Concurrent therapy to enhance radiotherapeutic outcomes in glioblastoma

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Abstract: Glioblastoma is one of the most fatal and incurable human cancers characterized by nuclear atypia, mitotic activity, intense microvascular proliferation and necrosis. The current standard of care includes maximal safe surgical resection followed by radiation therapy (RT) with concurrent and adjuvant temozolomide (TMZ). The prognosis remains poor with median survival of 14.6 months with RT plus TMZ. Majority will have a recurrence within 2 years from diagnosis despite adequate treatment. Radiosensitizers, radiotherapy dose escalation and altered fractionation have failed to improve outcome. The molecular biology of glioblastoma is complex and poses treatment challenges. High rate of mutation, genotypic and phenotypic heterogeneity, rapid development of resistance, existence of blood-brain barrier (BBB), multiple intracellular and intercellular signalling pathways, over-expression of growth factor receptors, angiogenesis and antigenic diversity renders the tumor cells differentially susceptible to various treatment modalities. Thus, the treatment strategies require personalised or individualized approach based on the characteristics of tumor. Several targeted agents have been evaluated in clinical trials but the results have been modest despite these advancements. This review summarizes the current standard of care, results of concurrent chemoradiation trials, evolving innovative treatments that use targeted therapy with standard chemoradiation or RT alone, outcome of various recent trials and future outlook.

Keywords: Chemoradiation; chemotherapy; concurrent; glioblastoma; radiation therapy (RT); temozolomide (TMZ)

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Introduction

Glioblastoma is the most common and most aggressive primary malignant brain tumor. It is classified as World Health Organization (WHO) grade IV glioma. WHO grade is a combination of criteria used to predict biological behaviour of tumor, response to therapy, outcome and prognosis. The WHO classification of brain tumors integrates nomenclature with grading system, thus correlating histological diagnosis to histological grade of the tumor (1). It is characterized histologically by nuclear atypia, mitotic activity, vascular proliferation, and necrosis. Because of the pleomorphic nature of cells, glioblastomas were called glioblastoma multiforme, a term which is no longer used. Glioblastoma accounts for 15.4% of all primary brain tumors and 45.6% of primary malignant brain tumors (2). It comprises of approximately 75% of all high-grade gliomas (3) with an annual incidence of 3.19 per 100,000 in the United States (2). The incidence of glioblastoma increases with age, with highest in 75 to 84 years of age and drops after 85 years (2).

Glioblastoma is one of the deadliest neoplasms, which has a median survival of 3 months if left untreated (4). The current standard of care for management of glioblastoma is multimodal approach comprising of maximal safe surgical resection, post-operative radiation therapy (RT), and concurrent and adjuvant temozolomide (TMZ). The median survival is only 14.6 months despite aggressive treatment with 2-year overall survival (OS) of 27% and only less than 5% surviving beyond 5 years (5-7). Patients who survived more than 2 years from diagnosis have a relatively

favourable conditional probability of survival into the future compared with newly diagnosed patients (8).

The prognosis of glioblastoma has traditionally been dismal. It is one of the most fatal types of cancer and is characterized by heterogeneity at the cellular, molecular, biological and genetic levels. Glioblastomas are characterized by extensive infiltration into the brain parenchyma, marked angiogenesis, intrinsic resistance to apoptosis and genomic instability (9). Due to diverse array of tumor cells and significant heterogeneity at the pathological, transcriptional and genomic levels, these tumors exhibit resistance to the available treatment modalities. Even with the best available treatment, survival rate is poor in glioblastoma. Eventually all patients of glioblastoma recur despite adequate treatment. A variety of treatments have been explored with limited success and single best treatment approach for all has not yet been established which could prolong the patient survival beyond the current level. Rational therapeutic approaches should be designed to combine targeted therapy in novel ways to target multiple targets synergistically which can inhibit growth factors, tumor proliferation, angiogenesis, and invasion and activate apoptosis. This article reviews the available treatment modalities, summarizes the results of important clinical trials, overview of newer innovative treatments which include signal transduction-modulating agents given in combination with chemoradiation or RT alone.

Radiation

Surgery is one of the most important and critical component in management of glioblastomas. It establishes histological diagnosis, provides symptomatic relief of mass effect, results in recovery of neurological function depending on location of tumor, reduces the number of tumor cells to facilitate the effect of adjuvant therapy, provides tissue material for molecular analysis and aids in identification of molecular targets for development of novel therapies. With surgical resection alone, median survival is approximately 6 months. Randomized clinical trials have demonstrated survival advantage with use of adjuvant whole brain radiotherapy (WBRT).

Involved field radiotherapy (IFRT) has become the standard of care for adjuvant RT in glioblastomas. Hochberg *et al.* (10) reported that glioblastoma recurred within a 2-cm margin of the primary site in 90% and multicentricity occurred in only 4% of untreated and 6% of treated (RT with or without chemotherapy) patients. In a study by Ramsey and Brand (11), significant increase in OS and tumor-free period was found in the limited field treatment group (median dose 53 Gy) as compared to WBRT group (median dose 44 Gy). In the Brain Tumor Cooperative Group trial (BTCG 80-01), patients with glioblastoma who received WBRT of 6,020 cGy or WBRT 4,300 cGy followed by IFRT to 1,720 cGy, survival differences between the radiotherapy groups were not significantly different (12).

There are two schools of thought for IFRT in glioblastoma. The RT Oncology Group (RTOG) favours a two-step cone down technique, with an initial phase clinical target volume (CTV1) including the entire T2-high signal intensity (T2/FLAIR hyperintensity; comprising of peritumoral edema and enhancing lesion) plus 2 cm margin and the initial planning target volume (PTV1) is an additional margin of 3–5 mm, for dose of 46 Gy in 23 fractions, followed by a boost field (CTV2) defined as the T1-enhancement and the surgical cavity plus 2 cm and PTV2 with an additional margin of 3–5 mm for dose of 14 Gy in 7 fractions. The European Organisation of Research and Treatment of Cancer (EORTC) recommend a single-phase technique in which GTV is defined as the T1 contrast enhancement region or the surgical tumor bed plus any residual enhancing tumor that is seen on the planning scan. Co-registration of pre- and postoperative MRI/CT is strongly encouraged. The CTV includes GTV with a margin of 2–3 cm, which can be modified in anatomic regions such as bony structures and adjacent normal meninges. The PTV margin to CTV is 0.5–0.7 cm to ensure adequate CTV coverage. A total dose of 60 Gy in 30 fractions is usually delivered.

Optimal radiotherapy dose for glioblastomas is 60 Gy in 30 fractions in 6 weeks. Dose escalation studies have failed to show any survival benefit (13,14). Combined, surgical resection and RT increases the median survival to 12.1 months (6).

Chemoradiation

Several challenges are associated with the management of glioblastoma. These tumors are inherently resistant to chemotherapeutic drugs. The mechanisms accounting for refractoriness to chemotherapy are inherent invasiveness of tumor cells, existence of a blood-brain barrier (BBB), interaction between anti-convulsant drugs and chemotherapy, genotypic and phenotypic heterogeneity, genetic mutations, existence of multiple signalling pathways, high angiogenicity, dysregulation of apoptosis-regulating

genes and proteins, *epidermal growth factor receptor (EGFR)* gene amplification or the EGFR vIII mutation, methylation of the O6-methylguanine-DNA methyltransferase (MGMT) and base excision repair pathway (15-17). Prior to the advent of TMZ, alkylating agents such as carmustine (BCNU), lomustine (CCNU) and procarbazine were used which readily cross the BBB because of their lipid solubility property. Despite the ability of these drugs to cross the BBB, glioblastomas are resistant to alkylating agents. The prolonged use of nitrosoureas is associated with myelotoxicity which is cumulative and dose-related risk of pulmonary fibrosis. In a meta-analysis of 16 randomized clinical trials involving more than 3,000 patients (18), the survival rates of patients who received RT alone or RT with chemotherapy were compared. The estimated increase in survival for patients treated with combination of RT and chemotherapy was 10.1% at 1 year and 8.6% at 2 years. The limitations of the study were heterogeneity, inclusion of other glioma types and different chemotherapeutic agents used. In a meta-analysis comprising of 3,004 patients from 12 randomised controlled trials by Stewart (19), the results showed 15% relative decrease in the risk of death or an absolute increase in 1-year survival of 6% from 40% to 46% and a 2-month increase in median survival time. There was no evidence that the effect of chemotherapy differed in any group of patients by age, sex, histology, performance status, or extent of resection.

Several studies have evaluated the role of chemotherapy given concurrently with external beam radiotherapy in glioblastoma. Cisplatin and carboplatin have been used as either single agents or in combination regimens along with radiotherapy (20,21). Response rates have been modest and their impact on survival is unclear. Topoisomerase I and topoisomerase II inhibitors were found to have only modest activity (22,23). Taxanes, such as paclitaxel, have not demonstrated any activity as single agents (24). The various phase II studies did not exhibit any improvement in survival. It was in 2002 when a phase II study by Stupp *et al.* (25) demonstrated an improvement in survival which redefined the role of chemotherapy in glioblastomas. Sixty-four patients were administered TMZ (75 mg/m^2 per day for 7 days per week for 6 weeks from first to last day of radiotherapy) orally concomitant with fractionated radiotherapy (60 Gy/30 fractions in 6 weeks) followed by TMZ monotherapy (200 mg/m^2 per day for 5 days, every 28 days for six cycles). Median survival was 16 months. The 1- and 2-year survival rates were 58% and 31%, respectively. These promising findings led way to large multi-institutional phase III cooperative group trial by Stupp *et al.* (6) conducted by the EORTC Brain and Radiotherapy Groups and National Cancer Institute of Canada Clinical Trials Group. In this trial, patients with newly diagnosed glioblastoma were randomly assigned to receive focal RT alone (fractionated focal irradiation for a total of 60 Gy in 30 fractions over 6 weeks) or RT plus concomitant TMZ (75 mg/m^2, 7 days per week from the first to the last day of radiotherapy), followed by six cycles of adjuvant TMZ (150–200 mg/m^2 for 5 days every 28-day). At a median follow-up of 28 months, the median survival was 14.6 months with RT plus TMZ and 12.1 months with RT alone (2.5 months benefit with RT plus TMZ). The 2-year survival rate was 26.5% with RT plus TMZ and 10.4% with RT alone. Grade 3 or 4 hematologic toxicity was seen in 7% of the patients with concomitant treatment with RT plus TMZ. Fourteen percent of the patients developed grade 3 or 4 hematologic toxicity during the adjuvant phase. The most common non-hematologic toxicity was moderate-to-severe fatigue in 26% of patients in the RT group and 33% in the RT plus TMZ group. This was the first phase III study which provided level 1 evidence of benefit of systemic chemotherapy in glioblastoma. TMZ was approved in 2005 after publication of this large trial. The long-term results and 5-year analysis were published in 2009 by Stupp *et al.* (26). Of 286 patients treated with radiotherapy alone, 97% [278] died and of 287 in the combined-treatment group, 89% [254] died during 5 years of follow-up. OS rates at 2, 3, 4 and 5 years were 27.2%, 16.0%, 12.1% and 9.8%, with combined treatment group, *vs.* 10.9%, 4.4%, 3.0% and 1.9% with radiotherapy alone (P<0.0001). The benefit of combined treatment was observed in all clinical prognostic subgroups and seems to last long into follow-up and reaches statistical significance even in patients with poor prognosis (age >60 years, class V). Methylation of the MGMT promoter was the strongest predictor for outcome and benefit from TMZ chemotherapy. Hence, the standard treatment for newly diagnosed glioblastoma is maximal surgical resection followed by concomitant radiotherapy and chemotherapy with TMZ followed by adjuvant TMZ. However, the contribution of adjuvant TMZ and optimal treatment duration needs to be defined. TMZ is usually well tolerated. Due to continued daily use of TMZ, there is risk of lymphocytopenia and subsequent opportunistic infection. Prophylaxis against Pneumocystis carinii pneumonia with oral trimethoprim-sulfamethoxazole or either inhaled pentamidine during concomitant treatment with radiotherapy and TMZ is required.

Hegi *et al.* (27) investigated the relationship between MGMT silencing in the tumor and the survival of patients who were enrolled in a randomized trial of chemoradiotherapy (TMZ plus RT) *vs.* RT alone (carried out by the EORTC and the National Cancer Institute of Canada). Irrespective of treatment assignment, MGMT promoter methylation was an independent favourable prognostic factor. The median OS among patients with methylation was 18.2 months as compared with 12.2 months among those without methylation. A survival benefit was observed in patients treated with TMZ and RT whose tumor contained a methylated MGMT promoter; their median survival was 21.7 months as compared with 15.3 months among those who were treated with only RT (P=0.007). The difference in OS was not statistically significant between the treatment groups in the absence of methylation of the MGMT promoter (median survival 12.7 months with TMZ and RT and 11.8 months with RT alone, P=0.06).

Glioblastoma exhibits the highest degree of vascular proliferation among human tumors and vascular endothelial growth factor (VEGF) is a key growth factor in regulating angiogenesis which is a crucial step in the development and progression (28,29). VEGF consists of a family of 5 glycoproteins named VEGF-A, VEGF-B, VEGF-C, VEGF-D, and placental growth factor. Bevacizumab (humanized monoclonal antibody against VEGF) blocks the binding of VEGF to its receptor on the surface of endothelial cells and prevents the migration and proliferation of endothelial cells, thereby decreasing tumor vascularisation and vasogenic brain edema resulting in hypoxia and cell death (30,31). Trials on recurrent glioblastoma have shown that bevacizumab alone is able to increase response rate on MRI, median and 6-month progression-free survival (PFS), and a reduction of corticosteroid usage (32-34). In the phase II BRAIN study, the median OS was 9.2 months in the group treated with bevacizumab alone and 8.7 months in the group treated with the bevacizumab in combination with irinotecan (33). The updated results reported a median OS of 8.9 months with the combination of bevacizumab plus irinotecan and 9.3 months with bevacizumab alone (35). The US Food and Drug Administration accelerated approval for bevacizumab in patients with recurrent glioblastoma in May 2009 was based on 2 phase II trials (33,34). None of the drug combination was superior over bevacizumab alone (erlotinib, etoposide, TMZ, cetuximab, carboplatin) (36-40).

Two multicentric, phase III, randomized, double-blind, placebo-controlled trials of bevacizumab in patients with newly diagnosed glioblastoma have recently been published: RTOG 0825 (NCT00884741) (41) and AVAglio (NCT00943826) (42). In both the studies, patients were randomly assigned to receive standard treatment (based on concurrent RT and TMZ) in combination with placebo or bevacizumab. The co-primary end points in both the trials were PFS and OS. The threshold for statistical significance was set at a two-sided P value of 0.046 for OS and 0.004 for PFS. The results of both the trials in terms of PFS and OS were comparable. Bevacizumab did not improve OS in either trial; however, it prolonged median PFS in both the trials but it did not reach the prespecified improvement target in RTOG trial. The median PFS in AVAglio trial was 10.6 in the bevacizumab group *vs.* 6.2 months in the placebo group (P<0.001) and in RTOG 0825 was 10.7 *vs.* 7.3 months, (P=0.007). In RTOG trial, patients receiving bevacizumab, as compared with placebo, had greater neurocognitive decline, increased symptom severity, and decline in health-related quality of life (HRQoL). On the contrary, in the AVAglio study, baseline HRQoL and performance status were maintained longer in the bevacizumab group. The secondary objective of AVAglio trial was to compare HRQoL between treatment arms in order to ensure that addition of bevacizumab to standard-of-care therapy was not associated with HRQoL detriment (43). HRQoL declined at progression in both arms. Patients in the bevacizumab arm experienced an extended deterioration free survival across all items, during which they reported maintained stable HRQoL and high levels of functioning. Retrospective analysis of AVAglio data suggests that patients with IDH1 wild-type proneural glioblastoma may derive an OS benefit from first-line bevacizumab treatment (17.1 *vs.* 12.8 months, respectively; P=0.002) (44).

The GLARIUS trial investigated the efficacy of bevacizumab plus irinotecan in comparison to standard TMZ in the first-line therapy of patients with newly diagnosed, MGMT-non-methylated glioblastoma (45). Patients received local radiotherapy and were randomized in 2:1 for experimental therapy with bevacizumab (10 mg/kg q2w) during RT followed by maintenance BEV (10 mg/kg q2w) plus irinotecan (125 mg/m^2 q2w) or standard therapy with daily TMZ (75 mg/m^2) during RT followed by 6 courses of TMZ (150–200 mg/m^2/day for 5 days q4w). PFS was significantly prolonged from a median of 5.9 to 9.7 months with bevacizumab and irinotecan combination (P<0.0001). There was no significant difference in OS between the two arms: median OS was 16.6 months in the bevacizumab/irinotecan arm and 17.3 months in the standard treatment

arm. The authors concluded that bevacizumab/irinotecan therapy was superior to TMZ in terms of PFS but OS was not improved. Bevacizumab/irinotecan therapy did not alter QoL as compared to TMZ therapy. A randomized, open-label, phase II trial (ARTE trial) is exploring the efficacy of bevacizumab combined with radiotherapy compared with radiotherapy alone in the treatment of newly diagnosed glioblastoma in the elderly (≥65 years).

EGFR is over-expressed in approximately 50% of patients with glioblastoma, and of those nearly 50% harbour the specific EGFRvIII mutant. Clinical trials evaluating the efficacy of EGFR inhibitors in glioblastomas have shown disappointing results. In a phase I/II study by RTOG 0211 (46), gefitinib, (EGFR tyrosine kinase inhibitor) was given in combination with RT for newly diagnosed glioblastoma patients. Median survival of RTOG 0211 patients treated with RT with concurrent and adjuvant gefitinib was similar to that in a historical control cohort treated with RT alone. The maximum tolerated dose (MTD) of gefitinib was 500 mg in patients on non-enzyme-inducing anticonvulsant drugs (non-EIAEDs). A phase II study assessing the safety and efficacy of erlotinib with RT and TMZ in newly diagnosed patients with glioblastoma was terminated after accrual of 27 of 30 planned patients. There were four deaths out of which three were treatment-related. Erlotinib administered with RT and TMZ had an unacceptable toxicity (47). Another phase II trial of erlotinib with RT and TMZ demonstrated better survival than historical controls (19.3 *vs.* 14.1 months) (48).

Vandetanib is a tyrosine kinase inhibitor of VEGFR, EGFR, and RET. Lee *et al.* (49) conducted a randomized, noncomparative, phase II study of RT and TMZ with or without vandetanib in patients with newly diagnosed glioblastoma. A total of 114 patients were randomized in 2:1 to standard RT and TMZ with (76 patients) or without (38 patients) vandetanib 100 mg daily. The study was terminated early based on the results of an interim analysis which failed to show OS benefit.

Cilengitide is an anti-angiogenic small molecule targeting the integrins αvβ3, αvβ5 and α5β1. These integrins mediate communication between glioblastoma cells and the brain microenvironment and are over-expressed on tumor cells and vasculature. These are involved in angiogenesis, cellular survival, proliferation, migration, and invasion. In the multicentre, open-label, phase III CENTRIC EORTC 26071-22072 study (50), Stupp *et al.* investigated the efficacy of cilengitide in patients with newly diagnosed glioblastoma with methylated MGMT promoter. Patients were randomised in a 1:1 ratio to TMZ chemoradiotherapy with cilengitide 2,000 mg intravenously twice weekly (cilengitide group) or TMZ chemoradiotherapy alone (control group). Adjuvant TMZ was given for six cycles, and cilengitide was given for up to 18 months or until disease progression or unacceptable toxic effects. Median OS was similar in the two groups (26.3 months in the cilengitide group and 26.3 months in the control group) irrespective of stratification factors. The addition of cilengitide to temozolomide chemoradiotherapy did not yield any improvement in outcome and its development as an anticancer drug has been terminated.

Results of the phase II, randomized, open-label, multicentre CORE trial (51) evaluating the efficacy and safety of 2 dose regimens of cilengitide (standard and intensive) combined with standard chemoradiotherapy in patients with newly diagnosed glioblastoma with an unmethylated MGMT promoter have been published. Inconsistent OS and PFS results between the cilengitide arms of this phase II study and a relatively small sample size did not allow firm conclusions regarding clinical efficacy in this exploratory phase II study.

Radiosensitizers

The results have been disappointing in most of the studies using radiosensitizers with RT in glioblastoma. EORTC trial (52) investigated the addition of carbogen, nicotinamide, or both to accelerated RT to overcome the effects of proliferation and hypoxia as potential causes of tumor radioresistance in glioblastoma. The incidence and severity of acute skin and mucous membrane toxicity were higher in patients who received nicotinamide. OS was similar in three groups and was comparable to results of other series that used RT alone.

Brachman *et al.* (53) recently published the final results of RTOG 0513. The aim of phase I was to establish the MTD of motexafin gadolinium (MGd) given concurrently with TMZ and RT in patients with newly diagnosed supratentorial glioblastoma. The objective of phase II was to determine whether this combination (MGd + TMZ + RT) improved OS and PFS in glioblastoma recursive partitioning analysis class III to V patients compared to historical controls. The MTD established was 5 mg/kg, given intravenously 5 days a week for the first 10 RT fractions, then 3 times a week for the duration of RT. Median survival time was 15.6 months, not significantly different from that of the historical control (P=0.36). Median PFS was 7.6 months.

Thus, the combination of standard RT with TMZ and MGd did not achieve a significant survival advantage.

In a recently published phase II study of concurrent RT, TMZ, and the histone deacetylase inhibitor valproic acid for patients with glioblastoma by Krauze *et al.* (54), median OS was 29.6 months and median PFS was 10.5 months. OS at 6, 12, and 24 months was 97%, 86%, and 56%, respectively. PFS at 6, 12, and 24 months was 70%, 43%, and 38%, respectively. Treatment was well tolerated. Addition of valproic acid to standard treatment may improve the outcome but needs to be validated in further studies.

Conclusions

Glioblastomas have dismal prognosis and remain incurable despite aggressive treatment. The most effective treatment for glioblastoma is maximal safe surgical resection followed by concurrent treatment with TMZ and RT followed by adjuvant TMZ. But the treatment efficacy is still suboptimal as two-thirds of patients die by 2 years from diagnosis. With the understanding of molecular biology and immunology, various targeted therapies have been devised. New treatment strategies that combine targeted therapy with cytotoxic chemotherapy and radiotherapy in novel ways to overcome tumor resistance, affect molecular, genetic and signal transduction pathways should be developed to improve survival and outcome in this deadly brain tumor. Till now there is no conclusive evidence that any targeted therapy is superior to RT and concomitant and adjuvant TMZ. But with improved technology and better understanding of the complex molecular biology of this tumor, various novel therapeutic approaches are under evaluation in trials. Despite all the efforts, the treatment of glioblastoma remains challenging.

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Footnote

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