EXPERT REVIEWS

Towards personalized therapy for patients with glioblastoma

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Combined therapy with temozolomide and radiotherapy is a standard treatment and improves the survival for patients with newly diagnosed glioblastoma. However, the prognosis remains poor, with a median survival time of 12–15 months. Currently, several clinical trials of dose-dense temozolomide regimen or molecular-targeting therapies have been performed to overcome the resistance of glioblastoma. In these therapies, rational prognostic biomarkers have also been investigated to predict their outcome and response to treatment. This advanced understanding of the biological markers can help to develop personalized therapies for glioblastoma patients. Generally, due to a reduced tolerance, elderly patients do not seem to benefit from intensive treatment. This population needs individual treatments depended on their age or performance status. In this article, we review the recent studies that can provide personalized therapy for glioblastoma, based on molecular tumor profiling or patients' physical status.

Keywords: elderly patients • glioblastoma • MGMT • personalized therapy • radiotherapy • targeting therapy • temozolomide

Glioblastoma, WHO grade 4 glioma, is the most common primary brain tumor seen in patients. The incidence of disease has increased over the past two decades [1]. Glioblastoma is characterized by a resistance to radiotherapy (RT) and chemotherapy, which is associated with a dismal prognosis. Stupp *et al.* demonstrated that postoperative RT with concurrent and adjuvant temozolomide (TMZ) improves the prognosis in newly diagnosed glioblastoma [2]. However, the prognosis remains poor, with a median survival time (MST) of 12–15 months. There is an urgent need for the development of a novel strategy to overcome the resistance of glioblastoma. Hegi *et al.* showed that the O^6-methylguanine-DNA methyltransferase (MGMT) promoter methylation status is an important prognostic factor in the treatment of glioblastoma [3]. This finding indicated that this promising biological marker can predict outcome, as well as provide personalized therapy, depending on the molecular profile. On the other hand, several targeting therapies have been performed to improve the survival of glioblastoma patients in clinical trials. Biological markers have also been investigated to predict response to each targeting therapy, providing a rational and personalized therapy. These aggressive treatments are promising for younger patients with better performance status, although elderly patients do not seem to benefit from these intensive treatments due to a reduced tolerance [4,5]. Furthermore, most elderly patients are often excluded from clinical trials and the standard treatment for this population has been unclear. The number of elderly patients with glioblastoma has been increasing, requiring the establishment of a strategy [6]. Recent studies of elderly patients have shed light on several approaches to provide the optimized treatment based on their status. In this review, we focus on recent studies that may provide personalized therapy in glioblastoma patients, depending on the molecular tumor profile or physical status of the patient.

Combination therapy with TMZ & RT

Adjuvant chemotherapy has been considered to give a small improvement in survival for newly diagnosed glioblastoma by meta-analyses [7]. Delivery of chemotherapy is inhibited by the blood–brain barrier, and only small and lipophilic molecules can reach their target. TMZ, a novel and oral alkylating agent, was developed to cross the blood–brain barrier because of its small size and lipophilic properties [8]. Brada *et al.* conducted a Phase II trial of TMZ for recurrent glioblastoma [9]. They showed that the objective response rate was 8% and the 6-month progression-free survival (PFS) was 18% without severe hematologic toxicity.

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Subsequently, a Phase II study was performed to evaluate the efficacy of TMZ and RT for newly diagnosed glioblastoma [10]. The regimen was well tolerated and MST was 16 months. Based on promising results, a Phase III trial was conducted to compare RT alone with RT plus concomitant and adjuvant TMZ by the European Organisation for research and Treatment of Cancer (EORTC) and the National Cancer Institute of Canada (NCIC) [2]. Treatment consisted of surgery and postoperative radiation (60 Gy in 30 fractions). TMZ was continuously administered during RT (75 mg/m^2), followed by six cycles of adjuvant TMZ (150–200 mg/m^2 daily for 5 days, every 28 days). They demonstrated that the TMZ/RT group had a significantly better MST than the RT alone group (14.6 vs 12.1 months; $p < 0.001$). The combined treatment was well tolerated and 7% of patients experienced grade 3 or 4 hematologic toxicities. Recently, Stupp *et al.* demonstrated long-term results of this Phase III trial [11]. With a median follow-up of 61 months, the 5-year overall survivals of the TMZ/RT and RT alone groups were 9.8 and 1.9%, respectively ($p < 0.001$). This study suggested that the survival advantage of a combined therapy of TMZ and RT lasts 5 years. Based on this evidence, this combination regimen is a standard therapy for patients with newly diagnosed glioblastoma. However, the prognosis has been poor despite multimodality therapy, and further strategy is needed to improve survival in glioblastoma.

This EORTC/NCIC trial reported that methylation of the *MGMT* promoter was the strongest predictor for overall survival in newly diagnosed glioblastoma [3]. The cytotoxicity of TMZ results from DNA alkylation at the O^6 position of guanine. The *MGMT* gene (10q26) encodes a DNA repair protein that removes the alkyl groups from the O^6 position of guanine, thereby neutralizing the cytotoxic effects of TMZ. The *MGMT* promoter is frequently methylated in glioblastoma, which inhibits the function [12]. Among patients whose tumors contained a methylated *MGMT* promoter, the TMZ/RT group had a significantly better overall survival than the RT alone group (21.7 vs 15.3 months; $p = 0.007$). Among patients with unmethylated *MGMT*, the TMZ/RT group tended to have a better overall survival than the RT alone group (12.7 months vs 11.8 months; $p = 0.06$). Furthermore, long-term results of this study showed that the 5-year overall survival for the TMZ/RT group was significantly longer than the RT alone group among patients with unmethylated *MGMT* (8.3 vs 0%; $p = 0.035$) [11]. These findings suggested that TMZ/RT is the standard of care independently of *MGMT* status.

O^6-benzylguanine, an MGMT inactivating drug, was considered an attractive therapeutic strategy to overcome MGMT-mediated resistance to alkylating agents, such as TMZ and carmustine, in glioblastoma patients [13]. Quinn *et al.* conducted a Phase II trial of 18 patients with recurrent malignant glioma treated with carmustine and O^6-benzylguanine [14]. There were no objective responders and 66% of patients had grade 3 or 4 hematologic toxicities. Another Phase II trial was conducted to determine the efficacy of TMZ plus O^6-benzylguanine in recurrent malignant glioma [15]. Response rates for recurrent glioblastoma and anaplastic glioma were 3 and 16%, respectively, and 48% of patients experienced grade 4 hematologic toxicities. These results indicated that additional O^6-benzylguanine to alkylating agents is not effective for glioblastoma patients due to the significant increase of hematologic toxicity.

Alternative dosing method of TMZ is another strategy to overcome MGMT-mediated resistance to TMZ, which can lead to the significant and prolonged depletion of MGMT activity [16]. Clarke *et al.* conducted a randomized Phase II trial to evaluate different TMZ regimens in the adjuvant setting for newly diagnosed glioblastoma [17]. Patients were treated with six cycles of dose-dense TMZ regimen (150 mg/m^2 days 1–7 and 15–21) or metronomic TMZ regimen (50 mg/m^2 continuous daily). They showed that MST of dose-dense and metronomic regimens were 17.1 and 15.1 months, respectively. These treatments were well tolerated, without significant adverse events. Dose-dense regimen achieved encouraging results, compared with MST of 14.6 months in the EORTC/NCIC trial. Furthermore, the unmethylated *MGMT* group had promising results with MST of 15.4 months in a dose-dense TMZ regimen, compared with 12.7 months in the EORTC/NCIC trial. The authors suggested that patients with unmethylated *MGMT* tumors also derived benefits from dose-dense TMZ. Brada *et al.* compared dose-dense TMZ (100 mg/m^2 daily for 21 days) and standard TMZ (200 mg/m^2 daily for 5 days) in a randomized study of recurrent malignant gliomas. However, dose-dense TMZ was inferior to standard TMZ in PFS, overall survival and global quality of life [18]. Given these findings, it is still unclear whether dose-dense TMZ is more effective for glioblastoma than standard TMZ. Radiation Therapy Oncology Group (RTOG) 0525 is one of the largest prospective studies to determine the efficacy of dose-dense TMZ for newly diagnosed glioblastoma [101]. Patients are randomly assigned to a standard adjuvant TMZ regimen (150–200 mg/m^2 daily for 5 days) and a dose-dense TMZ regimen (75–100 mg/m^2 daily for 21 days). *MGMT* promoter methylation status is prospectively assessed. This trial is expected to determine the optimized TMZ regimen depended on the *MGMT* methylation status in newly diagnosed glioblastoma.

Targeting therapy

Molecular targeting therapy is an attractive strategy to overcome the resistance of glioblastoma. Molecular profiling of gliomas reveals that signaling pathways drive the malignant behavior of tumor, such as anti-apoptosis, angiogenesis, cell migration and a invasiveness. A better understanding of these molecular and genetic pathways in glioblastoma can lead to direct targeting therapy. The identification of biological prognostic factors is also important, which provides personalized therapy depending on a individual biological profile. These investigations will develop the effective targeting therapy for glioblastoma and facilitate the discovery of subtypes that might respond to each targeting therapy.

Tyrosine kinase inhibitors

The EGF receptor (EGFR) is one of the most important pathways in glioblastoma [19]. *EGFR* gene amplification is a common

genetic feature in glioblastoma. The deregulated signaling pathway promotes proliferation, survival, invasion and inhibition of apoptosis. These observations make the EGFR tyrosine kinase inhibitor a logical approach for a targeting therapy in glioblastoma patients. Gefitinib and erlotinib are novel drugs that inhibit the tyrosine kinase activity associated with the EGFR. Several studies have been conducted to determine whether the EGFR inhibitor is implicated in the improvement of survival in glioblastoma (Table 1). Rich *et al.* showed a Phase II trial of gefitinib monotherapy in 53 recurrent glioblastoma [20]. No objective radiographic responses were seen and the 6-month PFS was 13%. van den Bent *et al.* conducted a randomized Phase II study of erlotinib versus alkylating agents for recurrent glioblastoma [21]. The 6-month PFS in the erlotinib and alkylating agents arms were 11.4 and 24%, respectively and the partial response was 3.7 and 9.6%, respectively. These results indicated that EGFR inhibitors alone did not improve the prognosis in recurrent glioblastoma. Chakravarti *et al.* performed a Phase I/II trial of 147 newly diagnosed glioblastoma patients treated by RT and gefitinib [22]. However, their MST was 11 months, and the combined therapy showed no major improvements. Brown *et al.* conducted a Phase I/II trial of erlotinib and TMZ/RT for 97 newly diagnosed glioblastoma patients [23]. This study showed that MST were 15.3 months and there were no significant differences in survival, compared with EORTC/NCIC trial. Recently, Prados *et al.* conducted a Phase II study of erlotinib plus TMZ/RT for newly diagnosed glioblastoma [24]. They showed promising results, indicating that MST was 19.3 months and treatment was well tolerated, compared with historical controls. These results indicate that the efficacy of EGFR inhibitors for glioblastoma has remained controversial. One possible reason is that single-drug activity is unlikely to control the complex biology of glioblastoma. Recent preclinical study has shown that multiple tyrosine kinases are coactivated and maintain downstream signaling, which limits the efficacy of single EGFR-targeting therapy [25]. The multiple agents for different signal transductions may overcome the resistance of glioblastoma.

As described above, benefits from EGFR inhibitors have not been well established, although there have been occasional long-lasting responders in several studies. These findings indicate that molecular biological markers are needed to predict response to EGFR inhibitors. Indeed, mutations in exons 19 and 21 of the EGFR tyrosine kinase domain are associated with response to gefitinib in lung cancer patients, which provides personalized therapy based on this mutation [26]. However, these mutations are not observed in glioblastoma [27]. Several studies have been investigated to determine the alternative markers in glioblastoma patients treated with EGFR inhibitors. *EGFR* gene amplification is often seen in glioblastoma patients, although this amplification did not predict the response to EGFR inhibitors and survival [28]. EGFRvIII is the most common deletion, accounting for 60–70% of EGFR mutations in glioblastoma, which involves exons 2 to 7 of the extracellular domain. Although EGFRvIII cannot bind their ligands, it constitutively activates the several signaling pathways, such as the PI3K pathway [19]. Mellinghoff *et al.* reported that EGFRvIII and phosphatase and tensin homolog deleted in chromosome 10 (PTEN), a tumor-suppressor protein to inhibit the PI3K pathway, are significantly associated with response to EGFR inhibitors [29]. However, other studies have not shown such a correlation between the coexpression and response to EGFR inhibitors. Haas-Kogan *et al.* showed that PTEN status does not account for EGFR-amplified erlotinib-resistant tumors [30]. A prospective EORTC study showed that none of the eight patients coexpressing EGFRvIII and PTEN had 6-month PFS in recurrent glioblastoma treated

Table 1. Summary of trials for patients with recurrent or newly diagnosed glioblastoma treated with epidermal growth factor receptor or vascular endothelial growth factor inhibitors.

Study (year)	Study design	Targeting therapy	Patients	n	6-month PFS (%)	MST (months)	Ref.
Rich *et al.* (2004)	Phase II	Gefitinib	Recurrent GBM	57	13	9.9	[20]
Van den Bent *et al.* (2009)	Phase II	Erlotinib	Recurrent GBM	54	11.4	7.7	[21]
Chakravarti *et al.* (2006)	Phase II	Gefitinib + RT	Newly diagnosed GBM	147		15.3	[22]
Brown *et al.* (2008)	Phase II	Erlotinib + TMZ/RT	Newly diagnosed GBM	97		15.3	[23]
Prados *et al.* (2009)	Phase II	Erlotinib + TMZ/RT	Newly diagnosed GBM	65		19.3	[24]
Vredenburgh *et al.* (2007)	Phase II	Bevacizumab + irinotecan	Recurrent GBM	35	46	10.5	[34]
Friedman *et al.* (2009)	Phase II	Bevacizumab Bevacizumab + irinotecan	Recurrent GBM Recurrent GBM	85 82	42.6 50.3	9.2 8.7	[36]
Kreisl *et al.* (2009)	Phase II	Bevacizumab	Recurrent GBM	48	29	7.7	[37]
Lai *et al.* (2011)	Phase II	Bevacizumab + TMZ/RT	Newly diagnosed GBM	70		19.6	[42]

GBM: Glioblastoma; MST: Median survival time; PFS: Progression-free survival; RT: Radiotherapy; TMZ: Temozolomide.

with erlotinib [21]. In this study, low and high phosphorylated AKT groups had 6-month PFS of 50 and 11%, respectively, and the authors suggested that phosphorylated AKT expression is a promising biomarker. These findings indicated the potential for improving patient care through a rational selection of patients, although it is still unclear which biomarker is important to predict the response to EGFR inhibitors. Further investigations are warranted to determine the prognostic markers, which provide personalized therapy of glioblastoma treated by EGFR inhibitors.

Antiangiogenesis therapy

Glioblastoma expresses high VEGF, an important regulator of angiogenesis [31]. Preclinical studies showed that monoclonal antibody against VEGF can inhibit the growth of glioma cells [32,33]. These findings suggested that VEGF inhibitors can be novel antiangiogenic therapies for glioblastoma patients. Bevacizumab is a humanized monoclonal antibody against VEGF. Recently, several trials of bevacizumab have been reported for newly diagnosed and recurrent glioblastoma (Table 1). Vredenburgh *et al.* conducted a Phase II trial of 35 recurrent glioblastoma patients treated with bevacizumab and irinotecan, a topoisomerase I inhibitor [34]. They showed that the 6-month PFS was 46% and response rate was 57%. Furthermore, most patients were able to decrease the corticosteroid dose by at least 50%. This result raised a further question as to whether additional irinotecan to bevacizumab is effective for recurrent glioblastoma, as irinotecan monotherapy was ineffective for this population [35]. Friedman *et al.* conducted a noncomparative Phase II study of recurrent glioblastoma treated with bevacizumab, with or without irinotecan [36]. They showed that in the combined therapy and bevacizumab alone groups, 6-month PFS was 50.2 and 42.6%, and response rates were 37.8% and 28.2%. Another Phase II study of bevacizumab alone for recurrent glioblastoma showed that 6-month PFS was 29% and the response rate was 35% [37]. Given the findings that bevacizumab alone is effective for recurrent glioblastoma and the addition of irinotecan does not clearly improve outcome, the US FDA approved bevacizumab for recurrent glioblastoma. Although these early results were encouraging, several problems were raised regarding to use of bevacizumab. There are potentially serious adverse events, such as intracranial hemorrhage, gastrointestinal perforation and thromboembolic complications [34,37]. Friedman *et al.* showed that grade 3 or 4 toxicities were observed in 46.4% of patients treated by bevacizumab alone [36]. Furthermore, because of the effect on the blood–brain barrier and on contrast enhancement alterations, 6-month PFS and response rate are debatable as a measure of anti-tumor activity in antiangiogenic therapy [38].

Several investigations have been performed to determine the reliable radiological modalities in antiangiogenic therapy. Chen *et al.* indicated that PET using [^{18}F]-fluorothymidine, an imaging biomarker of cell proliferation, was a strong predictive modality in patients with recurrent malignant gliomas treated by bevacizumab and irinotecan [39]. They showed that responders assessed by fluorothymidine-PET had significantly longer MST than nonresponders (10.8 vs 3.4 months; $p = 0.003$), whereas conventional imaging criteria of MRI was a relatively weak predictive modality for survival ($p = 0.06$). Molecular biological markers have also been investigated to predict prognosis. Sathornsumetee *et al.* retrospectively evaluated several components of the VEGF pathway and hypoxic markers in recurrent malignant glioma treated with bevacizumab and irinotecan [40]. They showed that response rates of high- and low-VEGF expression groups were 90 and 50%, respectively ($p = 0.024$). Furthermore, high expression of carbonic anhydrase 9, a hypoxia inducible transmembrane enzyme, was significantly associated with poor survival ($p = 0.016$). Larger prospective studies are warranted to assess the utility of these biological markers. A better understanding of the biomarkers can provide the rational and personalized therapy for glioblastoma patients treated by antiangiogenesis therapy.

The addition of bevacizumab to the initial treatment has also been expected to provide benefits in newly diagnosed glioblastoma. Lai *et al.* reported the preliminary results of a Phase II study testing the effects of additional bevacizumab administered to newly diagnosed glioblastoma patients, when compared to a standard TMZ/RT regimen [41]. Bevacizumab administered every 2 weeks from the first day of TMZ and RT. The authors suggest that the toxicities were acceptable, but initiation of bevacizumab within 3–5 weeks of surgery may be associated with a higher rate of wound breakdown. Recently, they reported the final results of this Phase II study, compared with a control group treated with first-line TMZ/RT who had mostly received bevacizumab at recurrence [42]. Additional bevacizumab to TMZ/RT improved PFS, but not overall survival, compared with the control group. Given these findings, efficacy of additional bevacizumab for newly diagnosed glioblastoma remains controversial. Randomized Phase III trials, RTOG 0825 and AVAGLIO, are currently ongoing for newly diagnosed glioblastoma treated by TMZ/RT with or without bevacizumab, which are expected to determine the efficacy and safety of additional bevacizumab [102,103].

Other targeting therapy

Several studies have reported on other targeting therapies against glioblastoma. Imatinib was developed to inhibit the signaling pathways of the PDGF receptor α, PDGF receptor β, and c-Kit receptor. Raymond *et al.* showed that imatinib had no clinically significant activity in 51 recurrent glioblastoma patients, with 6-month PFS of 16% and an observed response of 6% [43]. Dresemann *et al.* conducted a randomized Phase III study of 240 recurrent glioblastoma patients treated by hydroxyurea with or without imatinib [44]. However, 6-month PFS in combination treatments and hydroxyurea alone groups were 5 and 7%, respectively, and there were no clinical benefits from additional imatinib. These studies found no biological markers to influence prognosis. Taken together, these results suggested that imatinib is discouraged for recurrent glioblastoma patients. One possible reason is the insufficient exposure of these drugs to the tumor cells, because they cannot cross the blood–brain barrier by the P-glycoprotein efflux pump [45].

Talampanel was developed as an oral noncompetitive antagonist of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor with excellent brain penetration [46]. Blockage of the AMPA receptor can prevent the invasion and growth of glioblastoma cells [47]. Grossman *et al.* conducted a multicenter Phase II trial of talampanel in addition to standard TMZ/RT for 72 newly diagnosed glioblastoma patients [48]. They showed encouraging results demonstrating that MST was 20.3 months and the 2-year overall survival was 41.7% without severe adverse effects. Furthermore, this treatment seemed to improve survival in patients with unmethylated *MGMT* promoter tumors. Cilengitide, an inhibitor of αvβ3 and αvβ5 integrin receptors, has shown anti-tumor effect in glioblastoma xenografts *in vivo* study [49]. A Phase II study of cilengitide showed that 6-month PFS was 15% without significant toxicities in recurrent glioblastoma [50]. Stupp *et al.* conducted a Phase I/IIa study of cilengitide and TMZ/RT for newly diagnosed glioblastoma [51]. The MST was 16.1 months and the 2-year overall survival was 35%. The MST of patients with tumors with and without the methylated *MGMT* promoter were 23.2 and 13.1 months, respectively. Based on these results, two randomized trials, CENTRIC and CORE, are currently ongoing to determine the efficacy of cilengitide for newly diagnosed glioblastoma [52,53]. These trials perform different cilengitide regimens depended on *MGMT* methylation, which are expected to establish the optimized regimens of cilengitide. Bortezomib, the first proteasome inhibitor approved for use in clinical trials, is one of the attractive agents for glioblastoma. Preclinical studies demonstrated the anti-tumor effect of bortezomib on glioma cell lines [54,55]. Kubicek *et al.* showed that additional bortezomib to TMZ/RT was well tolerated and safe in malignant gliomas [56]. Their MST for malignant glioma was 15.0 months. Vorinostat, an inhibitor of histone deacetylation, can suppress the proliferation of glioblastoma cells *in vivo* and *in vitro* [57]. Galanis *et al.* conducted a Phase II trial of vorinostat for patients with recurrent glioblastoma [58]. They showed that vorinostat was well tolerated and had modest efficacy with a 6-month PFS of 17.3%. Recently, Grossman *et al.* summarized several Phase II studies of newly diagnosed glioblastoma treated by TMZ/RT with novel agents, such as talampanel, poly-ICLC and cilengitide [59]. The MST was 19.6 months and 2-year overall survival was 37%. These novel drugs and TMZ/RT significantly improved the survival, compared with the historical control. However, the comparison with historical control should be interpreted cautiously as the significant difference could come from changing patterns of care, such as better surgery or RT.

These targeting therapies could be a promising strategy to improve the outcome for patients with glioblastoma. However, most results have been shown by retrospective or Phase II studies, which were compared with historical studies. Therefore, it is still unclear whether glioblastoma patients can truly benefit from these new targeting therapies. Randomized studies are warranted to validate the efficacy of the new targeting therapy, and investigation of the rational biological marker is also required to contribute to the more effective personalized therapies for glioblastoma.

Elderly patients

The number of elderly patients with glioblastoma has been increasing, which requires an establishment of a strategy for this population [6]. Generally, older patients have a worse outcome than younger patients [4,5] and they are unlikely to benefit from intensive treatments due to a reduced tolerance. As a result of these findings, efforts have been made to reduce the inconvenience or morbidity associated with treatments. As most elderly patients are often excluded from clinical trials, the standard therapy for this population has been unclear. For instance, EORTC/NCIC trial which establish a TMZ/RT regimen in newly diagnosed glioblastoma did not include patients aged 70 years of age or older [2]. Recent studies have shed light on several approaches to establish optimized treatment based on their status for elderly patients (Table 2). Keime-Guibert *et al.* conducted a randomized Phase III trial of elderly glioblastoma patients to investigate whether postoperative RT improves survival [60]. Eligible patients were 70 years of age or older with a Karnofsky performance status (KPS) of 70–100. Patients were assigned to receive RT (50 Gy) or best supportive care alone. The RT group had a significantly longer overall survival than the best supportive care group (8.3 vs 4.2 months; p = 0.002). RT did not cause severe adverse events, and there were no significant differences in the quality of life and cognitive function between these treatment groups. This trial provided evidence that patients aged 70 years of age or older with a better KPS should be treated with postoperative RT.

Efforts have been made to relieve the burden of longer treatments on elderly patients with newly diagnosed glioblastoma. Hypofractionated and shorter RT has been shown to reduce the time, inconvenience and morbidity associated with treatments, compared with conventional RT. Roa *et al.* conducted a prospective randomized trial of patients aged 60 years of age or older to compare hypofractionated RT (40 Gy in 15 fractions over 3 weeks) with conventional RT (60 Gy in 30 fractions over 6 weeks) [61]. There were no differences in MST between these treatments (5.6 vs 5.1 months; p = 0.57). Hypofractionated RT decreased steroid requirement after RT and increased treatment completion rate. Lutterbach and Ostertag also reported a retrospective study to investigate the appropriate RT schedule for patients aged ≥60 years of age with a KPS of ≥70 [62]. They showed that there were no significant differences in MST between standard RT (60 Gy in 30 fractions over 6 weeks) and hypofractionated RT (42 Gy in 12 fractions over 2.5 weeks). Taken together, hypofractionated RT is a reasonable treatment strategy to relieve the burden on elderly patients with glioblastoma.

TMZ plays an important role for elderly patients with newly diagnosed glioblastoma, because of its safety and feasibility. Glantz *et al.* retrospectively evaluated the survival of glioblastoma patients, aged 70 years or older, treated with TMZ monotherapy or RT alone [63]. The MST of TMZ monotherapy and RT groups were 6.0 and 4.1 months, respectively, and there were no differences in survival between the two groups (p = 0.198). Furthermore, the authors advocated that TMZ is a less toxic oral agent that can be administered at home and improves quality of

Table 2. Elderly patients with newly diagnosed glioblastoma treated with radiation and/or temozolomide.

Study (year)	Study design	Radiotherapy	Chemotherapy	n	Age (years; median)	KPS (median)	MST (months)	Ref.
Keime-Guibert *et al.* (2007)	Phase III BSC	50 Gy/28 fr		39 42	≥70 (75) ≥70 (73)	≥70 (70) ≥70 (70)	8.3 4.2	[60]
Roa *et al.* (2004)	Phase III	40 Gy/15 fr 60 Gy/30 fr		41 59	≥60 ≥60	≥50 (70) ≥50 (70)	5.1 5.6	[61]
Glantz *et al.* (2003)	Retrospective	60 Gy/33 fr	TMZ alone	32 54	≥70 (73) ≥70 (75)	≥40 (67) ≥50 (68)	4.1 6.0	[63]
Brandes *et al.* (2003)	Prospective	60 Gy/30 fr 60 Gy/30 fr	Adjuvant TMZ	24 23	≥65 (70) ≥65 (68)	≥60 (73) ≥60 (77)	11.2 14.9	[67]
Chinot *et al.* (2004)	Phase II		TMZ alone	32	≥70 (75)	≥60 (70)	6.4	[64]
Combs *et al.* (2008)	Retrospective	60 Gy/30 fr	Concurrent TMZ	43	>65 (67)		11.0	[68]
Brandes *et al.* (2009)	Retrospective	60 Gy/30 fr	Concurrent + adjuvant TMZ	58	≥60 (68)	≥70 (80)	13.7	[69]
Malmstrom *et al.* (2010)	Phase III	60 Gy/30 fr 34 Gy/10 fr	TMZ alone	100 123 119	≥60 (70) ≥60 (70) ≥60 (70)		6.0 7.5 8.3	[65]
Wick *et al.* (2010)	Phase III	54–60 Gy	TMZ alone	178 193	>65 (71) >65 (72)	≥60 (80) ≥60 (80)	9.8 8.2	[66]

BSC: Best supportive care; fr: Fraction; KPS: Karnofsky performance status; MST: Median survival time; TMZ: Temozolomide.

life during treatment, compared with RT alone. Chinot *et al.* conducted a Phase II study of TMZ monotherapy in patients aged 70 years or older with newly diagnosed glioblastoma [64]. TMZ monotherapy was well tolerated in elderly patients and MST was 6.4 months. Recently, Malmstrom *et al.* reported a randomized Phase III study to compare standard RT (60 Gy in 30 fractions over 6 weeks), hypofractionated RT (34 Gy in ten fractions over 2 weeks) and TMZ monotherapy in elderly glioblastoma patients [65]. The MST of standard RT, hypofractionated RT and TMZ were 6.0, 7.5 and 8.3 months, respectively (p = 0.14). The authors concluded no advantage of standard RT compared with hypofractionated RT and TMZ monotherapy for elderly patients. Wick *et al.* conducted a randomized Phase III study to compare TMZ monotherapy (1 week on/1 week off) with RT alone (54–60 Gy) for elderly patients with glioblastoma and anaplastic astrocytomas [66]. MST of TMZ monotherapy and RT alone were 8.2 and 9.8 months, respectively. The authors concluded that this trial failed to show the non-inferiority of TMZ monotherapy compared with RT alone. These results indicated that the efficacy of TMZ monotherapy remains controversial, although this strategy may be an alternative treatment option for elderly patients with malignant glioblastoma.

A further question has arisen as to whether combined treatment with TMZ and RT improves the prognosis in elderly patients with newly diagnosed glioblastoma. Brandes *et al.* conducted a prospective trial to compare RT alone with RT plus adjuvant TMZ in elderly patients [67]. They showed that MST of RT plus adjuvant TMZ was significantly longer than RT alone (14.9 vs 11.2 months; p = 0.002). Combs *et al.* reported a retrospective study of concurrent TMZ and RT for patients aged 65 years or older [68]. This treatment was well tolerated and their MST was 11 months. Brandes *et al.* reported concurrent and adjuvant TMZ combined with RT for glioblastoma in patients aged 65 or older [69]. MST was 13.7 months, and mental deterioration grade 3 or 4 was detected in 25% of patients. Taken together, the results for combined TMZ and RT are feasible but may induce cognitive impairment in elderly patients. However, benefits from combined therapy with TMZ and RT in elderly patients have not been demonstrated by randomized studies. The NCIC/EORTC randomized Phase III trial is currently ongoing to compare short-course RT with or without TMZ for elderly glioblastoma patients, which is expected to show the efficacy and safety of combination therapy [104].

Some elderly patients with favorable factors can benefit from the intensive treatments, although it is difficult to select patients who are able to endure the therapy because of their heterogeneity. Patients who cannot endure the aggressive therapy should be treated with palliative therapy, such as RT alone or TMZ monotherapy. A classification among elderly patients is important to determine a therapeutic strategy, which provides personalized therapy for elderly patients. Several studies have shown that KPS is a predictive factor [63,67,69]. The *MGMT* methylation status can be an important biological factor in the elderly population [69]. Furthermore, *TP53* and *EGFR* amplification are reported as age-dependent prognostic molecular markers [70]. These predictive factors are required to validate further investigations. Currently, several trials for elderly patients are ongoing to investigate the tolerability and efficacy of the optimized RT course

and/or TMZ [71]. In the near future, these trials will solve the problems and provide strong evidence to establish the optimized treatment for elderly patients with glioblastoma.

Expert commentary

Combination therapy with TMZ and RT is a standard treatment for patients with newly diagnosed glioblastoma. However, long-term survival has remained poor with a 5-year survival of 9.8% [11]. The *MGMT* promoter methylation status is an important biomarker to predict the prognosis in glioblastoma. Patients with unmethylated *MGMT* tumors may have less benefits from this combined therapy of TMZ and RT. Several trials are currently ongoing to establish the therapeutic strategy based on *MGMT* methylation status, which provides the personalized therapy for glioblastoma patients.

To overcome the resistance of glioblastoma, several targeting therapies have been performed in clinical trials. Combination of erlotinib and TMZ/RT for newly diagnosed glioblastoma has shown promising result with an MST of 19.3 months [24]. Several biological markers, such as EGFRvIII, PTEN and pAkt, have also been reported to predict the responders to EGFR inhibitors. This identification of predictive biomarkers, in particular targeting therapy, will provide us with the important information to select the effective targeting therapy for each individual patient. Bevacizumab is a promising targeting therapy for recurrent glioblastoma, which has shown favorable response rates and PFS. In this treatment, high VEGF expression is related to a better radiographic response. However, the toxicity is relatively high, and patients should be carefully monitored. The addition of bevacizumab to an initial treatment for glioblastoma is expected to provide a benefit. RTOG 0825 and AVAGLIO will show the efficacy of combined bevacizumab with TMZ/RT for newly diagnosed glioblastoma. Other several targeting therapies, such as talampanel, cilengitide, bortezomib and vorinostat, have modest effects for glioblastoma without significant side effects. Larger randomized trials are required to validate the efficacy of these drugs and to investigate the reliable biological markers.

Recent evidence showed that RT alone improves survival of elderly patients with glioblastoma, compared with best supportive care. Hypofractionated RT (≤3 weeks) can relieve the burden on elderly patients without deterioration of survival, compared with standard RT (6 weeks). Combined therapy with RT and TMZ can be performed for selective elderly patients with favorable factors, although the adverse effects should be carefully monitored. TMZ monotherapy may be an attractive palliative option. A classification of elderly patients is needed to determine personalized therapy for each individual patient.

Five-year view

Glioblastoma patients consistently have a poor prognosis. Recent advances in molecular biology have shown the molecular and genetics heterogeneity of glioblastoma, and several clinical studies are currently ongoing to improve the survival and to investigate a novel prognostic biomarker. These investigations will lead to personalized therapy based on the molecular tumor profile in glioblastoma. Depending on the *MGMT* methylation status, optimized treatment regimens will be established by several randomized trials. In targeting therapy, a better understanding of biological and genetic alterations, such as EGFRvIII, PTEN, pAkt and VEGF, provides additional prognostic information. These investigations can decide on the optimal targeting therapy for each individual patient. In coming years, targeting therapy combined with cytotoxic agents will play an important role in glioblastoma patients. A classification of elderly patients will also be established to determine personalized treatment, such as TMZ/RT, TMZ monotherapy or RT alone.

Indeed, the prognostic biomarkers in breast cancer can predict the residual risk and potential value of additional treatments, providing a personalized therapy [72]. Likewise, glioblastoma patients will benefit from a personalized strategy, based on the molecular tumor profile or physical status of the patient.

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Key issues

- Combination therapy with temozolomide (TMZ) and radiotherapy is a standard treatment for patients with newly diagnosed glioblastoma. O^6-methylguanine-DNA methyltransferase methylation status is an important prognostic factor in this treatment. In the future, randomized trials will determine the efficacy of dose-dense TMZ regimens.
- A combination of erlotinib and TMZ/ radiotherapy (RT) potentially improve the prognosis for newly diagnosed glioblastoma. By contrast, monotherapy of EGF receptor inhibitors are less effective for recurrent glioblastoma.
- Antiangiogenic therapy is an effective strategy for recurrent glioblastoma patients. Clinical trials are currently ongoing to evaluate the efficacy of additional bevacizumab to TMZ/RT for newly diagnosed glioblastoma.
- Identification of reliable biological markers can provide personalized therapy depended on molecular tumor profile.
- Postoperative RT improves overall survival in elderly patients with newly diagnosed glioblastoma. When compared with conventional hypofractionated RT, is a reasonable treatment to relieve the burden on elderly patients. Concurrent chemoradiotherapy with TMZ can be performed for elderly patients with favorable factors.

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