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Recent therapeutic advances and insights of recurrent glioblastoma multiforme

Juxiang Chen[1], Tao Xu[1]

[1]Department of Neurosurgery, Shanghai Institute of Neurosurgery, Changzheng Hospital, Second Military Medical University, Shanghai 200003, China

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1. ABSTRACT

Despite recent therapeutic advances, most patients with glioblastoma multiforme (GBM) experience disease recurrence, with very poor prognosis. Much work still needs to done to improve the treatment efficacy. The optimal management of patients with recurrent GBM is still controversial. This article summarizes the current status of therapeutic strategies in recurrent glioblastoma patients, with an emphasis on more novel approaches and important recent progress. The clinical evidence of current treatment strategies were collected and reviewed. Patients still need comprehensive treatment for recurrent GBM. Surgery may be useful as adjuvant treatment for patients with symptoms due to the effect of the mass or for patients requiring definitive histopathology, but it generally should be combined with another treatment modality; high-precision re-irradiation such as stereotactic radiosurgery or gamma knife is another option. Chemotherapy like fotemustine, or a metronomic schedule of temozolomide regimens and anti-angiogenic agents like bevacizumab could also be considered. Other targeted molecular inhibitors or anti-angiogenic therapies, and immunotherapies are still under investigation and their efficacy needs to be evaluated further in the future.

2. INTRODUCTION

Gliomas are the most common primary tumors in the central nervous system (CNS) and malignant gliomas, which account for 70% of gliomas, are the most frequent and lethal cancers originating in the CNS with a high recurrence and mortality rate (1). The most biologically aggressive subtype of gliomas is glioblastoma multiforme (GBM) [World Health Organization (WHO) grade IV astrocytoma], a tumor associated with a rather dismal prognosis. Current standard treatment protocol includes maximal surgical resection followed by adjuvant chemotherapy with a DNA alkylator, temozolomide (TMZ), and radiotherapy. Despite the best available therapeutic regimen, the life expectancy of patients with GBM is still short, with a median survival of approximately 14-16 months (2). Almost all GBM patients will experience disease recurrence with a median time to progression in 6.2 months and a median survival following recurrence of only 25 to 30 weeks (3, 4); the majority of patients with GBM relapse following initial treatment and 10% of patients are alive at 5 years.

In contrast to the primary treatment of GBM, there is no consensus on the optimal approach for patients

with recurrent GBM, especially for patients who receive 12 or more cycles of TMZ as adjuvant therapy (5). The optional therapeutic protocols include re-operation, re-irradiation, chemotherapy, target therapy, etc. Agents that can be used for recurrent gliomas include TMZ, nitrosoureas, carboplatin, procarbazine, irinotecan, and etoposide. Carmustine wafers have modest activity, increasing the median survival by approximately 8 weeks in patients with recurrent glioblastomas(6). Other agents are still in phase II clinical trials and their efficacy remains to be evaluated.

The aim of this review is to discuss the evolution of treatment for recurrent GBM, and thus to provide a concise overview of the recent therapeutic strategies, and highlight some areas under investigation.

3. THERAPEUTIC STRATEGIES

3.1 Re-operation

3.1.1 General Description

In over 85% of recurrent glioblastoma relapse occurs locally, giving a chance for re-operation from the neurosurgical point of view(7). For neurosurgeons, glioblastoma is still a great challenge, not only from the point of resecting the outmost possible amount of tumor tissue but also from the point of preserving neurological function and, thus, quality of life. It is generally believed that re-operation for patients with recurrent GBM has a positive effect on outcome by relieving symptoms due to intracranial mass and reducing tumor burden to facilitate subsequent therapy. In addition, re-operation is an important method to confirm true tumor progression, compensating for the pitfalls of magnetic resonance imaging (MRI) to distinguish recurrence between pseudo-progressions or radiation necrosis. Pre- and intraoperative guidance by neuro-navigation, MRI, ultrasound, fluorescence guided resection and intraoperative photodynamic treatment are the major new achievements in order to facilitate tumor resection and cytoreduction to the greatest extent.

3.1.2 Benefits of Re-operation

Until now, prospective studies evaluating the survival benefit of re-operation were not available. Retrospective studies suggest that re-operation has a modest effect on prolonging survival in selected patients. Recently, Clarke *et al.* found that there is no significant difference in 6 months progression free survival (PFS6) between patients in surgical (14.8%) and nonsurgical (18.8%) groups at the time of tumor recurrence (8).

Despite limited benefit in survival provided by surgery alone, an obvious prolonged survival can be reached when surgery is followed by further treatment such as chemotherapy or radiotherapy. Mandl *et al.* found that the median overall survival after stand alone surgery is between 2 and 3 months, while the time increases to 12 months when combined with adjuvant chemotherapy and/or radiotherapy (9). The underlying mechanism may be that the relief of symptoms provides a better state to tolerate subsequent therapy.

As a result, there is no doubt that re-operation should always be considered in patients with recurrence of GBM, if the patient can get benefit from surgery and accept adjuvant therapies as further options, but how to determine whether to re-operate is difficult.

3.1.3. Decision-making in re-operation

At present, clear guidelines evaluating re-operation in patients with recurrent GBM have not been established. In general, surgery is not recommended alone. Location of tumor (eloquent or non-eloquent), performance status and resectability are commonly involved in making a decision (10). Park *et al.* devised a preoperative scale that predicts survival after surgery for recurrent glioblastoma multiforme and contains several factors associated with poor post-operative survival: tumor involvement of pre-specified eloquent/critical brain regions, low Karnofsky performance status score and tumor volume > or = 50 cm^3(11). This scale can identify patients likely to have poor, intermediate, and good relative outcomes after surgical resection, and thus help with decision making when choosing treatment options of individual patients. Mandl *et al.* proposed 7 items for screening patients. These are patient conditions, whether the tumor crosses the midline, involvement of eloquent areas, degree of resection, further treatment, benefit from re-operation and patient's wishes (9). Also the efficacy brought by re-operation is influenced by several elements such as operation method, further therapy and residual volume. Keles *et al.* suggest that patients with a smaller residual volume are coupled with a better response to chemotherapy and improved PFS6. Patients with less than 10 cm^3, 10–15 cm^3 and more than 15 cm^3 of residual disease in the beginning of chemotherapy had a PFS6 of 32%, 8% and 3%, respectively.

In conclusion, re-operation alone for treatment of patients with recurrent GBM is not recommended because of limited benefit in survival. It might be useful as adjuvant treatment for patients with symptoms due to mass effect or for patients requiring definitive histopathology, but it generally should be combined with other treatment modalities.

3.2. Radiotherapy and Gamma-knife surgery

3.2.1.Common radiotherapy

There are no randomized trials evaluating the benefit of re-irradiation in recurrent GBM. The role of radiotherapy for recurrent GBM remains controversial. Generally, re-irradiation is not recommended for patients who had received standard radiotherapy before GBM recurrence because of potential increased toxicity(12).

However, some recent advanced technologies provide new therapeutic options, suggesting that fractionated stereotactic radiotherapy and stereotactic radiosurgery may be beneficial. Several studies reported the efficacy of these techniques for recurrent GBM (13). Previous studies reported a median survival from 8 to 30 months for stereotactic radiosurgery and 6.7 to 50 months for fractionated stereotactic radiotherapy (14). Gutin *et al.* found that in patients with recurrent high grade glioma,

when used in combination with the humanized vascular endothelial growth factor (VEGF) antibody bevacizumab, hypofractionated radiotherapy (30 Gyin five fractions) is well tolerated and produced an encouraging response rate of 50% and 6-months progression free survival rate of 65%(15).

3.2.2. Gamma knife surgery (GKS)

GKS can deliver high radiation doses to the target volume with a sharp dose decrease toward the surrounding brain (16), thus, providing a non-invasive treatment option for GBM. It could be used as initial treatment in conjunction with surgery and external bean radiotherapy (17), but showed trends of more benefits when used in recurrent GBM patients. Hsieh *et al.* reported prolonged overall survival in a retrospective series of GBM patients when GKS was performed at the time of tumor progression (18).

In another recently published study, gamma knife surgery (GKS) was compared with re-operation in 77 consecutive recurrent GBM patients, Skeie *et al.* found that GKS may be an alternative option to open surgery for small GBMs at the time of recurrences, with a significantly lower complication rate and a possible survival benefit compared with re-operation(19). These results provided alternative options for treatment of recurrent GBM.

3.3. Chemotherapy

3.3.1. Temozolomide

TMZ is a new alkylating chemotherapeutic agent that is the standard treatment for newly diagnosed GBMs. A phase III trial showed that concomitant radiotherapy and TMZ plus six cycles of adjuvant TMZ improve 2-year survival versus radiotherapy alone from 10.4% to 26.5%(20). Several studies have suggested that resistance to TMZ is primarily mediated by O6-methylguanine DNA methyltransferase (MGMT) (21, 22) and protracted administration of TMZ results in more extensive and sustained depletion of MGMT (23).

Several clinical trials tried to evaluate the efficacy of TMZ in recurrent GBM with both standard 5-day schedule (24-30) and dose-dense schedule and showed varied results (31-38). With respect to tumor response, clinical benefit rate (complete response, partial response and stable disease) ranged from 36.7% to 90.5%. With respect to disease progression, the PFS-6 rate ranged from 18.0% to 48.0% while 12-month overall survival (OS-12) rate ranged from 14.6% to 81.0%.

A systematic review to determine the overall efficacy and to understand underlying causes of the variation was performed (39). The results showed that the overall rate of clinical benefit was 50.5% (95%CI: 44.3-56.7%), the overall PFS-6 rate was 27.8% (95%CI: 22.7-33.5%) and the overall OS-12 rate was 36.4% (95%CI 26.9-47.1%). Subgroup analysis showed that a dose-dense schedule achieves a better result than standard 5-day regimens in clinical benefit rate (61.4% versus 46.3%, P=0.037) and PFS-6 (33.1% versus 20.1%, P<0.001). The same trend was observed also in OS-12 although not significant (43.9% versus 27.4%, P=0.089).

Based on existing evidence, TMZ seems to be effective for recurrent GBMs, and its efficacy may be increased with a metronomic schedule.

3.3.2. Fotemustine

Fotemustine (FTM) is a third-generation member of nitrosourea agents (40). Previous studies had proved its ability to cross the blood-brain barrier, which makes it possible to be a therapeutic option for recurrent glioma patients (41-43). The efficacy of FTM in recurrent malignant glioma patients after standard TMZ treatment was studied in several European institutions. In these reports, the PFS-6 rates ranged from 21 to 52% (44, 45). In a retrospective pooled analysis, FTM is confirmed as a valuable therapeutic option for patients with recurrent GBM (PFS-6 = 33.1%), and is active in all study patient groups. They also found that time after the end of radiotherapy and second surgery are independent treatment-related risk factors. Presently, no prospective or randomized studies evaluating the efficacy of FTM have been conducted. As a result, the role of FTM, either alone or in combination with other agents, in salvage chemotherapy of GBM patients still needs further assessment in the future.

3.3.2. Other chemotherapy regimens

Several other chemotherapy regimens have also been evaluated, however, the results are disappointing. A retrospective analysis suggests that the ifosfamide, carboplatin and etoposide (ICE) regimen is not effective in patients with recurrent high-grade glioma if applied at second or third relapse (46). A randomized trial compared temozolomide versus procarbazine, lomustine, and vincristine (PCV) in recurrent high-grade glioma, and found that TMZ does not show a clear benefit compared with PCV (47). Single-agent carboplatin only has modest activity (48), with over two-thirds of patients having to discontinue treatment due to progressive disease. More effective but well tolerated regimens are required for this patient population.

For patients with recurrent glioblastoma who can undergo re-operation, the implantation of carmustine wafer (Gliadel) into the surgical cavity produces a modest increase in median survival of approximately 8 weeks (6).

3.4. Anti-angiogenic therapy

3.4.1 Bevacizumab

Several molecular mechanisms contribute to tumor angiogenesis but the VEGF pathway plays a particularly important role and has been a promising target in glioblastoma treatment. Angiogenesis in glioblastoma is primarily mediated by VEGF, and, thus, generates new blood vessels. Bevacizumab, the humanized monoclonal antibody against VEGF, in the only agent that has been approved by the U.S. Food and Drug Administration (FDA) for the treatment of recurrent glioblastoma. Preliminary results showed an increase in the PFS-6 to 35.1% for patients receiving bevacizumab alone and 50.3% for patients receiving bevacizumab combined with irinotecan.

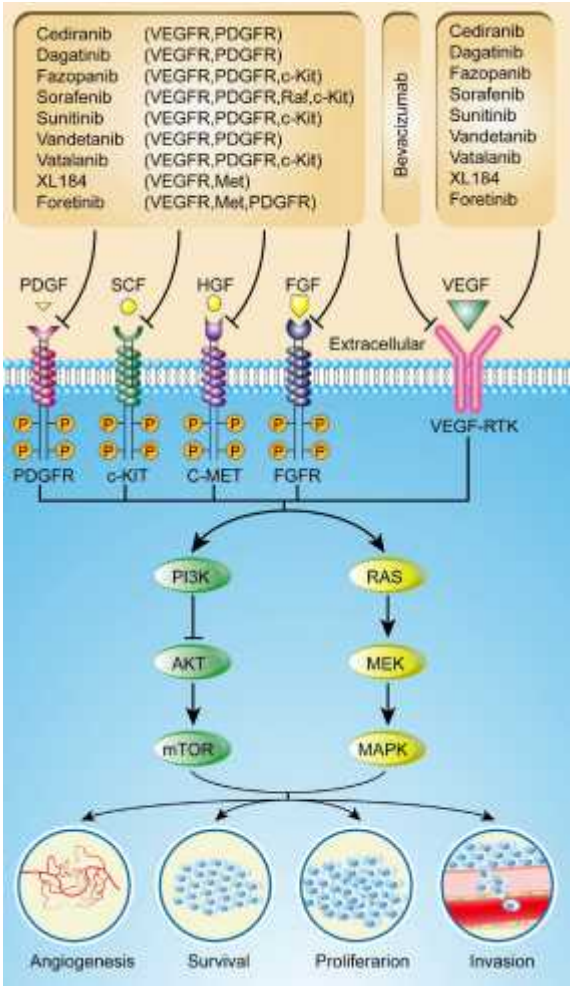

Figure 1. Overview of current targeted therapies of recurrent GBM. The PI3K-AKT and RAS oncogenic pathways frequent therapeutic targets. EGF, VEGF and PDGF, as well as their receptors, can be blocked by small molecular inhibitors or specific antibodies. Items in the boxes include examples of drugs that target the respective targets.

Common adverse events associated with bevacizumab include hypertension and proteinuria. (49, 50). Bevacizumab is also currently under investigation in combination with radiotherapy and temozolomide in newly diagnosed glioblastoma patients (51).

3.4.2. Other anti-VEGF receptor agents

In addition to strategies that target VEGF ligand, suppression of VEGF receptor (VEGFR) signaling can also be achieved. Many tyrosine kinase inhibitors can block the tyrosine kinase activation site of VEGFR (52-61), and are being studied in several phase I/II clinical trials (62-64). Notably, cediranib, a small-molecule inhibitor of VEGFR, demonstrated results comparable to bevacizumab, with a response rate of 56% and 6 M-PFS of 26% and has advanced to phase III investigation (65). Sorafenib and sunitinib are the other two agents approved by FDA that could target VEGFR, but they showed limited activity in human glioblastoma. Other anti-VEGFR agents, like Adnectin based CT-322 and XL-184, are still in early clinical development (66). Agents in clinical trials were shown in Figure 1. Advances in this field can provide more choice in the near future.

3.4.3. Updated criteria of treatment efficacy

Given the potent anti-permeability effect of VEGF inhibitors, and their intrinsic propensity to alter neuroradiological disease assessment by producing pseudo-progression, the role of PFS, which is based on neuroradiological assessment, should be reconsidered, while overall survival (OS) represents the gold standard end-point for measuring clinical efficacy (67). This is despite the disadvantage that OS is influenced by subsequent therapies and usually takes longer time to be evaluated. New criteria were recently implemented to better assess response of anti-angiogenic agents in patients with recurrent glioblastoma (68).

3.4.4. Potential image biomarkers

Besides contrast-enhanced MRI, position emission tomography (PET) can also be used in predicting treatment response. Schwarzenberg *et al* found that changes in tumor 3'-deoxy-3'-18F-fluorothymidine ((18)F-FLT) uptake are highly predictive of progression-free and overall survival in patients with recurrent malignant glioma on bevacizumab therapy. (18)F-FLT PET seems to be more predictive than MRI for early treatment response (69).

Meanwhile Hutterer *et al.* found in patients with recurrent high-grade glioma undergoing anti-angiogenic treatment that O-(2-18F-fluoroethyl)-L-tyrosine PET seems to be predictive for treatment failure in that it contributes important information to response assessment based solely on MRI and response assessment in neuro-oncology (RANO) criteria (70).These advances in neuroradiology help clinicians to get a more precise assessment of treatment response.

3.5. Immunotherapy

Immunotherapy for recurrent GBM is another promising treatment modality for patients, and there have been reports of encouraging results. The immunotherapy targets against the antigens that are over or specially expressed in brain tumors. The induced immune cells will kill the tumor cells while the normal cells will survive. The Dendritic cell (DC)-based vaccination targeting tumor-associated antigens is a “hot topic.” Several clinical trials evaluated the safety and immunogenicity of the novel vaccines.

3.5.1. Immunotherapy against glioma-associated antigen (GAA)

Okada *et al.* designed a novel vaccination withα-type 1 polarized dendritic cells (DC1) loaded with synthetic peptides for GAA epitopes and evaluated its effects on 19 HLA-A2+ patients with recurrent malignant gliomas. Positive immune response was observed in 58% patients after the first four vaccines. Significant increase in type 1 cytokines and chemokines is observed in peripheral blood.

Nine patients' progression-free status was at least 12 months. Sustained complete response was showed in one patient (71).

3.5.2. Immunotherapy against IL-13Rα2

Iwami *et al* evaluated the vaccine targeting IL-13Rα2-derived peptides restricted to HLA-A *0201 and -A *2402 in patients with recurrent malignant glioma. Two out of three HLA-A * 2402 patients, which could be evaluated, showed a positive T-cell response. One patient had stable disease for 16 months. One patient showed a dramatic regression for one lesion for 4 months(72).

3.5.3. Immunotherapy against Wilms tumor 1 (WT1) gen

In another phase II trial, safety and clinical responses of immunotherapy targeting the WT1 gene product was evaluated in 21 patients with recurrent GBM. They found that WT1 vaccine therapy for patients with WT1/HLA-A*2402-positive recurrent GBM was safe and produced a clinical response. Further more, none of these studies shows severe adverse events. All of the above results show a bright future of immunotherapy for recurrent GBM. (73)

4. CONCLUSION

Therapy for recurrent GBM may involve surgery, re-irradiation, chemotherapy, or novel agents, including anti-angiogenic therapies. Significant progress has been made in treating recurrent GBM. However, the prospects and prognosis for these patients remain bleak. Surgery and chemotherapy have a role in selected patients. The management of recurrent GBM is highly dependent on an integrated multidisciplinary approach. Currently, selected patients may benefit from reoperation, re-irradiation, anti-angiogenic therapy, metronomic dose schedule of temozolomide, salvage chemotherapy, and other biologic agents. With advances in molecular profiling, clinicians will be able to stratify patients by their response to different therapies, thus, determine the most appropriate and effective treatment for each individual patient. We believe improved trial design and more effective agents may eventually improve the outcome in recurrent GBM patients.

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6. REFERENCES

1. P. Y. Wen and S. Kesari: Malignant gliomas in adults. *N Engl J Med*, 359(5), 492-507 (2008)

2. E. G. Van Meir, C. G. Hadjipanayis, A. D. Norden, H. K. Shu, P. Y. Wen and J. J. Olson: Exciting new advances in neuro-oncology: the avenue to a cure for malignant glioma. *CA Cancer J Clin*, 60(3), 166-93 (2010)

3. K. R. Lamborn, W. K. Yung, S. M. Chang, P. Y. Wen, T. F. Cloughesy, L. M. DeAngelis, H. I. Robins, F. S. Lieberman, H. A. Fine, K. L. Fink, L. Junck, L. Abrey, M. R. Gilbert, M. Mehta, J. G. Kuhn, K. D. Aldape, J. Hibberts, P. M. Peterson and M. D. Prados: Progression-free survival: an important end point in evaluating therapy for recurrent high-grade gliomas. *Neuro Oncol*, 10(2), 162-70 (2008)

4. R. Stupp, M. E. Hegi, W. P. Mason, M. J. van den Bent, M. J. Taphoorn, R. C. Janzer, S. K. Ludwin, A. Allgeier, B. Fisher, K. Belanger, P. Hau, A. A. Brandes, J. Gijtenbeek, C. Marosi, C. J. Vecht, K. Mokhtari, P. Wesseling, S. Villa, E. Eisenhauer, T. Gorlia, M. Weller, D. Lacombe, J. G. Cairncross and R. O. Mirimanoff: Effects of radiotherapy with concomitant and adjuvant temozolomide versus radiotherapy alone on survival in glioblastoma in a randomised phase III study: 5-year analysis of the EORTC-NCIC trial. *Lancet Oncol*, 10(5), 459-66 (2009)

5. P. Hau, D. Koch, T. Hundsberger, E. Marg, B. Bauer, R. Rudolph, M. Rauch, A. Brenner, P. Rieckmann, J. Schuth, T. Jauch, H. Koch and U. Bogdahn: Safety and feasibility of long-term temozolomide treatment in patients with high-grade glioma. *Neurology*, 68(9), 688-90 (2007)

6. H. Brem, S. Piantadosi, P. C. Burger, M. Walker, R. Selker, N. A. Vick, K. Black, M. Sisti, S. Brem, G. Mohr and et al.: Placebo-controlled trial of safety and efficacy of intraoperative controlled delivery by biodegradable polymers of chemotherapy for recurrent gliomas. The Polymer-brain Tumor Treatment Group. *Lancet*, 345(8956), 1008-12 (1995)

7. H. Kostron and R. Bauer: Management of recurrent malignant glioma--neurosurgical strategies. *Wien Med Wochenschr*, 161(1-2), 20-1 (2011)

8. J. L. Clarke, M. M. Ennis, W. K. Yung, S. M. Chang, P. Y. Wen, T. F. Cloughesy, L. M. Deangelis, H. I. Robins, F. S. Lieberman, H. A. Fine, L. Abrey, M. R. Gilbert, M. Mehta, J. G. Kuhn, K. D. Aldape, K. R. Lamborn and M. D. Prados: Is surgery at progression a prognostic marker for improved 6-month progression-free survival or overall survival for patients with recurrent glioblastoma? *Neuro Oncol*, 13(10), 1118-24 (2011)

9. E. S. Mandl, C. M. Dirven, D. R. Buis, T. J. Postma and W. P. Vandertop: Repeated surgery for glioblastoma multiforme: only in combination with other salvage therapy. *Surg Neurol*, 69(5), 506-9; discussion 509 (2008)

10. J. C. Easaw, W. P. Mason, J. Perry, N. Laperriere, D. D. Eisenstat, R. Del Maestro, K. Belanger, D. Fulton and D. Macdonald: Canadian recommendations for the treatment of recurrent or progressive glioblastoma multiforme. *Curr Oncol*, 18(3), e126-e136 (2011)

11. J. K. Park, T. Hodges, L. Arko, M. Shen, D. Dello Iacono, A. McNabb, N. Olsen Bailey, T. N. Kreisl, F. M. Iwamoto, J. Sul, S. Auh, G. E. Park, H. A. Fine and P. M.

Black: Scale to predict survival after surgery for recurrent glioblastoma multiforme. *J Clin Oncol*, 28(24), 3838-43 (2010)

12. N. A. Butowski, P. K. Sneed and S. M. Chang: Diagnosis and treatment of recurrent high-grade astrocytoma. *J Clin Oncol*, 24(8), 1273-80 (2006)

13. C. Nieder, S. T. Astner, M. P. Mehta, A. L. Grosu and M. Molls: Improvement, clinical course, and quality of life after palliative radiotherapy for recurrent glioblastoma. *Am J Clin Oncol*, 31(3), 300-5 (2008)

14. S. E. Combs, J. Debus and D. Schulz-Ertner: Radiotherapeutic alternatives for previously irradiated recurrent gliomas. *BMC Cancer*, 7, 167 (2007)

15. P. H. Gutin, F. M. Iwamoto, K. Beal, N. A. Mohile, S. Karimi, B. L. Hou, S. Lymberis, Y. Yamada, J. Chang and L. E. Abrey: Safety and efficacy of bevacizumab with hypofractionated stereotactic irradiation for recurrent malignant gliomas. *Int J Radiat Oncol Biol Phys*, 75(1), 156-63 (2009)

16. D. Kondziolka, L. D. Lunsford and J. C. Flickinger: The application of stereotactic radiosurgery to disorders of the brain. *Neurosurgery*, 62 Suppl 2, 707-19; discussion 719-20 (2008)

17. E. C. Nwokedi, S. J. DiBiase, S. Jabbour, J. Herman, P. Amin and L. S. Chin: Gamma knife stereotactic radiosurgery for patients with glioblastoma multiforme. *Neurosurgery*, 50(1), 41-6; discussion 46-7 (2002)

18. P. C. Hsieh, J. P. Chandler, S. Bhangoo, K. Panagiotopoulos, J. A. Kalapurakal, M. H. Marymont, J. W. Cozzens, R. M. Levy and S. Salehi: Adjuvant gamma knife stereotactic radiosurgery at the time of tumor progression potentially improves survival for patients with glioblastoma multiforme. *Neurosurgery*, 57(4), 684-92; discussion 684-92 (2005)

19. B. S. Skeie, P. O. Enger, J. Brogger, J. C. Ganz, F. Thorsen, J. I. Heggdal and P. H. Pedersen: Gamma Knife Surgery versus Reoperation for Recurrent Glioblastoma Multiforme. *World Neurosurg* (2012)

20. R. Stupp, W. P. Mason, M. J. van den Bent, M. Weller, B. Fisher, M. J. Taphoorn, K. Belanger, A. A. Brandes, C. Marosi, U. Bogdahn, J. Curschmann, R. C. Janzer, S. K. Ludwin, T. Gorlia, A. Allgeier, D. Lacombe, J. G. Cairncross, E. Eisenhauer and R. O. Mirimanoff: Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. *N Engl J Med*, 352(10), 987-96 (2005)

21. A. E. Pegg: Repair of O(6)-alkylguanine by alkyltransferases. *Mutat Res*, 462(2-3), 83-100 (2000)

22. M. E. Hegi, A. C. Diserens, T. Gorlia, M. F. Hamou, N. de Tribolet, M. Weller, J. M. Kros, J. A. Hainfellner, W. Mason, L. Mariani, J. E. Bromberg, P. Hau, R. O. Mirimanoff, J. G. Cairncross, R. C. Janzer and R. Stupp: MGMT gene silencing and benefit from temozolomide in glioblastoma. *N Engl J Med*, 352(10), 997-1003 (2005)

23. A. W. Tolcher, S. L. Gerson, L. Denis, C. Geyer, L. A. Hammond, A. Patnaik, A. D. Goetz, G. Schwartz, T. Edwards, L. Reyderman, P. Statkevich, D. L. Cutler and E. K. Rowinsky: Marked inactivation of O6-alkylguanine-DNA alkyltransferase activity with protracted temozolomide schedules. *Br J Cancer*, 88(7), 1004-11 (2003)

24. W. K. Yung, R. E. Albright, J. Olson, R. Fredericks, K. Fink, M. D. Prados, M. Brada, A. Spence, R. J. Hohl, W. Shapiro, M. Glantz, H. Greenberg, R. G. Selker, N. A. Vick, R. Rampling, H. Friedman, P. Phillips, J. Bruner, N. Yue, D. Osoba, S. Zaknoen and V. A. Levin: A phase II study of temozolomide vs. procarbazine in patients with glioblastoma multiforme at first relapse. *Br J Cancer*, 83(5), 588-93 (2000)

25. M. Brada, K. Hoang-Xuan, R. Rampling, P. Y. Dietrich, L. Y. Dirix, D. Macdonald, J. J. Heimans, B. A. Zonnenberg, J. M. Bravo-Marques, R. Henriksson, R. Stupp, N. Yue, J. Bruner, M. Dugan, S. Rao and S. Zaknoen: Multicenter phase II trial of temozolomide in patients with glioblastoma multiforme at first relapse. *Ann Oncol*, 12(2), 259-66 (2001)

26. A. A. Brandes, M. Ermani, U. Basso, P. Amista, F. Berti, R. Scienza, A. Rotilio, G. Pinna, M. Gardiman and S. Monfardini: Temozolomide as a second-line systemic regimen in recurrent high-grade glioma: a phase II study. *Ann Oncol*, 12(2), 255-7 (2001)

27. M. T. Harris, M. A. Rosenthal, D. L. Ashley and L. Cher: An Australian experience with temozolomide for the treatment of recurrent high grade gliomas. *J Clin Neurosci*, 8(4), 325-7 (2001)

28. A. A. Brandes, M. Ermani, U. Basso, M. K. Paris, F. Lumachi, F. Berti, P. Amista, M. Gardiman, P. Iuzzolino, S. Turazzi and S. Monfardini: Temozolomide in patients with glioblastoma at second relapse after first line nitrosourea-procarbazine failure: a phase II study. *Oncology*, 63(1), 38-41 (2002)

29. S. M. Chang, P. Theodosopoulos, K. Lamborn, M. Malec, J. Rabbitt, M. Page and M. D. Prados: Temozolomide in the treatment of recurrent malignant glioma. *Cancer*, 100(3), 605-11 (2004)

30. M. Hassler, M. Micksche, G. Stockhammer, J. Pichler, F. Payer, B. Abuja, R. Deinsberger and C. Marosi: Temozolomide for recurrent or progressive high-grade malignant glioma: results of an Austrian multicenter observational study. *Wien Klin Wochenschr*, 118(7-8), 230-8 (2006)

31. R. B. Khan, J. J. Raizer, M. G. Malkin, K. A. Bazylewicz and L. E. Abrey: A phase II study of extended low-dose temozolomide in recurrent malignant gliomas. *Neuro Oncol*, 4(1), 39-43 (2002)

32. W. Wick, J. P. Steinbach, W. M. Kuker, J. Dichgans, M. Bamberg and M. Weller: One week on/one week off: a novel active regimen of temozolomide for recurrent glioblastoma. *Neurology*, 62(11), 2113-5 (2004)

33. A. A. Brandes, A. Tosoni, G. Cavallo, R. Bertorelle, V. Gioia, E. Franceschi, M. Biscuola, V. Blatt, L. Crino and M. Ermani: Temozolomide 3 weeks on and 1 week off as first-line therapy for recurrent glioblastoma: phase II study from gruppo italiano cooperativo di neuro-oncologia (GICNO). *Br J Cancer*, 95(9), 1155-60 (2006)

34. M. Caroli, M. Locatelli, R. Campanella, F. Motta, A. Mora, F. Prada, S. Borsa, F. Martinelli-Boneschi, A. Saladino and S. M. Gaini: Temozolomide in glioblastoma: results of administration at first relapse and in newly diagnosed cases. Is still proposable an alternative schedule to concomitant protocol? *J Neurooncol*, 84(1), 71-7 (2007)

35. A. Wick, J. Felsberg, J. P. Steinbach, U. Herrlinger, M. Platten, B. Blaschke, R. Meyermann, G. Reifenberger, M. Weller and W. Wick: Efficacy and tolerability of temozolomide in an alternating weekly regimen in patients with recurrent glioma. *J Clin Oncol*, 25(22), 3357-61 (2007)

36. C. Balmaceda, D. Peereboom, S. Pannullo, Y. K. Cheung, P. G. Fisher, J. Alavi, M. Sisti, J. Chen and R. L. Fine: Multi-institutional phase II study of temozolomide administered twice daily in the treatment of recurrent high-grade gliomas. *Cancer*, 112(5), 1139-46 (2008)

37. D. S. Kong, J. I. Lee, J. H. Kim, S. T. Kim, W. S. Kim, Y. L. Suh, S. M. Dong and D. H. Nam: Phase II trial of low-dose continuous (metronomic) treatment of temozolomide for recurrent glioblastoma. *Neuro Oncol*, 12(3), 289-96 (2010)

38. J. R. Perry, K. Belanger, W. P. Mason, D. Fulton, P. Kavan, J. Easaw, C. Shields, S. Kirby, D. R. Macdonald, D. D. Eisenstat, B. Thiessen, P. Forsyth and J. F. Pouliot: Phase II trial of continuous dose-intense temozolomide in recurrent malignant glioma: RESCUE study. *J Clin Oncol*, 28(12), 2051-7 (2010)

39. C. Chen, T. Xu, Y. Lu, J. Chen and S. Wu: The efficacy of temozolomide for recurrent glioblastoma multiforme. *Eur J Neurol* (2012)

40. A. De Rossi, L. Rossi, A. Laudisi, V. Sini, L. Toppo, F. Marchesi, G. Tortorelli, M. Leti, M. Turriziani, A. Aquino, E. Bonmassar, L. De Vecchis and F. Torino: Focus on Fotemustine. *J Exp Clin Cancer Res*, 25(4), 461-8 (2006)

41. A. Meulemans, B. Giroux, P. Hannoun, D. Henzel, J. P. Bizzari and J. Mohler: Permeability of two nitrosoureas, carmustine and fotemustine in rat cortex. *Chemotherapy*, 35(5), 313-9 (1989)

42. A. Meulemans, B. Giroux, P. Hannoun, D. Robine and D. Henzel: Comparative diffusion study of two nitrosoureas: carmustine and fotemustine in normal rat brain, human and rat brain biopsies. *Chemotherapy*, 37(2), 86-92 (1991)

43. A. Silvani, P. Gaviani, E. Lamperti, A. Botturi, D. Ferrari, G. Simonetti and A. Salmaggi: Lecture: fotemustine in brain tumors. *Neurol Sci*, 32 Suppl 2, S255-7 (2011)

44. A. A. Brandes, A. Tosoni, E. Franceschi, V. Blatt, A. Santoro, M. Faedi, P. Amista, M. Gardiman, R. Labianca, C. Bianchini, M. Ermani and M. Reni: Fotemustine as second-line treatment for recurrent or progressive glioblastoma after concomitant and/or adjuvant temozolomide: a phase II trial of Gruppo Italiano Cooperativo di Neuro-Oncologia (GICNO). *Cancer Chemother Pharmacol*, 64(4), 769-75 (2009)

45. M. G. Fabrini, G. Silvano, I. Lolli, F. Perrone, A. Marsella, V. Scotti and L. Cionini: A multi-institutional phase II study on second-line Fotemustine chemotherapy in recurrent glioblastoma. *J Neurooncol*, 92(1), 79-86 (2009)

46. N. Schafer, J. Tichy, S. Thanendrarajan, Y. Kim, M. Stuplich, F. Mack, J. Rieger, M. Simon, B. Scheffler, J. Bostrom, J. P. Steinbach, U. Herrlinger and M. Glas: Ifosfamide, carboplatin and etoposide in recurrent malignant glioma. *Oncology*, 80(5-6), 330-2 (2011)

47. M. Brada, S. Stenning, R. Gabe, L. C. Thompson, D. Levy, R. Rampling, S. Erridge, F. Saran, R. Gattamaneni, K. Hopkins, S. Beall, V. P. Collins and S. M. Lee: Temozolomide versus procarbazine, lomustine, and vincristine in recurrent high-grade glioma. *J Clin Oncol*, 28(30), 4601-8 (2010)

48. L. J. Murray, C. H. Bridgewater and D. Levy: Carboplatin chemotherapy in patients with recurrent high-grade glioma. *Clin Oncol (R Coll Radiol)*, 23(1), 55-61 (2011)

49. T. F. Cloughesy, M. D. Prados, P. Y. Wen, T. Mikkelsen, L. E. Abrey, D. Schiff, W. K. Yung, Z. Maoxia, I. Dimery and H. S. Friedman: A phase II, randomized, non-comparative clinical trial of the effect of bevacizumab alone or in combination with irinotecan on 6-month progression free survival in recurrent, treatment-refractory glioblastoma. *J Clin Oncol*, 26(suppl), abstr 2010b (2008)

50. T. Xu, J. Chen, Y. Lu and J. E. Wolff: Effects of bevacizumab plus irinotecan on response and survival in patients with recurrent malignant glioma: a systematic review and survival-gain analysis. *BMC Cancer*, 10, 252 (2010)

51. A. Lai, E. Filka, B. McGibbon, P. L. Nghiemphu, C. Graham, W. H. Yong, P. Mischel, L. M. Liau, M. Bergsneider, W. Pope, M. Selch and T. Cloughesy: Phase II pilot study of bevacizumab in combination with temozolomide and regional radiation therapy for up-front treatment of patients with newly diagnosed glioblastoma multiforme: interim analysis of safety and tolerability. *Int J Radiat Oncol Biol Phys*, 71(5), 1372-80 (2008)

52. A. J. Schueneman, E. Himmelfarb, L. Geng, J. Tan, E. Donnelly, D. Mendel, G. McMahon and D. E. Hallahan: SU11248 maintenance therapy prevents tumor regrowth after fractionated irradiation of murine tumor models. *Cancer Res*, 63(14), 4009-16 (2003)

53. V. Damiano, D. Melisi, C. Bianco, D. Raben, R. Caputo, G. Fontanini, R. Bianco, A. Ryan, A. R. Bianco, S. De Placido, F. Ciardiello and G. Tortora: Cooperative antitumor effect of multitargeted kinase inhibitor ZD6474 and ionizing radiation in glioblastoma. *Clin Cancer Res*, 11(15), 5639-44 (2005)

54. J. N. Rich, S. Sathornsumetee, S. T. Keir, M. W. Kieran, A. Laforme, A. Kaipainen, R. E. McLendon, M. W. Graner, B. K. Rasheed, L. Wang, D. A. Reardon, A. J. Ryan, C. Wheeler, I. Dimery, D. D. Bigner and H. S. Friedman: ZD6474, a novel tyrosine kinase inhibitor of vascular endothelial growth factor receptor and epidermal growth factor receptor, inhibits tumor growth of multiple nervous system tumors. *Clin Cancer Res*, 11(22), 8145-57 (2005)

55. S. de Bouard, P. Herlin, J. G. Christensen, E. Lemoisson, P. Gauduchon, E. Raymond and J. S. Guillamo: Antiangiogenic and anti-invasive effects of sunitinib on experimental human glioblastoma. *Neuro Oncol*, 9(4), 412-23 (2007)

56. F. Hilberg, G. J. Roth, M. Krssak, S. Kautschitsch, W. Sommergruber, U. Tontsch-Grunt, P. Garin-Chesa, G. Bader, A. Zoephel, J. Quant, A. Heckel and W. J. Rettig: BIBF 1120: triple angiokinase inhibitor with sustained receptor blockade and good antitumor efficacy. *Cancer Res*, 68(12), 4774-82 (2008)

57. Q. Zhou, P. Guo and J. M. Gallo: Impact of angiogenesis inhibition by sunitinib on tumor distribution of temozolomide. *Clin Cancer Res*, 14(5), 1540-9 (2008)

58. C. G. Slatore, J. W. Chien, D. H. Au, J. A. Satia and E. White: Lung cancer and hormone replacement therapy: association in the vitamins and lifestyle study. *J Clin Oncol*, 28(9), 1540-6 (2010)

59. F. Yang, C. Brown, R. Buettner, M. Hedvat, R. Starr, A. Scuto, A. Schroeder, M. Jensen and R. Jove: Sorafenib induces growth arrest and apoptosis of human glioblastoma cells through the dephosphorylation of signal transducers and activators of transcription 3. *Mol Cancer Ther*, 9(4), 953-62 (2010)

60. J. J. Yiin, B. Hu, P. A. Schornack, R. S. Sengar, K. W. Liu, H. Feng, F. S. Lieberman, S. H. Chiou, J. N. Sarkaria, E. C. Wiener, H. I. Ma and S. Y. Cheng: ZD6474, a multitargeted inhibitor for receptor tyrosine kinases, suppresses growth of gliomas expressing an epidermal growth factor receptor mutant, EGFRvIII, in the brain. *Mol Cancer Ther*, 9(4), 929-41 (2010)

61. Y. Zhang, F. Guessous, A. Kofman, D. Schiff and R. Abounader: XL-184, a MET, VEGFR-2 and RET kinase inhibitor for the treatment of thyroid cancer, glioblastoma multiforme and NSCLC. *IDrugs*, 13(2), 112-21 (2010)

62. A. A. Brandes, R. Stupp, P. Hau, D. Lacombe, T. Gorlia, A. Tosoni, R. O. Mirimanoff, J. M. Kros and M. J. van den Bent: EORTC study 26041-22041: phase I/II study on concomitant and adjuvant temozolomide (TMZ) and radiotherapy (RT) with PTK787/ZK222584 (PTK/ZK) in newly diagnosed glioblastoma. *Eur J Cancer*, 46(2), 348-54 (2010)

63. F. M. Iwamoto, K. R. Lamborn, H. I. Robins, M. P. Mehta, S. M. Chang, N. A. Butowski, L. M. Deangelis, L. E. Abrey, W. T. Zhang, M. D. Prados and H. A. Fine: Phase II trial of pazopanib (GW786034), an oral multi-targeted angiogenesis inhibitor, for adults with recurrent glioblastoma (North American Brain Tumor Consortium Study 06-02). *Neuro Oncol*, 12(8), 855-61 (2010)

64. B. Neyns, J. Sadones, C. Chaskis, M. Dujardin, H. Everaert, S. Lv, J. Duerinck, O. Tynninen, N. Nupponen, A. Michotte and J. De Greve: Phase II study of sunitinib malate in patients with recurrent high-grade glioma. *J Neurooncol*, 103(3), 491-501 (2011)

65. T. Batchelor, P. Mulholland, B. Neyns, L. B. Nabors, M. Campone, A. Wick, W. Mason, J. Xu, Q. Liu and M. J. van den Bent: A phase III randomized study comparing the effcacy of cediranib as monotherapy, and in combination with lomustine, with lomustine alone in recurrent glioblastoma patients. *Ann Oncol*, 21(Suppl 8), Abstract LBA7 (2010)

66. D. A. Reardon, S. Turner, K. B. Peters, A. Desjardins, S. Gururangan, J. H. Sampson, R. E. McLendon, J. E. Herndon, 2nd, L. W. Jones, J. P. Kirkpatrick, A. H. Friedman, J. J. Vredenburgh, D. D. Bigner and H. S. Friedman: A review of VEGF/VEGFR-targeted therapeutics for recurrent glioblastoma. *J Natl Compr Canc Netw*, 9(4), 414-27 (2011)

67. A. A. Brandes, E. Franceschi, T. Gorlia, W. Wick, A. H. Jacobs, B. G. Baumert, M. van den Bent, M. Weller and R. Stupp: Appropriate end-points for right results in the age of antiangiogenic agents: future options for phase II trials in patients with recurrent glioblastoma. *Eur J Cancer*, 48(6), 896-903 (2012)

68. P. Y. Wen, D. R. Macdonald, D. A. Reardon, T. F. Cloughesy, A. G. Sorensen, E. Galanis, J. Degroot, W. Wick, M. R. Gilbert, A. B. Lassman, C. Tsien, T. Mikkelsen, E. T. Wong, M. C. Chamberlain, R. Stupp, K. R. Lamborn, M. A. Vogelbaum, M. J. van den Bent and S. M. Chang: Updated response assessment criteria for high-grade gliomas: response assessment in neuro-oncology working group. *J Clin Oncol*, 28(11), 1963-72 (2010)

69. J. Schwarzenberg, J. Czernin, T. F. Cloughesy, B. M. Ellingson, W. B. Pope, C. Geist, M. Dahlbom, D. H. Silverman, N. Satyamurthy, M. E. Phelps and W. Chen: 3'-deoxy-3'-18F-fluorothymidine PET and MRI for early survival predictions in patients with recurrent malignant

glioma treated with bevacizumab. *J Nucl Med,* 53(1), 29-36 (2012)

70. M. Hutterer, M. Nowosielski, D. Putzer, D. Waitz, G. Tinkhauser, H. Kostron, A. Muigg, I. J. Virgolini, W. Staffen, E. Trinka, T. Gotwald, A. H. Jacobs and G. Stockhammer: O-(2-18F-fluoroethyl)-L-tyrosine PET predicts failure of antiangiogenic treatment in patients with recurrent high-grade glioma. *J Nucl Med,* 52(6), 856-64 (2011)

71. H. Okada, P. Kalinski, R. Ueda, A. Hoji, G. Kohanbash, T. E. Donegan, A. H. Mintz, J. A. Engh, D. L. Bartlett, C. K. Brown, H. Zeh, M. P. Holtzman, T. A. Reinhart, T. L. Whiteside, L. H. Butterfield, R. L. Hamilton, D. M. Potter, I. F. Pollack, A. M. Salazar and F. S. Lieberman: Induction of CD8+ T-cell responses against novel glioma-associated antigen peptides and clinical activity by vaccinations with {alpha}-type 1 polarized dendritic cells and polyinosinic-polycytidylic acid stabilized by lysine and carboxymethylcellulose in patients with recurrent malignant glioma. *J Clin Oncol,* 29(3), 330-6 (2011)

72. K. Iwami, S. Shimato, M. Ohno, H. Okada, N. Nakahara, Y. Sato, J. Yoshida, S. Suzuki, H. Nishikawa, H. Shiku, A. Natsume and T. Wakabayashi: Peptide-pulsed dendritic cell vaccination targeting interleukin-13 receptor alpha2 chain in recurrent malignant glioma patients with HLA-A*24/A*02 allele. *Cytotherapy,* 14(6), 733-42 (2012)

73. S. Izumoto, A. Tsuboi, Y. Oka, T. Suzuki, T. Hashiba, N. Kagawa, N. Hashimoto, M. Maruno, O. A. Elisseeva, T. Shirakata, M. Kawakami, Y. Oji, S. Nishida, S. Ohno, I. Kawase, J. Hatazawa, S. Nakatsuka, K. Aozasa, S. Morita, J. Sakamoto, H. Sugiyama and T. Yoshimine: Phase II clinical trial of Wilms tumor 1 peptide vaccination for patients with recurrent glioblastoma multiforme. *J Neurosurg,* 108(5), 963-71 (2008)

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Send correspondence to: Juxiang Chen. Department of Neurosurgery, Changzheng Hospital, Second Military Medical University, No. 415 Fengyang Road, Shanghai, China, 200003, Tel: 86-21-81885677, Fax: 86-21-63520020, E-mail: juxiangchen@yeah.net