non-antiglioma research contained three fields as follows: (1) imaging or nuclear medicine research in glioma; (2) molecular markers for diagnosis, prognosis, or prediction as well as molecular profile research in glioma; (3) patients supportive therapy for treating adverse effects (thrombocytopenia, nausea and vomit induced by chemotherapy, weakness caused by steroid therapy, etc.), and glioma complications (brain edema, epilepsy, venous thromboembolism, fatigue, neurological function deficits, etc.). Perioperative anesthetic management, psychological or social support care, and intervention improving quality of life also belonged to supportive therapy. If hyperbaric oxygen was used to improve cognitive deficits, it was considered as supportive therapy.

Data acquisition
Information about trial characteristics were collected from each trial, including phase, study design ('randomized' or 'non-randomized'), study type ('interventional' or 'observational'), funding source, tumor site, histological grade ['high-grade (WHO III-IV)', 'low-grade (WHO I-II)' or 'malignant glioma (WHO II-IV)'], pathological subtype, age ('child', 'adult', 'older adult', 'child and adult', 'child, adult and older adult', or 'adult and older adult'), enrollment number of patients, enrollment patient status ('new diagnosis', 'recurrence', 'new and recurrence', or 'pseudoprogression'), trial purpose, and register start year. 'Child' referred to patients younger than 18 years,[12] and 'older adult' was identified as patients older than 65 years.[13] The tumor site was categorized into 'brain', 'brainstem', 'optic pathway', 'spinal cord', 'brain and brainstem', 'brain and optic pathway', 'brain and

spinal cord', 'brain, brainstem and optic pathway', and 'brain, brainstem and spinal cord'. The funding source was classified as industry, the National Institutes of Health (NIH) and other sources based on methods described in the previous studies.[14,15] The histological grade and pathological classification for glioma was according to the 2016 version of the WHO classification of the central nervous system tumors.[1]

Statistical analysis
Descriptive statistics were used to summarize the characteristics of the clinical trials, and categorical data were reported as frequencies and percentages. The trend of glioma trials was analyzed by chi-square trend test (Cochran–Armitage trend test). All the statistical analyses were performed using the R foundation for statistical computing version 3.6.1. The world map and bubble figures were produced using Tableau Software (v2019.4.4).

Results

Baseline characteristics
The landscape of the included glioma trials was displayed in Figure 1 and their baseline characteristics were summarized in Table 1. A total of 1531 glioma trials were registered on ClinicalTrials.gov from January 1, 2006, to December 31, 2021, with a gradually annual increasing in the total number of trials, among which 1427 trials were known to be registered in 58 participating countries with Unite States contributing to the largest amount (Supplemental Figure S1). Around 90% of trials were interventional and 77% were nonrandomized designed. The funding source of 25.4% trials came from industry or NIH. The proportions of trials to be phase 0 to 2|3, 3 and 4 were 72.7%, 4.8% and 0.7%, respectively. As for the enrollment number of patients, more than 60% of registered trials

Table 1. Characteristics of Glioma trials registered on ClinicalTrials.gov from January 1, 2006, to December 31, 2021.

Characteristic	Total trials ($n=1531$)
Phase	
0	78 (5.1)
1	353 (23.1)
1|2	191 (12.5)
2	471 (30.8)
2|3	18 (1.2)
3	73 (4.8)
4	10 (0.7)
Not applicable	337 (22.0)
Enrollment number of patients	
<50	934 (61.0)
50–100	349 (22.8)
>100	248 (16.2)
Study design	
Randomized	349 (22.8)
Nonrandomized	1182 (77.2)
Study type	
Interventional	1365 (89.2)
Observational	166 (10.8)
Funding source	
Industry	299 (19.5)
NIH	90 (5.9)
Other	1142 (74.6)
Histological grade	
High-grade (WHO III–IV)	1273 (83.2)
Low-grade (WHO I–II)	80 (5.2)
Malignant glioma (WHO II–IV)	178 (11.6)
Enrollment patient status	
New diagnosis	878 (57.4)

(Continued)

Table 1. (Continued)

Characteristic	Total trials ($n=1531$)
Recurrence	586 (38.2)
New and recurrence	61 (4.0)
Pseudoprogression	6 (0.4)
Trial purpose	
Surgery	54 (3.5)
Radiotherapy	100 (6.5)
Chemotherapy (cytotoxic drug)	145 (9.5)
Targeted therapy	443 (28.9)
Tumor-treating fields	31 (2.0)
Immunotherapy	251 (16.4)
T-cell-targeted immunomodulatory	80 (5.2)
Cancer vaccine	95 (6.2)
Cellular immunotherapy	29 (1.9)
CART	18 (1.2)
Oncolytic virus	18 (1.2)
Immunomodulatory drug	11 (0.7)
Other antiglioma therapy	191 (12.5)
Other drugs	116 (7.6)
Other ways to antiglioma	75 (4.9)
Non-antiglioma research	316 (20.6)
CT/MR/PET imaging research	123 (8.0)
Molecular research	89 (5.8)
Support care treatment	104 (6.8)

CART, Chimeric antigen receptor T-cell therapy; NIH, National Institutes of Health; WHO, World Health Organization.

enrolled less than 50 patients, while around 22% from 50 to 100 patients and 16% more than 100 patients. Most of the trials were overlapped with adult and older adult patients, making up 85.2% of the total trials, and the numbers of trials for only child, adult, or older adult patients were 18, 8, and 14, respectively (Supplemental Figure S2A). In regard to the tumor site, 93.4% of glioma trials'
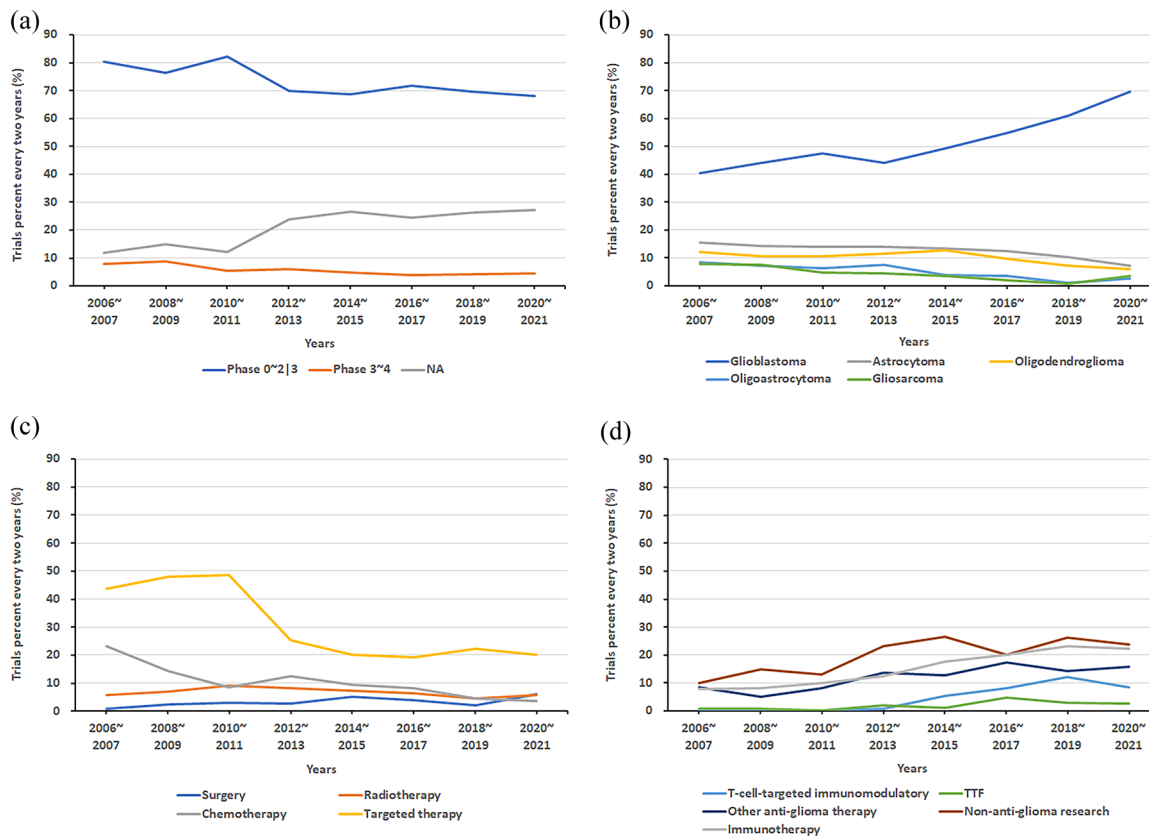
Figure 2. The trends of glioma trials. (a) Trend of trial phase in three groups. The first group was phase 0 to 2|3. The second group was phase 3 to 4. The third group was not applicable (NA) to phase. p_{trend} were <0.001, 0.023 and <0.001, respectively. (b) Trends of trials in enrolled pathological subtype of gliomas. p_{trend} for glioblastoma, astrocytoma, oligodendroglioma, oligoastrocytoma, and gliosarcoma were <0.001, 0.002, 0.009, <0.001, and <0.001, respectively. (c) Trends of trial purpose for surgery, radiotherapy, chemotherapy, and targeted therapy. p_{trend} were 0.022, 0.289, <0.001, and <0.001, respectively. (d) Trends of trial purpose for T-cell-targeted immunomodulatory, TTF, immunotherapy, other antiglioma therapy, and non-antiglioma research. p_{trend} were <0.001, 0.004, <0.001, <0.001, and <0.001, respectively.

inclusion criteria were that the tumor located in the brain, with few in the brainstem (3.4%), optic pathway (0.3%), spinal cord (0.1%), and more than one site (2.5%) (Supplemental Figure S2B). High-grade glioma accounted for the vast majority as much as 83.2%, and low-grade and malignant glioma made up 5.2% and 11.6%, respectively. More than 50% of the trials enrolled newly diagnosed patients, while 38.2%, 4.0% and 0.4% of trials focused on patients with diagnoses of recurrence, new or recurrence, and pseudoprogression. Based on the trial purpose, we classified the registered trials into 8 categories. Targeted therapy owned the highest proportion with 28.9%, followed by non-antiglioma research with 20.6% and immunotherapy with 16.4%. The composition of immunotherapy was diverse and complex, including 5.2% T-cell-targeted immunomodulatory,

6.2% cancer vaccine, 1.9% cellular immunotherapy, 1.2% CART, 1.2% oncolytic virus, and 0.7% immunomodulatory drug. As for the three conventional therapy modalities, the proportions for surgery, radiotherapy and chemotherapy (cytotoxic drug) were 3.5%, 6.5%, and 9.5%, respectively. TTF, as a new treatment, accounted for 2.0% (Supplemental Figure S12).

Chronological shifts in trial characteristics
The trend for trials to be phase 0 to 2|3 has presented a gradual decline since 2006, as well as in the trials to be phase 3 and 4. On the contrary, the trend for other trials without applicable phase information increased between 2006 and 2021 [Figure 2(a)]. Regarding to the specific pathological subtypes of glioma [Figure 2(b)],

the number of glioblastoma trials has been experiencing a steady increase since 2006, while other pathological subtypes of astrocytoma, oligoastrocytoma and gliosarcoma declined gradually. Figure 2(c) demonstrated the trends of three fundamental treatment modalities for glioma. The trends for surgery and radiotherapy were stable with a slight increase, while the number of chemotherapy trials decreased year by year. As for the novel oncological treatments, the trend for targeted therapy reached the peak at the period between 2009 and 2010, and then the number shrank down and remained stable in the recent years. Figure 2(d) showed that the trials for immune checkpoint inhibitors and TTF sprang out at the latter half period between 2006 and 2021. The number of trials regarding immunotherapy, other anti-glioma therapy, and non-anti-glioma research had increased during the past 16 years.

In addition, trends for the proportions of enrollment population sample size (less than 50 *versus* between 50 and 100 *versus* more than 100), trial study design (nonrandomized *versus* randomized), histological grade (high-grade *versus* low-grade *versus* malignant glioma) and enrollment population status (new diagnosis *versus* recurrence) held steady during the past 16 years (Supplemental Figures S3–S6). The proportions of interventional trials and trials with funding from industry or NIH reduced at the latter half period between 2006 and 2021 (Supplemental Figures S7 and S8).

Landscape analysis of registered trials involved with drugs

Altogether, the chemotherapy trials included temozolomide and other 44 cytotoxic drugs (Supplemental Table S1). There were 443 trials containing 186 targeted drugs involving with 85 targets [Table 1, Figure 3(a) and (c); Supplemental Table S1]. Inhibitors of vascular endothelial growth factor (VEGF), vascular endothelial growth factor receptor (VEGFR), and epidermal growth factor receptor (EGFR) were the three most prevalent classes of therapies in targeted molecule trials. Bevacizumab was the most popular targeted drug registered with 91 trials. Eighty trials involved with 19 ICI which consisted of 27 nivolumab trials, 26 pembrolizumab trials, 11 ipilimumab trials, and so on [Table 1, Figure 3(b); Supplemental Table S1]. The immune checkpoint targets covered programmed cell death 1 (PD1), programmed cell death 1 ligand 1 (PD-L1), cytotoxic T-lymphocyte associated protein 4 (CTLA4), lymphocyte-activation gene 3 (LAG3), T-cell immunoglobulin Mucin 3 (TIM3), T-cell immunoglobulin and ITIM domain (TIGIT), glucocorticoid-induced tumor necrosis factor receptor (GITR), and 4-1BB(CD137). In regard to other 78 antiglioma drugs (noncytotoxic drug), ranking the first three were disulfiram, valganciclovir or ganciclovir, and metformin [Figure 3(d); Supplemental Table S1].

Other antiglioma therapy and non-antiglioma research

As demonstrated in Supplemental Figure S9, there were 13 kinds of treatments included in other ways to antiglioma. Treatment by means of virus (nononcolytic virus) made up the largest amount of 13 trials in total, followed by Ketogenic or Atkins diet of 12 trials, internal irradiation of 12 trials and blood–brain barrier disruption of 12 trials. Electrochemotherapy and traditional Chinese medicine accounted for the least amount, all of which were only one trial registered in the past decade. The proportions of other drugs and other ways to antiglioma trials were showed in Supplemental Figure S10. The proportions of imaging research, molecular research and support care treatment were exhibited in Supplemental Figure S11.

Publication status of the registered trials

By the end of December 31, 2021, 309 trials have published 388 papers of their results in PubMed, among which 73 trials have published more than one paper. The annual publications increased year by year attributed to more and more completed trials (Figure 4). Of note, 52 papers were published in *JAMA*, *JAMA oncology*, *JCO*, *Lancet*, *Lancet oncology*, or *NEJM* (alphabetical order). However, only two of them demonstrated clinical benefit. One was the addition of TTF to temozolomide maintenance after chemoradiotherapy for glioblastoma. The other one was oral everolimus to treat a specific type of glioma named subependymal giant cell astrocytomas concomitant with tuberous sclerosis. The publications of phase 3 trials and other important researches were summarized in Supplemental Table S2.

(a)

(b)

(c)

(d)
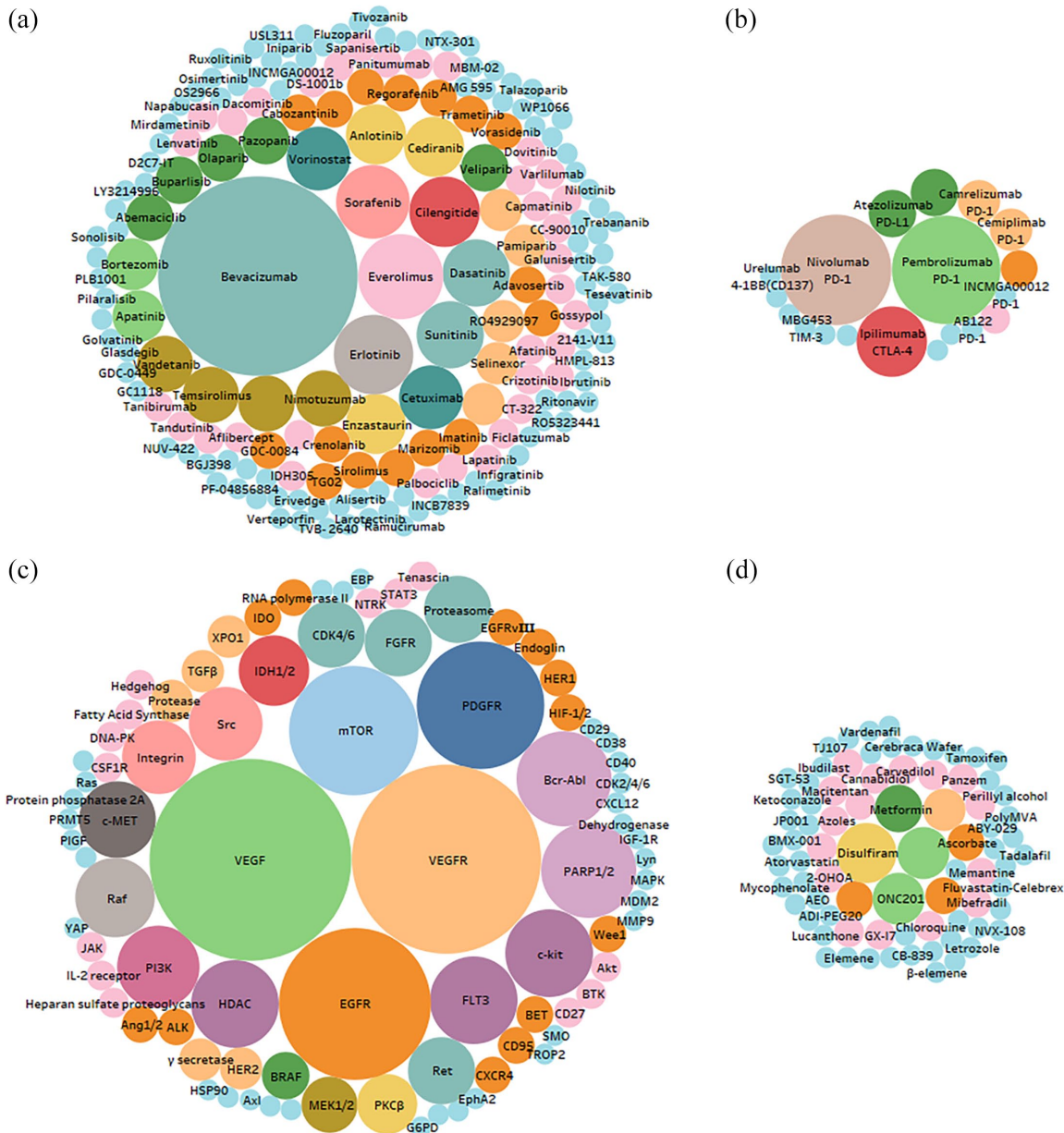
Figure 3. The landscape analysis of drugs involved in glioma trials. (a) The targeted drugs involved in glioma trials. (b) The immune checkpoint inhibitors involved in glioma trials. (c) The targeted molecules involved in glioma trials. (d) The other drugs (noncytotoxic drug) involved in glioma trials. The size of the bubble was correlated with the number of trials. Because of the crowed space, some names were not shown. The name and trial counts of every drug or targeted molecule can be reviewed in Supplemental Table S1.

Discussion

As what is indicated in our analysis, a great amount of effort has been made to improve the prognosis of glioma over the past decade. On one hand, conventional treatment strategies including surgery, radiotherapy, and chemotherapy have been kept trying different modifications, but the number of chemotherapy trial is decreasing gradually. On the other hand, novel treatment modalities such as targeted therapy, immunotherapy, and TTF have attracted huge attention and taken up larger and larger proportions of the total amount of registered clinical trials. However, according to the available published studies, only the addition of TTF to maintenance temozolomide claimed satisfactory clinical benefit for glioblastoma, demonstrating statistically
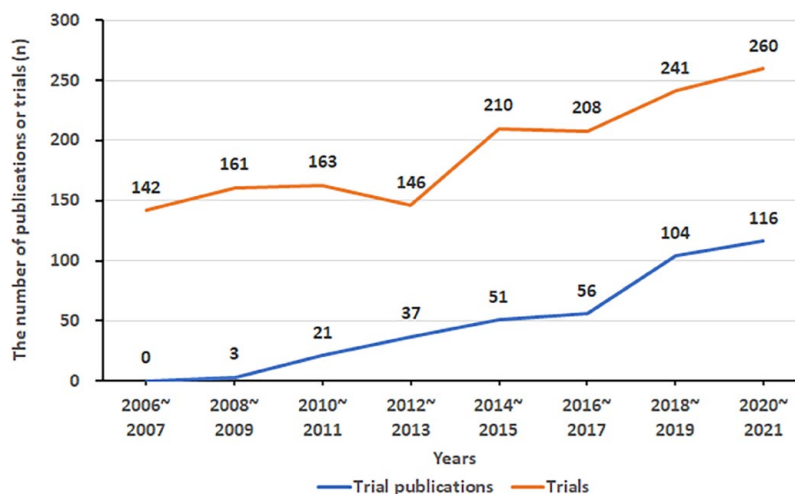
Figure 4. The numbers of trial publications every 2 years at period between 2006 and 2021. The end date of registered trial start year was December 31, 2021.

significant improvement in progress-free survival from 4.0–6.7 months as well as overall survival from 16.0–20.9 months *versus* maintenance temozolomide alone.[16] Everolimus is the only one targeted drug found to prolong the time to progression in a specific type of glioma named subependymal giant cell astrocytomas concomitant with tuberous sclerosis.[17,18] In addition, for older adult glioblastoma, optimizations of radiotherapy regiments have been carried out in three clinical trials.[13,19,20] Furthermore, temozolomide has also demonstrated its therapeutic effect in adjuvant chemotherapy in 1p/19q non-co-deleted anaplastic glioma and low-grade glioma[21,22] (Supplemental Table S2).

Epigenetic therapies refer to treat the DNA methylation patterns and posttranslational modifications return to normal by drugs acted on the epigenetic regulators. Seven category inhibitors included in epigenetic therapy as follow: DNA methyltransferase (DNMT) inhibitor, isocitrate dehydrogenase (IDH) 1/2 inhibitor, histone deacetylase (HDAC) inhibitor, enhancer of zeste homolog 2 (EZH2) methyltransferase inhibitor, disruptor of telomeric silencing 1-like (DOT1L) methyltransferase inhibitor, lysine-specific demethylase 1 (LSD1) inhibitor, and bromodomain and extraterminal (BET) inhibitor.[23] In all these glioma trials, six drugs belonged epigenetic therapy: one DNMT inhibitor (azacytidine), two IDH 1/2 inhibitors (ivosidenib and vorasidenib), two HDAC inhibitors (panobinostat and vorinostat), and one BET inhibitor (birabresib). Ivosidenib has reported its clinical pharmacokinetics and pharmacodynamics.[24] Two HDAC inhibitors have been reported clinical trial results: The addition of panobinostat to bevacizumab did not significantly improve 6-month progression-fee survival compared with historical controls of bevacizumab monotherapy;[25] vorinostat combined with standard chemoradiation had acceptable tolerability in newly diagnosed glioblastoma but did not meet the primary efficacy endpoint.[26] As we know, some epigenetic agents were approved to treat specific cancer. Because not many epigenetic drugs registered in glioma trials, the glioma epigenetic therapy still has research space.

In the past few years, advances in immunotherapy, especially monoclonal antibodies against PD1, PD-L1 and CTLA4, have been changing the standard of care of many types of cancer due to the promising therapeutic effect showed in clinical trials.[11] As demonstrated in our analysis, the immunotherapy trials for glioma registered on ClinicalTrials.gov was only seven in 2006. Then, the amount increased enormously and reached as many as 251 in the end of 2021, with ICI and cancer vaccine as the dominating research focus. However, nivolumab, one of the ICI, and rindopepimut, one of the two vaccines, did not exhibit survival benefit in patients with glioblastoma in phase 3 trials based on the current data results.[17,27] DCVax, the other one vaccine, has published first results,[28] and we look forward to its final reports. Recently, a case report published in the journal of NEJM presented the evidence that CAR-engineered T-cells targeting the tumor-associated antigen

interleukin-13 receptor α2 could achieve regression of all intracranial and spinal tumors in a patient with recurrent glioblastoma, and the duration of response of that patient was 7.5 months.[29]

Oncolytic virus immunotherapy is a therapeutic approach to cancer treatment that utilizes native or genetically modified viruses that selectively replicate within tumor cells. This therapeutic strategy can break the stranglehold of a tumor on the microenvironment to shift the brain tumor from cold to hot and provoke a strong immune backlash. There were 18 oncolytic virus trials registered in glioma. Those trials included seven oncolytic viruses been published: reolysin (an unmodified reovirus),[30] DNX-2401 (a adenovirus with Arg-Gly-Asp insertion enabling itself to use integrins to enter tumor cells),[31] DNX-2440 (a adenovirus expressing OX40 L),[32] PSVRIPO (a modified poliovirus with a tropism for CD155),[33] TG6002 (a FCU1 expressed vaccinia virus with RR and TK genes deletions),[34,35] G207 [a herpes simplex virus (HSV) type-1 containing deletion of the diploid γ1 34.5 neurovirulence gene and having viral ribonucleotide reductase (UL 39) disabled by insertion of *Escherichia coli* lacZ],[36] and VB-111 [a replication-deficient adenovirus type 5 vector carrying a transgene for a chimeric death receptor that connects intracellular Fas to human tumor necrosis factor (TNF) receptor 1].[37] Four of them have been reported clinical trial results. DNX-2401 enabled 20% of 25 patients with recurrent high-grade glioma to survive more than 3 years.[31] PSVRIPO achieved that the 2-year survival rate of patient with recurrent glioblastoma was 1.5 times to the historical control group (21% *versus* 14%).[33] G207 obtained a median overall survival of 12.2 months in patients with recurrent or progressive pediatric high-grade glioma.[36] VB-111 combined with bevacizumab failed to improve overall survival and progression-free survival in recurrent glioblastoma.[37] Undoubtedly, oncolytic virus immunotherapy is very promising and probably has the potential to make breakthroughs in improving the prognosis of glioma. However, it still requires more robust evidence from large scale randomized clinical trials in the future.

Furthermore, our analysis of the characteristics of the clinical trials highlighted some issues. Around 70% of the registered trials were phase 0 to 2|3, and only 5.1% were phase 3. This partially reflects that most of clinical trials were designed to assess the therapeutic efficacy of novel treatment modalities, while few of them showed positive results that can enter phase 3. Since conventional antiglioma methods including surgery, chemotherapy, and radiotherapy showed no sign to further improve the survival of patients with glioma, investigators have shifted their focus on new methods, such as TTF and immunotherapy, and to study the molecular profile of glioma so as to have a thorough knowledge of this disease. As we know, the incidence of glioma is lower compared with other malignant tumors, which may lead to the poor efficiency of clinical trials in glioma as traditional phase II and III trials require randomizer, larger, multicenter patient cohorts and longer timeframes. In this case, Bayesian adaptive platform trials (APT), such as GBM AGILE (NCT03970447)[38] or INSIGhT (NCT02977780),[39] have been implemented as potential solutions to some of these problems, especially to address multiple therapeutic and biomarker hypotheses in glioblastoma. Bayesian adaptively randomized screening stage to identify effective therapies based on impact on overall survival compared with a common control. INSIGhT is an ongoing novel biomarker-based, Bayesian APT for patients with newly diagnosed unmethylated GBM. This trial has tried three drugs abemaciclib, CC-115, and neratinib in three experimental arms compared with one control arm.[39] The results of this trial have not published yet but have stood in our expectation.

Conclusion

This study is a comprehensive overview of the clinical trials for glioma during the past 16 years. This study presented the development and progress of the latest clinical research, and indicated that most drugs and methods used for antiglioma were failed. Bayesian adaptive platform trials may accelerate clinical research in glioma.

Declarations

ORCID iD
Xiaofang He https://orcid.org/0000-0002-2266-8111

Supplemental material
Supplemental material for this article is available online.

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