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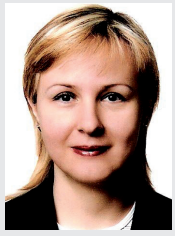

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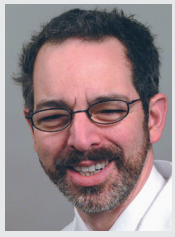

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"Glioblastoma multiforme is among the most difficult of tumors to treat ... medial overall survival remains at approximately 12 months."

Glioblastoma multiforme (GBM) is among the most difficult of tumors to treat and, despite all efforts, median overall survival (mOS) remains at approximately 12 months [1]. Neurological morbidity at diagnosis and progression of disease is high. The established therapies for GBM include surgery, radiotherapy (RT) and local or systemic chemotherapy. Significant progress has been achieved in the past decade in the understanding of the molecular biology of GBM histology and, as a consequence, there is renewed clinical trial activity in this area focused on improving quality of life, treatment-related morbidity and outcomes [2].

In this review, we discuss several controversies and unmet needs in the diagnosis and treatment of GBM.

Elderly

The peak incidence of GBM occurs in individuals aged 65 years and older; in this population, GBM accounts for a majority of primary brain tumors [3]. Additionally, the incidence of GBM in older adults has been increasing [4–6]. Optimal management of older patients with GBM remains uncertain because their survival tends to be short and they are at greater risk for surgery, radiation treatment and chemotherapy complications owing to their comorbidities. Older GBM patients are relatively understudied and often underrepresented in clinical trials. For example, the landmark trial establishing the benefit of concomitant temozolomide excluded patients older than 70 years of age, and observed that patients between 60 and 70 years of age did not do as well as those aged younger than 60 years [7]. In another study that evaluated the patterns of care in elderly GBM patients, the mOS of patients with GBM older than 65 years of age was found to be 4 months and only 61% of patients underwent resection at diagnosis, 65% received RT and 10% received chemotherapy within 3 months of diagnosis. Besides their age, unmarried marital status and comorbidities influenced the low probability of receiving RT or chemotherapy [8]. A randomized trial compared RT and supportive care with supportive care alone for the treatment of GBM in patients 70 years of age or older. Focal radiation in daily fractions of 1.8 Gy given 5 days per week for a total dose of 50 Gy was administered in the study group. The trial was discontinued at the first interim analysis, which showed that RT and supportive care were superior to supportive care alone. The median survival for the 39 patients who received RT plus supportive care was 29.1 weeks, compared with 16.9 weeks for the 42 patients who received supportive care alone. This study established that RT was beneficial and well tolerated in elderly patients with GBM [9].

"...patients between 60 and 70 years of age did not do as well as those aged younger than 60 years."

The optimal dose and schedule of irradiation in elderly patients are still controversial. A short course of RT (40 Gy in 15 fractions over 3 weeks) [10] or hypofractionated RT (six fractions of 5 Gy each for a total of 30 Gy over 2 weeks) [11] were recommended. Concomitant and adjuvant chemotherapy is still under debate in elderly patients with GBM. There is an

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ongoing Phase III study (26062/22061- NCIC CE.5 and European Organisation for Research and Treatment of Cancer [EORTC]) in elderly patients with GBM exploring hypofractionated RT with or without temozolomide.

Preoperative radiological evaluation

Glioblastomas and brain metastases are the two most common brain neoplasms in adults [12,13]. Preoperative distinction of GBM from other intracranial lesions, especially with brain metastases of unknown origin, is sometimes challenging [14]. Both GBMs and metastases may exhibit ring enhancement and extensive edema on MRI [15].

One distinguishing feature of GBM is its tendency to invasion compared with metastases, which are usually well-circumscribed. MR images, particularly T2-weighted images, may demonstrate the tumor invasion [16]; however, T2 hyperintensity demarcates vasogenic peritumoral edema as well as invasive tumor. Further studies are being performed to determine whether diffusion tensor imaging (DTI), fluid-attenuated inversion recovery (FLAIR) images and MR spectroscopy may help differentiate GBMs from brain metastases [17–19]. These new, noninvasive modalities are unlikely to provide completely reliable differentiation from metastases and other glial neoplasms; moreover, they will not provide molecular data that may be essential for treatment allocation. Consequently, tissue sampling with histopathological diagnosis will remain the gold standard.

Molecular diagnostic studies

The epigenetic, transcriptional and translational regulation and expression of *O6*-methylguanine-methyltransferase (MGMT) are relevant for prognostic and predictive considerations in GBM patients [20]. However, several different methods and protocols have been used for MGMT analysis and it is unclear which methods harbor the greatest potential for translation into routine clinical use. DNA-based methods for MGMT analysis appear more promising for translation into the clinical setting than RNA- or protein-based methods. However, at present, there are a lack of data on which to base recommendations for a specific method or protocol for MGMT testing. There is a strong need for systematic comparisons and validation of intra- and inter-laboratory reproducibility and clinical performance of different methods for MGMT assessment to identify the best method for clinical MGMT testing. The current practice of formalin-fixation of neurosurgical specimens considerably limits the spectrum of methods that can be applied for molecular diagnosis in clinical neuro-oncology [21].

Although epigenetic inactivation of the *MGMT* gene promoter remained the most prominent predictive factor, expression signatures allowed identification of patient subgroups that may benefit from specific additional therapies targeting particular mechanisms of resistance [22].

Surgery

The main purposes of surgery are to obtain tissue samples and achieve cytoreduction, where possible, in patients with GBM. The benefit from cytoreductive surgical therapy in the treatment of GBM is still controversial; however, the neurosurgery literature provides growing evidence on behalf of gross total resection of the enhancing tumor [23–30].

In one study, patients who underwent subtotal surgery postoperatively had a 6.6-fold higher risk of death in comparison with patients who underwent complete resection [31]. Nevertheless, surgery carries the risks of neurological and systemic complications. Intraoperative neuroimaging and neuromonitoring modalities are becoming more instrumental to achieve the goal of gross total resection with the least possible morbidity [32,33]. Intraoperative image-guided stereotactic surgery, functional MRI, cortical mapping, intraoperative MRI and awake craniotomy are surgical adjuncts for allowing gross total resection without neurological deterioration. A large, prospectively randomized controlled Phase III trial using fluorescence-guided resections with 5-aminolevulinic acid-induced tumor fluorescence, compared with conventional microsurgery, disclosed a significantly greater gross total resection (65 vs 36%) [34]. Patients were allocated into Radiation Therapy Oncology Group (RTOG)-recursive partitioning analysis (RPA) classes III–V based on age, Karnofsky Performance Scale (KPS), neurological condition and mental status. mOS among RPA classes III, IV and V was 17.8, 14.7 and 10.7 months, respectively. Stratified for degree of resection, survival of patients with complete resections was clearly longer in RPA classes IV and V (17.7 vs 12.9 months, and 13.7 vs 10.4 months) [35].

The surgical management of recurrent GBM is also controversial. Reoperation may provide 3–5 months' median survival, without significant increases in morbidity or mortality in selected patients. Re-resection not only improves symptoms and maintains quality of life, it can delay symptom progression, reduce corticosteroid doses and also improve response to (and allow intraoperative) chemotherapy and/or RT [36].

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In most other trials, postoperative radio- and/or chemotherapy were administered. Therefore, the impact of re-resection by itself is not entirely clear. Barker *et al.* reported the results of re-resection plus individual additional treatment (chemotherapy in 85% of cases) for GBM [37]. Median survival was 36 weeks, suggesting a moderate improvement when compared with a group of 130 patients who received comparable first-line treatment and chemotherapy without re-resection (median survival 23 weeks).

Surgical resection is performed only for the enhancing nodule; however, infiltrative tumor cells remain within remote sites and may cause recurrences. That is why complete resection versus suboptimal resections has always been discussed in the neurosurgery literature. The balance of the extent of resection with the development of new neurological and neurocognitive deficit appears central to the decision-making process. Besides cytoreductive surgery, new techniques allow the delivery of local therapy to improve survival and quality of life in patients [38].

Surgery plus local therapy

The major advantages of re-resection for recurrent GBM are rapid palliation of symptoms and histological diagnosis. Placement of carmustine (BCNU) polymers (Gliadel®) significantly improves the outcome after re-resection [39]. Median survival was 31 versus 23 weeks – that is, significantly better for the BCNU group.

Re-resection plus intracavitary application of paclitaxel and carboplatin encapsulated in a liquid crystalline cubic-phase system was reported by von Eckardstein *et al.* [40]. Their median survival was 28 weeks after the repeat surgery (16.5 months from initial diagnosis). Stylli *et al.* reported the results of re-resection followed by photodynamic therapy [41]. Prior to surgery, a hemetaporphyrin derivate was injected intravenously. The principle is that this sensitizer is taken up by the tumor cells. After maximal resection, the tumor bed area receives irradiation by laser light of the appropriate wavelength, leading to activation of the retained sensitizer and destruction of residual tumor cells. Median survival was surprising at 59 weeks for GBM.

Other groups studied the intratumoral delivery of agents via stereotactically placed catheters. IL-13 receptors are overexpressed in GBM. The presence of IL-13 binding sites in GBM and their absence in normal brain tissue validates the IL-13 receptor as an important target in human GBM. A recombinant cytotoxin composed of human IL-13 and a truncated form of *Pseudomonas* exotoxin A (PE38QQR), delivered via convection-enhanced delivery (CED), has been used in GBM treatment. The Phase III PRECISE clinical trial recruited patients with resectable GBM at first recurrence. The patients were randomized in a ratio of 2:1 to receive either cintredekin besudotox (CB) via CED or Gliadel wafers. Median survival did not differ significantly between treatment groups, with a median survival of 36.4 weeks for the patients receiving CB via CED compared with 35.3 weeks for the patients receiving Gliadel wafers. On the other hand, progression-free survival (PFS) was longer in CB patients (PFS: 17.7 weeks) than in Gliadel patients (11.4 weeks) [42,43].

The immunotoxin used (TP-38) was a recombinant chimeric protein composed of the EGF receptor-binding ligand TGF-α and a genetically engineered form of the *Pseudomonas* exotoxin, PE-38. Median survival after TP-38 was 28 weeks (95% CI: 26.5–102.8). Of 15 patients treated with residual disease, two (13.3%) demonstrated radiographic responses, including one patient with GBM who had a nearly complete response and remained alive 260 weeks after therapy [44].

> "Combining Gliadel® and temozolomide therapy is safe and may further improve survival in newly diagnosed glioblastoma multiforme."

A better outcome was observed after re-resection, with intralesional delivery of autologous lymphokine-activated killer cells in 40 patients with GBM. Median survival was 39 weeks (17.5 months from initial diagnosis of GBM) [45].

Another strategy is delivery of the herpes simplex virus thymidine kinase (*HSV-tk*) gene by re-resection, injection of vector producing cells into the adjacent brain, placement of an Ommaya reservoir for further cell injection 7 days after surgery and treatment with repeat cycles of ganciclovir, a nucleoside prodrug that is activated by HSV-tk; median survival was 37 weeks [46].

Gliadel wafer and concomitant temozolomide therapy, when used individually as adjuvant therapies, extend survival from that achieved by resection and radiation therapy for GBM. Combining Gliadel and temozolomide therapy is safe is safe and may further improve survival in newly diagnosed GBM. A total of 33 patients were treated with RT plus Gliadel plus temozolomide. The median survival in this group was 20.7 months, with a 2-year survival rate of 36%. In these patients, RT plus Gliadel plus temozolomide were not associated with an increase in perioperative morbidity in comparison with RT plus Gliadel. In this experience, concomitant temozolomide therapy in addition to Gliadel wafer implantation was associated with a median survival of nearly 21 versus 12.4 months, without increased perioperative morbidity. Temozolomide can be safely administered to patients receiving Gliadel wafers after resection of GBM [47].

Stereotactic radiosurgery

There are contradictory data regarding stereotactic radiosurgery in treatment of GBM. Single-institution retrospective and Phase II studies have suggested potential benefit of adjuvant radiosurgery. However, a careful prospective randomized trial did not confirm this. RTOG 9305 randomized patients with newly diagnosed GBM to RT and BCNU with or without upfront radiosurgery.There was no survival benefit (the median survival with stereotactic radiosurgery was 14.1 months, compared with 13.7 months for patients who received only RT with BCNU) [48].

Chemotherapy

First-line therapy

Standard chemoradiotherapy includes concomitant and adjuvant temozolomide chemotherapy and leads to a median PFS of 6.9 months and an mOS of 14.6 months [7].

Although the 5-day regimen of temozolomide is the standard adjuvant therapy, alternative dosing schedules with more prolonged exposure have recently been tested to deplete MGMT in tumor cells, thus sensitizing tumor cells to the toxic effects of temozolomide. In the study by Tolcher *et al.*, MGMT activity appeared to decrease by 63 and 73% after 14 and 21 days of temozolomide treatment, respectively [49]. Thus, MGMT depletion, which is potentially achieved with the alternative-dosing schedule, may circumvent the disadvantage of an unmethylated *MGMT* gene promoter. However, these dose-dense regimens may cause more hematological toxicity. Dose-escalation was studied to evaluate whether temozoloide was better tolerated hematologically with the advantage of MGMT depletion. In that study, patients received 12 cycles of 1-week-on/1-week-off temozolomide, with 75 mg/m^2 for the first cycle, 100 mg/m^2 for the second, 125 mg/m^2 for the third and 150 mg/m^2 from the fourth to the 12th cycles. This dose-intensified regimen gave similar overall survival compared with the standard-dosing schedule, with tolerable hematological toxicity [50].

Alternative chemoradiotherapy protocols have been investigated. Recently, Glas *et al.* reported on the long-term survival of 39 prospectively documented patients who received RT and combined iomustine/temozolomide chemotherapy as first-line therapy for GBM. The rate of long-term survivors of greater than 24 months was 47.4%. Methylation status was a predictor of response to the combined protocol [51].

Second-line therapy

Clinical management of recurrent GBM is currently an open challenge [52]. The impact of re-resection before chemotherapy or RT is not clearly established [53]. This is why second-line chemotherapy options have been evaluated in several clinical trials for feasibility and effectiveness [54–56]. Recently, second-line Fotemustine chemotherapy was administered after the completion of a standard RT course and temozolomide chemotherapy. The disease control was 62%. PFS was 6.1 months and mOS survival from primary diagnosis was 24.5 months [57].

Targeted therapy

An improved understanding of the molecular biology underlying GBM has resulted in development of rational targeted therapies. Targets include angiogenesis, such as VEGF inhibitors, tyrosine kinase receptors including EGF or PDGF receptors and signal-transduction pathways components including mTOR, PI3K, farnesyltransferase and tumor progenitor cells.

Owing to the lack of effective treatments and the high vascularity that characterizes these tumors, anti-angiogenic therapy of gliomas is being studied. This approach is supported by encouraging preclinical data in both *in vitro* and *in vivo* models. Clinical studies have shown that these agents do not cause high toxicity.

Preclinical studies suggest that inhibition of VEGF improves glioma response to RT. Bevacizumab, a monoclonal antibody against VEGF, has shown promise in recurrent gliomas, but the safety and efficacy of concurrent bevacizumab with brain irradiation has not been extensively studied. Overall response rate of recurrent GBM to bevacizumab was 50%, 6-month PFS was 65%, mOS was 12.5 months and 1-year survival was 54% [58].

"Owing to the lack of effective treatments and the high vascularity that characterizes these tumors, anti-angiogenic therapy of gliomas is being studied."

Treatment efficacy, safety and pattern of response and recurrence in patients with recurrent high-grade glioma were assessed with the treatment of bevacizumab (an antibody that binds VEGF) and irinotecan (topoisomerase 1 inhibitor). The 6-month PFS was 63.7% and the overall survival was 11.5 months [59]. Resistance to angiogenic therapy is already evident and, in studies performed in animal models, this resistance was associated with the appearance of more invasive phenotypes. Future studies are aimed at determining whether it is possible to target not only the bulk of the tumor but also the putative tumor niche composed of tumor cells, vessels and stroma [60].

Timing of postsurgical therapy

Another concern is when to start adjuvant therapy after surgery. Adjuvant therapy consisting of concurrent RT and chemotherapy is usually not initiated until 4–5 weeks following surgery in order to allow sufficient recovery time and permit wound healing.

There is no evident reduction in survival by delaying initiation of RT within the relatively narrow constraint of 6 weeks. An unanticipated yet significantly superior outcome was identified for patients for whom RT was delayed beyond 4 weeks from surgery [61].

"The major expectation is targeted therapies tailored for each patient with the aid of molecular diagnostic tools."

Incidence and degree of regrowth in GBM between surgery and RT and correlation of regrowth with presurgical imaging and survival were assessed by Pirzkall *et al.* [62]. Adjuvant therapy was initiated at a median of 32.5 days (range: 14–46 days). In 53% of patients, new contrast enhancement was assumed to be indicative of tumor growth or a combination of tumor growth and surgical injury, and tumor regrowth was confirmed with the diffusion-weighted images and MR spectroscopy. Median survival was 14.6 months in patients with interim tumor growth and 24 months in patients with no growth.

Pseudoprogression

The occurrence of progressive MRI lesions immediately after the end of concurrent chemoirradiation with temozolomide, with spontaneous improvement without further treatment other than adjuvant temozolomide, is termed pseudoprogression [63]. Overall, 31 out of the 68 patients (45%; 95% CI: 33.2–56.8) with GBM had early progression on the first follow-up scan 4 weeks after RT and concomitant temozolomide, compared with the preradiotherapy imaging. Pseudo-early progression was noted in 15 out of the 31 patients (48%; 95% CI: 30.4–65.6) with GBM. In another study by Gerstner *et al.*, 18 out of 47 patients (38%) treated with radiation alone demonstrated enlargement on their first postradiation MRI scan and 11 of these 18 (61%) proved to have pseudoprogression, as defined by no further enlargement on stable therapy for 3 months following radiation treatment [64]. In total, 24 out of 45 patients (53%) treated with radiation and temozolomide had enlargement on their first postradiation MRI scan and 13 of these 24 (54%) had pseudoprogression. mOS in patients with pseudoprogression treated with radiation alone was 15.6 versus 12.8 months in those without pseudoprogression. mOS in patients treated with radiation and concomitant temozolomide who had pseudoprogression was 24.4 versus 15.9 months in those who did not have pseudoprogression. Presence of pseudoprogression, independent of treatment, was associated with prolonged PFS but not overall survival. In Brandes' study, after the administration of temozolomide concomitant with and adjuvant to RT in patients with GBM, the pattern of, and time to, recurrence are strictly correlated with MGMT methylation status [20]. Differential diagnosis of early clinical and neuroradiological worsening with treatment of RT concomitant with temozolomide followed by the adjuvant

temozolomide includes pseudoprogression, tumor recurrence and radiation necrosis. Further studies are needed to avoid useless reoperation and incorrect withdrawal of temozolomide [65]. According to National Cancer Institute of Canada recommendations, progressive disease is not declared until a patient is 3 months out from RT with temozolomide [66].

Epilepsy, antiepileptic drugs: chemotherapy interaction

The use of antiepileptic drugs is not well established in patients with GBM. Seizures may be the presenting symptom or develop during the course of the disease [67]. Although epilepsy was less frequent in high-grade glioma, in these patients, seizures were more difficult to control [68]. Neurosurgeons mostly use antiepileptic prophylaxis because intralesional bleeding, increase of edema and local electrolytic/pH changes may provoke seizure. However, the neuro-oncology literature does not support the prophylactic use of antiepileptics that do not prevent epileptogenesis [69] and most of these drugs may reduce antitumoral drug levels and chemotherapy efficacy [70]. Phenytoin is an old anticonvulsant drug commonly used in neurosurgery for its feasibility and rapid titration. Increasing evidence suggests that levetiracetam is effective in tumoral epilepsy. It is a new-generation drug that, because of the absence of interactions, is especially effective in patients with polytherapy and in those who need chemotherapy [71,72].

Who should receive which therapy?

Glioblastoma is a common and lethal primary brain tumor in adults. GBM is heterogeneous and notorious for resistance to therapy, which has been attributed to a multitude of deregulated molecular pathways. The expectation from preoperative neuroimaging studies is that they will be predictive of survival, utilizing anatomic, physiological and metabolic MR parameters to stratify patients to specific treatment protocols and for planning focal therapy [73]. The expectation from surgery is to remove as much tumor as possible for a survival benefit while preserving the quality of life of patients. The major expectation is targeted therapies tailored for each patient with the aid of molecular diagnostic tools.

Over the next 5 years, the question of importance of MGMT as a mechanism of GBM alkylator resistance will be resolved, and dose-dense temozolomide will either become the norm or will be discarded. Similarly, the role of *MGMT* promotor hypermethylation both for determining which patients should receive temozolomide and which patients receiving temozolomide have pseudoprogression will be clarified. The impact of anti-VEGF-targeted therapy on overall survival and quality of life will be elucidated. There will be more emphasis on targeted therapies based on profiling of the individual's tumor.

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David Schiff has served on advisory boards for Genentech, Schering-Plough, Exelixis, Pfizer and Bayer Pharmaceuticals. 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.

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