Treatment advances for glioblastoma

Glioblastoma is a deadly disease and modest improvement has been made in patient survival in previous decades. At initial diagnosis, treatment consists of maximum safe surgical resection, followed by temozolomide chemoradiation and then adjuvant temozolomide alone [1]. This treatment results in a median survival of 14.6 months, a 2-year survival of 27.2% and a 5-year survival of 9.8% [1]. At the time of tumor progression, the best available treatment option consists of single-agent bevacizumab, a humanized monoclonal antibody against VEGF, or in combination with irinotecan or other cytotoxic chemotherapies [2]. Although patients experience improved neurological function, this improvement is nevertheless transient and overall survival is not prolonged. Therefore, new treatment strategies are being sought.

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Building on the initial benefit of bevacizumab in recurrent glioblastomas, a number of newer antiangiogenesis agents have entered clinical trials. Unfortunately, they have all failed. For example, small-molecule VEGF receptor inhibitors, such as cediranib, sunitinib, ZD6474 and XL-184, are no better than salvage cytotoxic chemotherapies [3]. Although neuro-oncologists initially thought that anti-VEGF ligand and anti-VEGF receptor therapies are pharmacodynamically equivalent to achieving the antiangiogenesis effect, it is becoming clear that their biological and clinical efficacies are not. This is probably a result of differences in their mechanisms of action. Bevacizumab works by neutralizing VEGF from the circulation and the extracellular matrix of tumor cells. This action would most likely result in an exponential decrease in VEGF receptor signaling within the endothelial cells as removal of each VEGF ligand would prevent its interaction with multiple receptors. Therefore, no angiogenesis would occur once VEGF reaches a threshold level and bevacizumab does not need to neutralize all VEGF ligands in order to achieve a biological effect. There is strong evidence for this threshold effect. A meta-analysis of published trials on bevacizumab for glioblastomas did not find any evidence for a dose–response effect – 5 mg/kg works just as well as 10 or 15 mg/kg with respect to overall survival, progression-free survival at 6 months and response rate [2]. Furthermore, aflibercept (Kd = 0.5 pmole/l), which has an affinity to VEGF 1000-times higher than bevacizumab (Kd = 0.5 nmole/l), did not offer better clinical efficacy in a single-arm Phase II trial when compared with historical control [4]. By contrast, the

**Keywords:** antiangiogenesis • glioblastoma • immunotherapy • ketogenic diet • tumor-treating (electromagnetic) field
pharmacodynamic interaction of VEGF receptor tyrosine kinase inhibitors is different from that of anti-VEGF agents. The shut down of angiogenesis by a VEGF receptor tyrosine kinase inhibitor is probably a linear phenomenon, requiring the persistent and stoichiometric presence of one inhibitor per receptor. There is support for this notion because sunitinib is not as effective as bevacizumab in blocking the migration of proangiogenic VEGF receptor-1-expressing CD11b+ myeloid cells into glioblastoma that is orthotopically implanted in mice [5]. Furthermore, patients who have progressive glioblastoma after the failure of VEGF receptor tyrosine kinase inhibitors would still derive benefit from bevacizumab treatment [6]. Therefore, anti-VEGF therapy has a greater therapeutic index than inhibitors of VEGF receptor.

Invasion is an observed pattern of failure during antiangiogenesis treatment. Although it is poorly visualized using our existing MRI technology, this phenomenon is manifested as increased hyperintensity adjacent to the glioblastoma seen in the fluid-attenuated inversion-recovery sequence on MRI [7]. To counteract this invasion process, cilengitide, an inhibitor of the αvβ3 and αvβ5 integrins, has been brought into clinical trial settings. It has been demonstrated to have an acceptable toxicity profile in Phase I testing and, at a dose of 2000 mg/m² twice weekly in a randomized Phase II trial, it offers a 6-month progression-free survival of 15% and a median overall survival of 9.9 months [8]. Cilengitide is now under investigation in a Phase III clinical trial combined with temozolomide chemotherapy versus temozolomide chemotherapy alone in newly diagnosed glioblastoma patients.

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Multitargeted small-molecule inhibitors would be better utilized when drug specificity is matched with the specific mutational pattern in the glioblastoma. Predictive biomarkers for a specific pharmacological effect would fulfill this promise. To date, only MGMT promoter methylation is clinically validated, which predicts the response to temozolomide during radiation therapy [9]. Major limitations of promoter methylation testing include the requirement of adequate tumor tissue and that, as the glioblastoma undergoes clonal evolution and selection by chemotherapy and radiation, the methylation pattern may change and additional tissue sampling would be necessary in order to determine the methylation status. Unfortunately, there is currently no clinically validated biomarker that allows the real-time monitoring of glioblastoma activity. However, promising real-time biomarkers can potentially be obtained from the plasma, such as circulating tumor cells, or the cerebrospinal fluid, including IGF-2 and tumor metabolites. For example, in patients with metastatic breast cancer, the number of circulating tumor cells detected in the blood predicts progression-free survival and overall survival [10]. In glioblastoma patients, such circulating tumor cells are probably present at a low level as glioblastomas located in extracranial organs have been reported and they are thought to arrive there via the bloodstream [11]. Furthermore, biomarkers such as IGF-2 and specific tumor metabolites in the cerebrospinal fluid are associated with progressive glioblastoma [12,13]. However, further clinical validation would be needed to determine the sensitivity and specificity of these real-time biomarkers.

There are a number of novel treatments that may complement currently available treatments for glioblastoma. These treatments include the NovoTTF-100A device, the ketogenic diet and immunotherapy. First, the NovoTTF-100A device, which emits an intermediate frequency 100–200-kHz electromagnetic field or tumor-treating field (TTT), has won approval recently from the US FDA for use in patients with progressive glioblastomas [10]. TTT works by physically interfering with cell division during the metaphase to anaphase transition, causing the disruption of chromosome segregation, failure of cytokinetic furrow formation, blebbing of the cytoplasmic membrane and eventual cell death [14,15]. In a randomized Phase III clinical trial, the NovoTTF-100A device has at least equivalent efficacy, and with fewer treatment-related side effects, to the salvage cytotoxic chemotherapies that have established efficacy against recurrent glioblastoma [16]. Second, the ketogenic diet, which is an accepted treatment for childhood epilepsy, has been anecdotally used to control glioblastoma. The rationale behind this therapy is based on the Warburg effect in which tumor cells preferentially undergo aerobic glycolysis, a metabolically inefficient process of generating adenosine triphosphate, while utilizing high levels of glucose [17]. The ketogenic diet would limit the amount of available glucose and carbohydrate to the patient while shifting their dietary energy source to mostly fat and protein. Doing so would theoretically slow down the growth of tumors. Anecdotally cases of tumor control in glioblastoma patients have been reported from use of the ketogenic diet in combination with standard treatment [18]. Last, immunotherapy with a vaccine for glioblastoma is a promising approach, at least experimentally at this time. The goal is, of course, to utilize the patient’s own immune system to destroy the glioblastoma. The vaccine against EGFRvIII has been shown to have efficacy in small Phase II clinical trials [19] and randomized Phase III trials are needed to test its efficacy definitively. It is important to appreciate the complex interactions among the tumor, the immune system and existing treatments. As the glioblastoma adapts to and coexists with the host’s immune system, while simultaneously escaping attack by immune cells, some patients may develop resistance to immunotherapy. Furthermore, glioblastoma patients receive corticosteroid treatment and the subsequent drop in CD4 count may further weaken the immune system. It remains to be seen how much of an impact immunotherapy has in controlling glioblastoma.

In conclusion, progress has been made in the past decade to firmly establish the utility of cytotoxic chemotherapy and antiangiogenesis drugs as efficacious treatments for glioblastoma. These advances include the concurrent administration of temozolomide during initial radiation therapy for newly diagnosed glioblastoma patients and the use of bevacizumab and the NovoTTF-100A device for those with progressive or recurrent disease. New and novel treatments, such as anti-invasion treatment with cilengitide, the ketogenic diet and immunotherapy, may offer additional ways to control glioblastoma.
Financial & competing interests disclosure

Eric T Wong has received research grants from AstraZeneca, Exelixis and NovoCure. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

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