Management of Glioblastoma: State of the Art and Future Directions

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Abstract: Glioblastoma is the most common malignant primary brain tumor. Overall, the prognosis for patients with this disease is poor, with a median survival of <2 years. There is a slight predominance in males, and incidence increases with age. The standard approach to therapy in the newly diagnosed setting includes surgery followed by concurrent radiotherapy with temozolomide and further adjuvant temozolomide. Tumor-treating fields, delivering low-intensity alternating electric fields, can also be given concurrently with adjuvant temozolomide. At recurrence, there is no standard of care; however, surgery, radiotherapy, and systemic therapy with chemotherapy or bevacizumab are all potential options, depending on the patient's circumstances. Supportive and palliative care remain important considerations throughout the disease course in the multimodality approach to management. The recently revised classification of glioblastoma based on molecular profiling, notably isocitrate dehydrogenase (*IDH*) mutation status, is a result of enhanced understanding of the underlying pathogenesis of disease. There is a clear need for better therapeutic options, and there have been substantial efforts exploring immunotherapy and precision oncology approaches. In contrast to other solid tumors, however, biological factors, such as the blood-brain barrier and the unique tumor and immune microenvironment, represent significant challenges in the development of novel therapies. Innovative clinical trial designs with biomarker-enrichment strategies are needed to ultimately improve the outcome of patients with glioblastoma. **CA Cancer J Clin 2020;0:1-14. © 2020 American Cancer Society.**

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Introduction

Glioblastoma is the most common malignant primary brain tumor, representing approximately 57% of all gliomas and 48% of all primary malignant central nervous system (CNS) tumors.[1] Despite recent advances in multimodality therapy for glioblastoma incorporating surgery, radiotherapy, systemic therapy (chemotherapy, targeted therapy), and supportive care, the overall prognosis remains poor, and long-term survival is rare. Furthermore, the associated morbidity with progressive decline in neurologic function and quality of life can have a devastating impact on patients, caregivers, and families alike.[2] The era of precision oncology and immunotherapy heralds much promise in developing more efficacious and tolerable therapies to combat this aggressive disease. This review encompasses the latest advances in treatment for glioblastoma and future directions for precision oncology and immunotherapy approaches.

Incidence and Mortality

In the United States, the average annual age-adjusted incidence of glioblastoma is 3.21 per 100,000 population, based on registry data from 2011 through 2015.[1] Incidence varies by age and sex. The median age at diagnosis is 65 years, with rates

TABLE 1. Incidence and Relative Survival Rates of Glioblastoma in the United States (2000-2014) by Race or Ethnicity

RACE/ETHNICITY	AVERAGE ANNUAL AGE-ADJUSTED INCIDENCE RATE PER 100,000 POPULATION	1-YEAR RELATIVE SURVIVAL, %	5-YEAR RELATIVE SURVIVAL, %
Overall	4.23	41.4	5.4
Non-Hispanic white	4.71	40.7	4.8
Hispanic white	3.34	42.9	7.8
Black	2.24	42.0	6.8
Asian/Pacific Islander	2.00	50.2	8.8
American Indian/Alaska Native	1.88	Not presented	Not presented

Data source: Ostrom QT, Cote DJ, Ascha M, Kruchko C, Barnholtz-Sloan JS. Adult glioma incidence and survival by race or ethnicity in the United States from 2000 to 2014. *JAMA Oncol*. 2018;4:1254-1262.[3]

highest in the group aged 75 to 84 years. Glioblastoma is 1.58 times more common in males compared with females, with an annual age-adjusted incidence of 4.00 compared with 2.53 per 100,000 population, respectively. In terms of race or ethnicity (Table 1),[3] incidence is highest in non-Hispanic whites and lowest in American Indians or Alaska Natives, at an approximately 40% lower incidence.[3] Globally, glioblastoma incidence is highest in North America, Australia, and Northern and Western Europe.[4] The overall prevalence of glioblastoma in the United States is 9.23 per 100,000 population.[1]

There are few validated risk factors for glioblastoma. Exposure to ionizing radiation is the strongest risk factor associated with glioblastoma and is the only known potentially modifiable risk factor.[5] An inverse association between glioblastoma and a history of atopy, allergies, and other immune-related conditions has also been identified, although the exact underlying biological reasons for this have not been elucidated.[6,7] There are rare genetic syndromes that are associated with glioblastoma, such as Li-Fraumeni syndrome and Lynch syndrome; however, these account for <1% of cases.[8] Notably, there is no strong, conclusive evidence between mobile phone use and the development of glioma, but further studies are required, and the association remains controversial.[9]

Glioblastoma continues to have a poor prognosis. Advanced age, poor performance status, and incomplete extent of resection are all well established negative prognostic factors.[10,11] In elderly patients, the median survival is <4 months with best supportive care alone.[12] Molecular features, however, such as isocitrate dehydrogenase 1 (IDH-1) and IDH-2 mutation and MGMT methylation, confer a favorable prognosis[13,14] and are discussed in more detail below. Therapeutic advances have improved the median survival to >15 months in patients who receive treatment.[15,16] Overall, the 1-year relative survival rate was 41.4% for patients diagnosed in the United States between 2000 and 2014, with an improvement from 34.4% to 44.6% for the periods 2000 to 2004 and 2005 to 2014, respectively.[3] Despite these incremental improvements in shorter term survival rates over time, the 5-year survival rate has remained relatively constant, with a survival rate of only 5.8% at 5 years postdiagnosis.[1,3,17]

Histopathogenesis and Classification

Glioblastomas, along with other gliomas, are thought to arise from neuroglial progenitor cells.[18] The 2016 revision of the World Health Organization classification of CNS tumors restructured the classification of gliomas, predominantly with the incorporation of molecular features in addition to histopathologic appearance.[19] Importantly for the diagnosis of glioblastoma, the determination of IDH mutation status was included, resulting in distinct subgroups, namely, *glioblastoma, IDH–wild-type* and *glioblastoma, IDH-mutant* (Table 2).[19,20] A further subgroup, *glioblastoma, not otherwise specified* is reserved for cases in which full IDH evaluation is unable to be performed.

Histologically, both subtypes of glioblastoma remain characterized by high-grade astrocytic tumors that contain areas of microvascular proliferation and/or focal necrosis (Fig. 1).[21] Within IDH–wild-type glioblastoma, however, there also exist several specific histologic variants. Giant cell glioblastomas contain large, highly pleomorphic, multinucleated giant cells. Gliosarcomas display alternating areas with high-grade, malignant astrocytic features and sarcoma-like mesenchymal metaplasia.[22] Finally, epithelioid glioblastoma, a newly accepted variant, is characterized by tumor cells with prominent epithelioid morphology.[23] This variant is notable for a high proportion (approximately one-half) that harbors *BRAF* V600E mutations.[24] Currently, however, treatment recommendations do not differ based on histologic variant.[25] The characteristic magnetic resonance imaging (MRI) appearances of glioblastoma and the gliosarcoma variant are shown in Figure 1. There are no imaging features of giant cell glioblastoma or epithelioid glioblastoma that reliably distinguish these tumors.

IDH–wild-type glioblastoma corresponds to the clinically defined primary glioblastoma characterized by de novo development with no identifiable precursor lesion. This

TABLE 2. Features of IDH–Wild-Type and IDH-Mutant Glioblastomas

FEATURE	IDH–WILD-TYPE GLIOBLASTOMA	IDH-MUTANT GLIOBLASTOMA
Precursor lesion	Develops de novo	Diffuse astrocytoma, anaplastic astrocytoma
Proportion	Approximately 90%	Approximately 10%
Median age at diagnosis, y	62	44
Location	Supratentorial	Preferentially frontal
Histologic variants	Giant cell glioblastoma, gliosarcoma, epithelioid glioblastoma	—
Necrosis	Extensive	Limited
Molecular pathogenesis	*TERT* promoter mutation, *EGFR* amplification, LOH 10q, LOH 10p, *PTEN* deletion, MGMT promoter methylation, *BRAF* V600E mutation[a]	*IDH1/IDH2* mutation, *TP53* mutation, *ATRX* mutation, *PDGFRA* amplification, LOH 10q, LOH 19q

Abbreviations: IDH, isocitrate dehydrogenase; LOH, loss of heterozygosity.
[a]These apply to the epithelioid histologic variant only.
Adapted from Louis DN, Perry A, Reifenberger G, et al. The 2016 World Health Organization Classification of Tumors of the Central Nervous System: a summary. *Acta Neuropathol*. 2016;131:803-820[19] and Ohgaki H, Kleihues P. The definition of primary and secondary glioblastoma. *Clin Cancer Res*. 2013;19:764-772.[20]

cohort represents the overwhelming majority of patients with glioblastoma (approximately 90%), is more commonly diagnosed in older patients, and has a more aggressive clinical course.[20] Conversely, IDH-mutant glioblastoma or secondary glioblastoma typically arises from a precursor diffuse or anaplastic astrocytoma. This cohort represents approximately 10% of patients, it predominates in younger patients with a median age at diagnosis of 44 years, and it generally carries a better prognosis.

In addition to IDH mutation status, there is substantial evidence for other genetic and epigenetic changes characterizing differences in the pathogenesis of these 2 subgroups (Table 2).[19,20] For example, IDH–wild-type glioblastomas typically contain greater rates of epidermal growth factor receptor (*EGFR*) amplification, *TERT* promoter mutations, and *PTEN* deletion.[26-29] MGMT promoter methylation, seen in 30% to 50% of IDH–wild-type glioblastomas, may confer a favorable prognosis and response to alkylating chemotherapy, such as temozolomide.[30] IDH-mutant glioblastomas, having progressed from low-grade astrocytomas, are distinguished by the presence of *ATRX* and *TP53* mutations.[28,31,32] A CpG island hypermethylation phenotype may also characterize a subset of IDH-mutant glioblastomas, with promoter methylation at a large number of loci; these tumors may be associated with a better prognosis.[33]

The World Health Organization 2016 classification also added a new subtype under grade IV gliomas: *H3F3A* or *HIST1H3B/C* K27M (H3-K27M)-mutant, diffuse midline gliomas.[23] They occur predominantly in children and young adults and are characterized by an extremely poor prognosis.[34] These tumors may have previously been classified as glioblastomas but are now considered a distinct and separate entity.

Management

Multimodality Approach

The standard initial approach for most primary CNS tumors is maximal safe surgical resection, which allows for accurate histological diagnosis, tumor genotyping, and a reduction in tumor volume. For glioblastoma, based on the pivotal phase 3 trial published in 2005, this is followed by radiotherapy (60 Gray [Gy] over 6 weeks) with concomitant daily temozolomide and a further 6 cycles of maintenance temozolomide.[35] Compared with radiotherapy alone, in patients with good performance status (Karnofsky performance status ≥60), the median overall survival (OS) was 14.6 months for radiotherapy plus temozolomide versus 12.1 months for radiotherapy alone (hazard ratio [HR], 0.63; 95% CI, 0.52-0.75 [$P < .001$]). The addition of tumor-treating fields (TTFs)—low-intensity, alternating electric fields delivered by transducer arrays applied to the scalp for antimitotic therapy and given during maintenance temozolomide—also prolonged survival in patients with supratentorial disease.[36] The phase 3 trial demonstrated an improvement in progression-free survival (PFS) of 6.7 months for TTF plus maintenance temozolomide versus 4.0 months for temozolomide alone (HR, 0.63; 95% CI, 0.52-0.76 [$P < .001$]). There was also an OS benefit, with a median of 20.9 months versus 16.0 months noted in both groups, respectively (HR, 0.63; 95% CI, 0.53-0.76 [$P < .001$]).

Treatment options in the relapsed or recurrent setting are less well defined, with no established standard of care and little evidence for any interventions that prolong OS. Indeed, a significant proportion of patients may not even be eligible for second-line therapy.[37,38] Options include further surgical resection, reirradiation, systemic therapies such as lomustine or bevacizumab, combined approaches, or supportive care alone. A therapeutic treatment algorithm based on the most recent National Comprehensive Cancer Network guidelines is provided in Figure 2.[39] In both the newly diagnosed and recurrent setting, consideration of factors such as age, performance status, and genotype is also crucial. These are discussed below in greater detail.

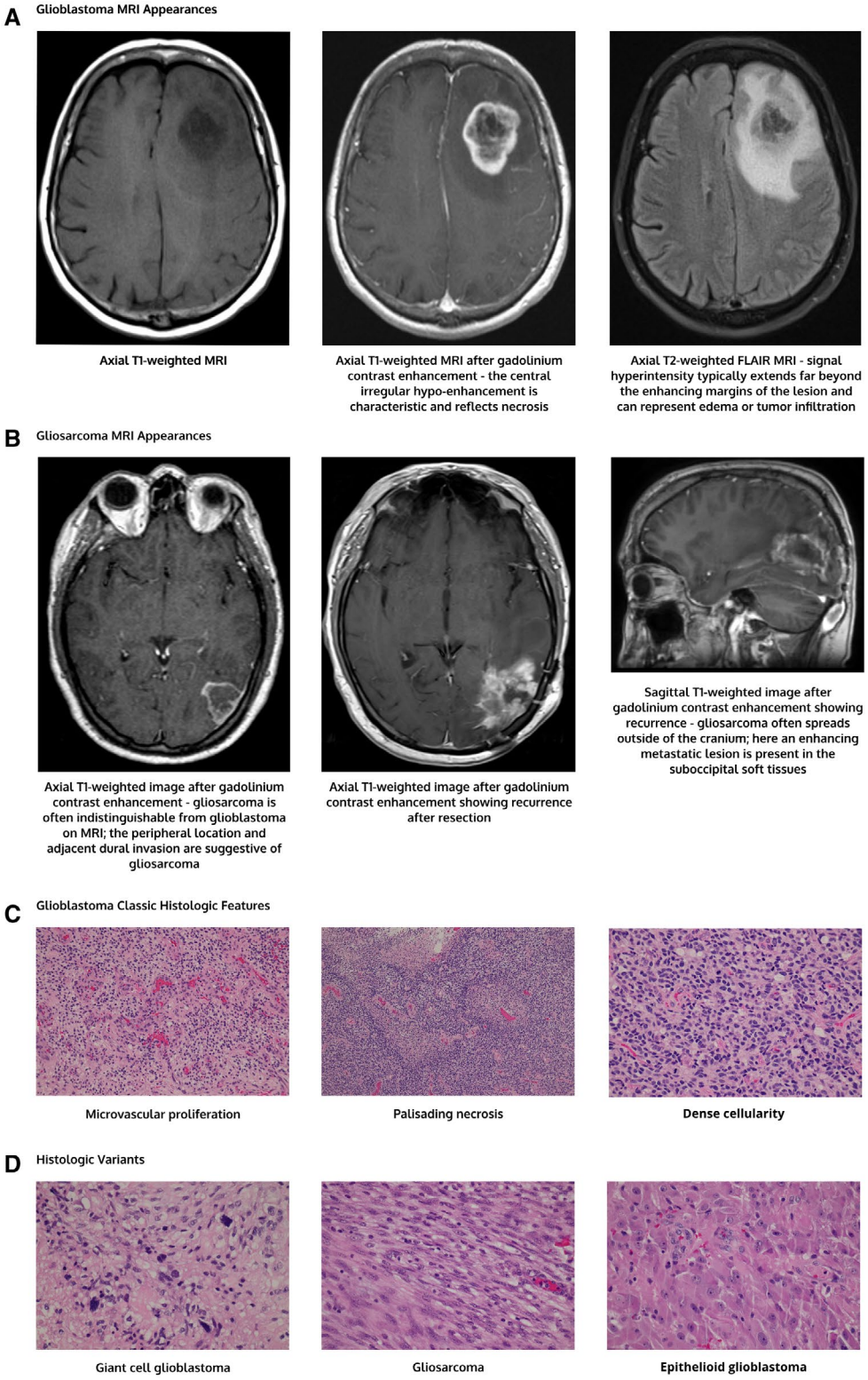

FIGURE 1. Radiographic and Histologic Appearances of Glioblastoma. (A) Typical magnetic resonance imaging (MRI) images of glioblastoma, (B) MRI images of gliosarcoma, (C) classic histologic features of glioblastoma, and (D) histologic variants of glioblastoma are shown. FLAIR indicates fluid-attenuated inversion recovery.

Surgery

The maximal resection that is safely feasible is the guiding principle for glioblastoma surgery. Although there are no randomized clinical trials to determine the extent of surgery, gross total resection (GTR) is generally recommended, if feasible. Retrospective analyses have indicated

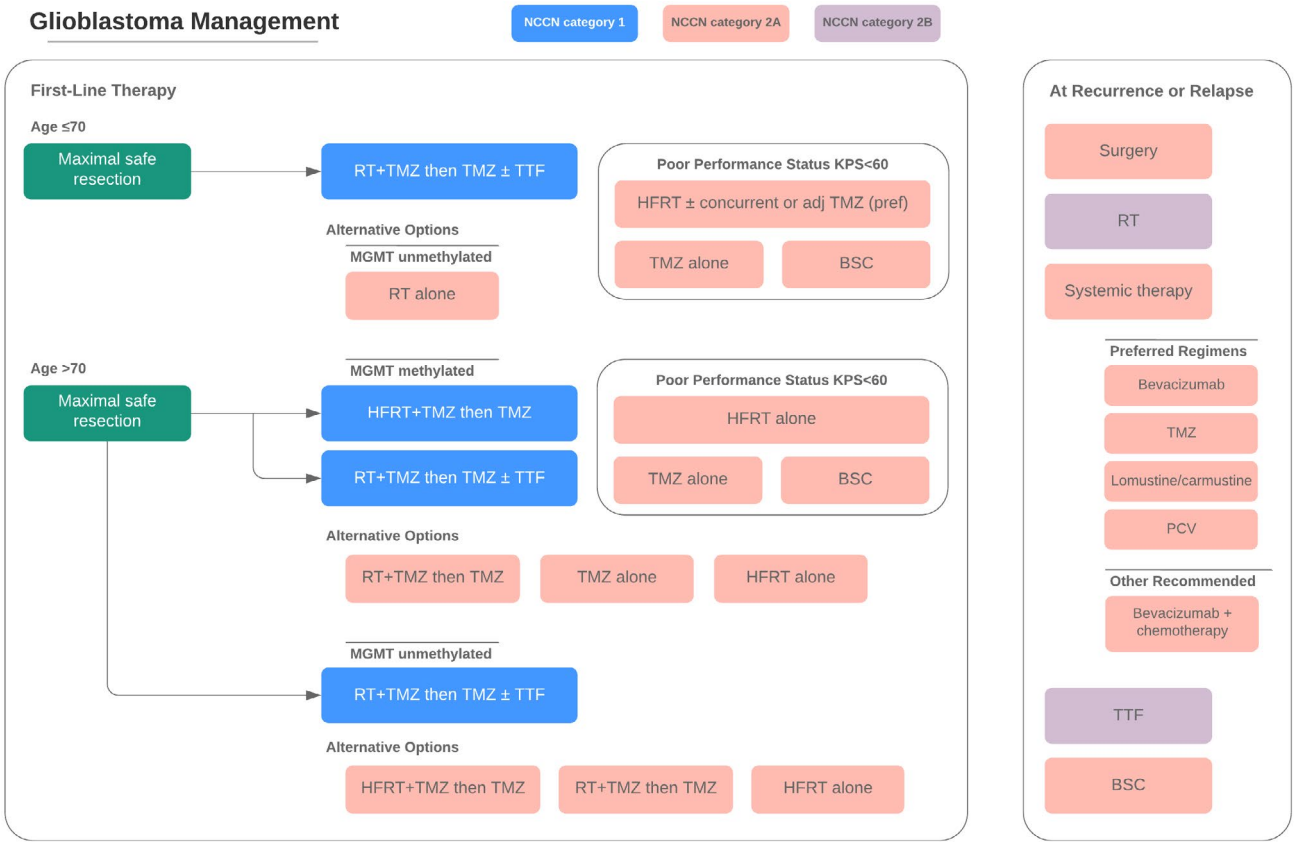

FIGURE 2. Treatment Algorithm for Glioblastoma. ± Indicates with or without; adj, adjuvant; BSC, best supportive care; HFRT, hyperfractionated radiotherapy; KPS, Karnofsky performance status; NCCN, National Comprehensive Cancer Network; pref, preferred; PCV, procarbazine, lomustine, and vincristine regimen; RT, radiotherapy; TMZ, temozolomide; TTF, tumor-treating fields.

that GTR may improve survival outcomes, even in elderly patients.[40-42] Survival may also be improved with maximal resection regardless of molecular status.[43] Prospective data from a randomized trial of fluorescence-guided resection with 5-aminolevulinic acid (5-ALA) also demonstrated an improvement in PFS.[44] A postoperative contrast-enhanced MRI should be performed within 48 hours, allowing determination of the extent of resection and serving as a baseline study for subsequent therapeutic interventions. For situations in which surgery or microsurgical resection is not possible, such as medical contraindication or patient refusal, stereotactic biopsy or open biopsy are also options.[45] This remains important for not only histological diagnosis but for further molecular testing, which can determine subsequent therapy.

There are numerous preoperative and intraoperative surgical adjuncts that can be used to facilitate safe and feasible resections and minimize surgical morbidity. These include preoperative imaging studies, such as functional MRI, and diffusion tensor imaging fiber tracking, particularly when tumors are located adjacent to or involve eloquent brain regions.[46-48] More commonly, awake craniotomy with motor and speech mapping through intraoperative cortical electrodes may be used and still results in good long-term functional outcomes.[49] Intraoperative fluorescence-guided surgery with 5-ALA is also increasingly used, and the previously mentioned randomized trial resulted in a 6-month PFS rate of 46.0% compared with 28.3% for conventional microsurgery with white light.[44,50] Nevertheless, uptake is limited by the cost of 5-ALA and the need for specialized equipment. Intraoperative imaging guidance with MRI may also help identify residual tumor volume and optimize the extent of resection.[51] Similarly, the requirement for specialized MRI-compatible operating room equipment, additional training, and costs limits its use to specialized centers.

In the recurrent setting, GTR, if feasible, should be considered, particularly if >6 months have elapsed since the initial surgery and in younger patients with good performance status.[52] A subgroup analysis of the DIRECTOR trial (Comparison of Two Dosing Regimens of Temozolomide in Patients With Progressive or Recurrent Glioblastoma; ClinicalTrials.gov identifier NCT00941460), although it was not designed to answer this question, indicated that survival and quality of life may be improved with GTR.[53] There have been no randomized trials specifically investigating the survival benefit of surgery in the recurrent setting.

The use of carmustine polymer wafers placed in the tumor resection cavity is also approved in both the initial

and recurrent settings and may be considered.[54] However, there are limited strong, prospective data on survival outcomes, especially when followed by standard radiotherapy and concomitant temozolomide, in newly diagnosed glioblastoma, with safety concerns remaining.[55-57] At recurrence, improved survival without increased toxicity has been demonstrated in a placebo-controlled randomized trial in patients with malignant glioma.[58] Nonetheless, more recent data, especially incorporating advances in our understanding of different molecular subgroups in glioblastoma, are lacking.

Radiotherapy

Radiotherapy has long been used in the treatment of glioblastoma to improve both local control and survival, and it remains an important modality. Currently, conventional radiotherapy after surgery delivers 60 Gy in 2-Gy fractions over 6 weeks in combination with temozolomide.[35] Other dose schedules have been investigated but without clear benefit. In particular, there is no indication for fractionated doses >60 Gy.[59] The risk of radiation necrosis with concurrent chemotherapy, depending on the volume of brain irradiated, and the dose to critical structures are important considerations. For example, with brainstem involvement or very large tumor volume, a slightly lower dose of 54 to 55.8 Gy in 1.8-Gy fractions or 57 Gy in 1.9-Gy fractions could be used. Tumor volumes are defined based on preoperative and postoperative MRI imaging with enhanced T1 and fluid-attenuated inversion recovery (FLAIR)/T2 sequences to first determine the gross tumor volume. There is some minor variation in the clinical tumor volume margins and for the use of 2 phases (primary and boost volumes) or 1 phase (single volume) for target volume definition, according to local institutional practice.[60] Other adjuncts or novel techniques to deliver radiation have also been investigated. So far, none have demonstrated superior efficacy over standard fractionated radiotherapy.

Elderly patients aged ≥70 years are known to have a worse prognosis and thus represent an important subgroup. Radiotherapy (50 Gy in 1.8-Gy fractions over 5 weeks) had a proven OS benefit compared with supportive care alone (29.1 weeks vs 16.9 weeks; HR, 0.47; 95% CI, 0.29-0.76 [$P = .002$]).[12] However, the benefit was modest, and many elderly patients may not be suitable for conventional long-course radiation. Consequently, studies have investigated other alternative approaches in these patients. Hypofractionated radiotherapy, with a biologically equivalent dose of 40 Gy delivered in 2.67-Gy fractions over 3 weeks, has been shown to result in similar survival outcomes.[61] Furthermore, hypofractionated radiotherapy in combination with concurrent and adjuvant temozolomide has since demonstrated improved OS compared with hypofractionated radiotherapy alone (9.3 vs 7.6 months; HR, 0.67; 95% CI, 0.56-0.80 [$P < .001$]).[62] Importantly, there was no difference in quality of life noted between the 2 groups. Even shorter fractionation schedules, such as 34 Gy in 3.4-Gy fractions or 25 Gy in 5-Gy fractions, can also be considered, especially in extremely frail patients.[63] It should be noted, however, that those trials did not contain control arms with standard, long-course, concurrent chemoradiation. In elderly patients with MGMT promoter methylation, temozolomide alone without radiation is another option and is discussed below. Ultimately, it is imperative to be cognizant that age alone should not represent the sole determining factor for duration and intensity of therapy. A detailed assessment of function in combination with molecular parameters is crucial before any intervention.[64]

At recurrence, reirradiation is an appropriate option in selected circumstances. Typically, this would be reserved for younger patients with good performance status.[60] Similar to surgery, there are no randomized trials demonstrating survival benefit. Nevertheless, there is retrospective evidence for improved outcomes with stereotactic radiosurgery (SRS) and short-course hypofractionated stereotactic radiotherapy, as most recurrences occur within previously irradiated brain.[60] The safety of SRS in this setting has been demonstrated in a phase 1 study.[65] Hypofractionated stereotactic radiotherapy may confer a lower risk for radionecrosis, although there is no direct comparison with SRS.[66] There is no standard with regard to dose fractionation regimen, target volume, or stereotactic system. Combining reirradiation with systemic therapy, particularly bevacizumab, has also been explored prospectively and potentially may also reduce rates of radionecrosis.[67,68]

Systemic Therapies

Standard first-line chemotherapy consists of temozolomide (75 mg/m^2 daily) during radiotherapy followed by a further 6 cycles of temozolomide (150-200 mg/m^2 on days 1-5 every 28 days).[35] Common toxicities of temozolomide include nausea and myelosuppression, especially thrombocytopenia and neutropenia, and occur more commonly during the adjuvant therapy period. The benefit from temozolomide may be driven largely by patients who have MGMT promoter methylation, which epigenetically silences the gene.[13] MGMT is crucial in DNA repair activity, resulting in resistance to temozolomide therapy. Therefore, in patients aged ≥70 years with good performance status and MGMT promoter methylation, concurrent chemoradiation with adjuvant temozolomide remains the treatment of choice. There are no data directly comparing chemoradiation with temozolomide monotherapy. However, in this patient population (or in MGMT-methylated younger patients with poor performance status [Karnofsky performance status < 60]), in which there are concerns for tolerability or because of patient preference, single-agent temozolomide (150-200 mg/m^2 on days 1-5

every 28 days) for 6 cycles after surgery is an option based on previous trials.[63,69] There has been no benefit demonstrated with longer or dose-dense regimens of temozolomide,[70,71] and such higher doses are associated with greater toxicity and deterioration in function and quality of life. The addition of antiangiogenic therapy with bevacizumab, a humanized monoclonal antibody that inhibits VEGF, has been investigated in 2 large randomized trials. Despite prolonging PFS in both trials, bevacizumab was associated with increased toxicity, whereas there was no difference in OS.[72,73]

After standard concurrent chemoradiation and adjuvant chemotherapy, most patients recur within 6 months. There is no standard-of-care systemic therapy in the second-line setting; however, alkylating chemotherapy is commonly used. Lomustine, carmustine, and rechallenge with temozolomide are all potential options, although the benefits are modest, and only patients with MGMT promoter methylation are likely to benefit.[74-76] Salvage chemotherapy with combined procarbazine, lomustine, and vincristine may have some activity, although this is limited by much greater toxicity.[77,78] Overall, the quality of data for individual chemotherapy agents or regimens is poor, and comparison across studies is difficult. Early studies were conducted before standard temozolomide in the first-line setting, and many did not account for our improved molecular understanding, particularly with regard to IDH mutation status.

Single-agent bevacizumab was initially granted accelerated US Food and Drug Administration (FDA) approval based on early phase 2 data indicating improved PFS, although no OS benefit was seen.[79,80] Subsequent randomized phase 3 trials have demonstrated that bevacizumab in combination with lomustine improves PFS compared with lomustine alone (4.2 months vs 1.5 months; HR, 0.49; 95% CI, 0.39-0.61 [$P < .001$]), but again without OS benefit.[81] Typically, the combination of bevacizumab with chemotherapy is recommended after failure on bevacizumab alone.[39] A range of chemotherapy partners, including lomustine, carmustine, and temozolomide, has been studied.[81-83] However, there are no data demonstrating a survival benefit with any of these regimens. The lack of OS benefit with single-agent bevacizumab also remains a point of contention[84] and, notably, it is not approved in Europe. Nevertheless, it can improve quality of life with decreased corticosteroid use[37] and thus sometimes is reserved for symptomatic patients at later recurrences.[25]

Locoregional Therapies

TTF is approved as adjuvant therapy in combination with temozolomide based on the PFS and OS benefit demonstrated in the open-label phase 3 EF-14 trial (Effect of NovoTTF-100A Together With Temozolomide in Newly Diagnosed Glioblastoma Multiforme; ClinicalTrials.gov identifier NCT00916409).[36] The earlier phase 3 EF-11 trial (Effect of NovoTTF-100A Recurrent Glioblastoma Multiforme; ClinicalTrials.gov identifier NCT00379470) also demonstrated efficacy in the recurrent setting, with an objective response rate of 14% compared with 9.6% for physician's-choice chemotherapy, although the primary endpoint of OS was not met.[85] Practically, TTF consists of 4 transducer arrays applied for at least 18 hours daily to the shaved scalp and connected to a portable device.[86] Despite FDA approval, there remains debate and controversy regarding the evidence and use of TTF. In particular, the unblinded nature and delayed time of randomization in the EF-14 trial are prominent concerns.[87] Cost, treatment compliance, and skin toxicity are additional barriers limiting the uptake of this treatment modality. Nevertheless, secondary analysis of the EF-14 trial demonstrated no difference in health-related quality of life with the use of TTF apart from increased itchy skin.[88] Consequently, TTF can be considered as an option in willing and eligible patients.

Supportive Care

Patients with glioblastoma frequently experience significant and progressive neurologic symptoms throughout their disease course, both from the primary tumor itself and because of toxicities from therapy. This interferes with daily functioning and usual life activities, commonly with an inability to work; consequently, these patients often require greater levels of nursing and social support.[89] Furthermore, these issues can become more pronounced and prominent during the end-of-life phase.[90] Supportive care remains of paramount importance in the multimodality approach to the management of glioblastoma.

Seizures may occur in up to 80% of patients at some time during the disease course, and many will require long-term antiepileptic therapy.[91] The principles of antiepileptic therapy should aim for the lowest dose possible for seizure control to avoid side effects and minimize drug-drug interactions.[92] Levetiracetam has been studied most extensively in patients with glioblastoma, is safe, and has relatively few interactions with other commonly used drugs.[93] The routine prophylactic use of antiepileptic drugs in patients with no history of seizures is not recommended, although they may be used temporarily in the perioperative setting.[94]

Corticosteroids are frequently used to reduce peritumoral vasogenic edema for symptomatic benefit. Dexamethasone is generally preferred because of its lack of mineralocorticoid activity.[95] Side effects limit the long-term use of corticosteroids; therefore, the lowest dose for the shortest time possible is recommended. There is also growing evidence that corticosteroid use may be associated

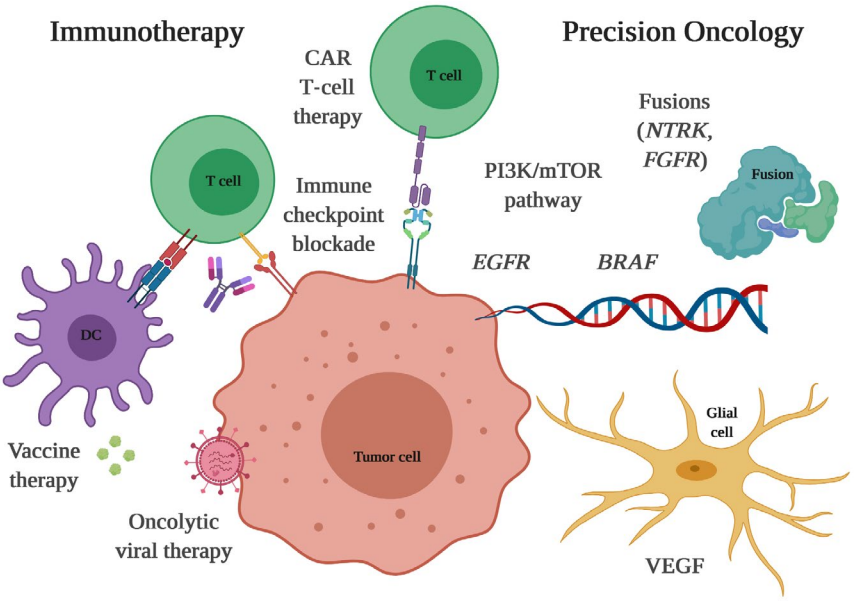

FIGURE 3. Novel Therapeutic Targets for Glioblastoma. CAR indicates chimeric antigen receptor; DC, dendritic cell; *EGFR*, epidermal growth factor receptor; *FGFR*, fibroblast growth factor receptor; mTOR, mammalian target of rapamycin; VEGF, vascular endothelial growth factor.

with shorter survival, possibly related to protective effects from radiotherapy-induced and chemotherapy-induced genotoxic stress.[96]

Glioblastoma and other high-grade gliomas confer a high risk for venous thromboembolism (VTE), which occurs in up to 20% of patients at 1 year.[97] Multiple factors contribute to this increased risk, including increased activation of clotting factors and thrombin in glioblastoma, the need for neurosurgical procedures, and high rates of impaired limb motility.[95,98] VTE prophylaxis with low-molecular-weight heparin should be started within 24 hours postoperatively, after the induction of anesthesia, to reduce the perioperative risk of intracranial hemorrhage.[99] Prolonged VTE prophylaxis after the perioperative period also increases the risk of intracranial hemorrhage.[100,101] Treatment of VTE is generally lifelong with low-molecular-weight heparin unless there are contraindications, and there is a lack of evidence for newer oral anticoagulants.[102]

Lymphopenia occurs commonly with corticosteroid use, temozolomide chemotherapy, and radiotherapy, with each treatment modality causing toxicity to lymphocytes. Consequently, particularly during concurrent chemoradiation in newly diagnosed glioblastoma, patients are at risk for opportunistic infections such as Pneumocystis jirovecii pneumonia, and antibiotic Pneumocystis jirovecii pneumonia prophylaxis is recommended.[103]

Finally, the importance of the active and early involvement of palliative care services is increasingly recognized as awareness of the complex care needs of patients with glioblastoma and their caregivers improves. The management of symptoms, such as fatigue, mood and behavioral disorders, and impaired cognition, and advanced care planning are all crucial components in improving quality of life and reducing symptom burden.[102]

Future Directions

Despite incremental advances in the therapeutic approach to glioblastoma, 5-year survival rates remain <10%.[104] There is a clear need for improved therapeutic strategies, and there have been substantial efforts exploring novel approaches in areas such as immunotherapy and precision oncology. This is driven by an enhanced understanding of the underlying molecular biology of glioblastoma and its interaction with the immune system. In contrast to other solid tumors, however, biological factors such as the blood-brain barrier and the unique tumor and immune microenvironment represent significant challenges in the development of novel therapies. Innovative clinical trial designs with biomarker-enrichment strategies are needed to ultimately improve the outcome of patients with glioblastoma. Indeed, National Comprehensive Cancer Network guidelines emphasize the importance of clinical trials in the optimal management of patients with glioblastoma, encouraging participation where possible.[39] An exhaustive discussion on the many novel diagnostic, monitoring, and therapeutic approaches for glioblastoma currently under investigation is not within the scope of the current article. The reader is encouraged to further explore many excellent reviews on these topics elsewhere. Herein, we highlight the current state of and future directions for immunotherapy and precision oncology approaches for glioblastoma (Fig. 3).

Immunotherapy

Immunotherapy has transformed the management of many cancers, and consequently there has been considerable investigation and research into immune-based therapeutic approaches for glioblastoma. The CNS has a unique immune microenvironment and was long thought to simply be an immune-privileged site. However immune surveillance in the CNS and the role of myeloid cells is now known to be much more complex.[105] For example, recent findings have revealed dedicated lymphatic channels that run parallel to dural venous sinuses, which allow antigen-presenting cells in the brain to traverse to deep cervical lymph nodes for T-lymphocyte and B-lymphocyte priming.[106] Evidence in glioblastoma also indicates there may be distinct cancer-associated immunosuppressive mechanisms at play.[107] In general, glioblastomas have a relative paucity of tumor-infiltrating lymphocytes[108]; the lymphocytes that are present demonstrate increased fractions of CD4-positive T cells and FoxP3-positive regulatory T cells.[109,110] Signaling pathways may be induced that suppress the immune response, such as the expression of IDO enzymes[111] and STAT3 signaling.[112] Furthermore, standard therapies with surgery, radiotherapy, temozolomide chemotherapy, and corticosteroids may all have immunosuppressive effects, further emphasizing opportunities to target the immune response for novel therapies.[113] Immunotherapy modalities that have been investigated in glioblastoma can be broadly categorized into vaccine therapies, immune checkpoint blockade, oncolytic viral therapies, and chimeric antigen receptor T-cell therapies.

Vaccine approaches that may harness the adaptive immune system studied to date include rindopepimut, a peptide vaccine that targets EGFR variant III (EGFRvIII). This mutant variant of EGFR is constitutively expressed in up to 20% of patients with glioblastoma.[114] The randomized phase 3 trial, however, failed to show an improvement in OS for rindopepimut when given after surgery and chemoradiation with adjuvant temozolomide in EGFRvIII-positive patients.[115] A randomized phase 2 trial of rindopepimut in combination with bevacizumab, compared with bevacizumab plus control, in recurrent, EGFRvIII-positive glioblastoma suggested a potential PFS benefit, indicating that the timing of therapy or combination approaches may be important.[116] Dendritic cell (DC)-based vaccines have also been developed, such as DCVax-L (Northwest Biotherapeutics Inc), using autologous tumor tissue to generate tumor antigens, and early readouts from the randomized phase 3 trial of DCVax-L in combination with adjuvant temozolomide are promising.[117] Numerous other vaccines are in clinical development in early-phase trials, with targets such as IDH1 or multipeptide vaccines.[113]

Oncolytic viral therapies may activate antitumor immune responses[118] and, prominently, a recombinant oncolytic poliovirus, PVSRIPO, has received FDA *breakthrough therapy* designation. This was based on early data from a phase 1 trial of PVSRIPO in recurrent glioblastoma that demonstrated a 21% OS rate at 2 years that was sustained at 3 years.[119] The virus, delivered by intratumoral infusion, has its internal ribosome entry site replaced with human rhinovirus type 2 to eliminate neurovirulence.[120] Uptake by glioblastoma cells is enhanced because of increased cell surface expression of CD155, the poliovirus receptor.[121]

Trials of immune checkpoint inhibitors, predominantly targeting PD-1/PD-L1 and/or CTLA-4, have been ongoing in glioblastoma, although initial results have been disappointing. The phase 3 trial of nivolumab versus bevacizumab in recurrent glioblastoma demonstrated no improvement in OS.[122] Exploratory phase 1 cohorts within this trial, investigating combination nivolumab and ipilimumab, indicated increased rates of toxicity, and this combination has not been pursued further.[112] Nevertheless, there have been isolated reports of responses to anti–PD-1 inhibitors in patients with germline mismatch repair-deficient (dMMR) tumors (Lynch syndrome) or microsatellite instability (MSI)-high status.[113,114] This is consistent with the tumor-agnostic FDA approval for pembrolizumab in patients who have microsatellite instability-high status or mismatch repair–deficient tumors,[115] representing a rare subset of patients with glioblastoma.[116] Similarly, in the phase 1a trial of atezolizumab (an anti–PD-L1 inhibitor), prolonged disease control was seen in a patient with *POLE*-mutant glioblastoma who had a hypermutant phenotype.[123]

Finally, chimeric antigen receptor (CAR) T-cell therapy with genetically modified T cells is another rapidly expanding area of investigation, with dramatic responses seen in an individual case.[124] Preliminary findings from early trials indicate that on-target activity may be seen with increased T-cell infiltration.[125] However, further data are required to understand potential efficacy.

Precision Oncology and Targeted Therapy

Advances in next-generation sequencing technology have allowed for a greater understanding of the molecular underpinnings and genomic landscape of glioblastoma.[126] Subsequently identifying targetable and actionable driver genomic alterations promises to expand the list of therapeutic options. Intratumoral heterogeneity, clonal selection, and tumor evolution over time, particularly in response to therapy, also are crucial to guide the selection and sequencing of therapies. Emerging evidence suggests that the strongest selective pressures may occur early during glioblastoma development,[127] highlighting the importance of upfront, comprehensive molecular profiling for optimal management.

In addition to immunotherapy approaches, EGFR-targeted therapies with tyrosine kinase inhibitors (TKIs) have been explored. They have largely failed to demonstrate significant efficacy, although early trials were conducted in unselected populations, and the evidence of on-target effects varied.[128-130] Depatuxizumab mafodotin, an antibody drug

conjugate targeting EGFR, has more recently shown promising activity in a phase 2 trial in combination with temozolomide for recurrent, *EGFR*-amplified glioblastoma.[131] However, the phase 3 trial of depatuxizumab mafodotin in combination with standard therapy for newly diagnosed, *EGFR*-amplified glioblastoma was stopped early because of futility, and no OS benefit was observed at an interim analysis.[132]

The PI3K/mTOR pathway is commonly dysregulated in IDH–wild-type glioblastoma, with frequent *PTEN* deletions, *PIK3CA* mutations, or *PIK3R1* mutations,[126] although trials of targeted agents so far have not shown efficacy. Buparlisib, a pan-PI3K TKI, demonstrated minimal single-agent efficacy in patients with recurrent, PI3K-activated glioblastoma.[133] Importantly, however, incomplete PI3K pathway blockade was seen in correlative tumor tissue analyses. mTOR inhibitors, such as everolimus and temsirolimus, have also demonstrated a lack of efficacy in phase 2 trials.[134,135]

Following on from bevacizumab, there have been several trials of VEGF or multikinase TKIs to target the tumor microenvironment, with mixed results. Cediranib, an oral VEGF TKI, failed to show a survival benefit in a randomized phase 3 trial, either as monotherapy or in combination with lomustine, in recurrent glioblastoma.[136] More recently, a phase 2 trial of regorafenib in the relapsed setting showed an efficacy signal with an OS benefit compared with lomustine.[137] Trials of other agents, however, such as tivozanib,[138] pazopanib,[139] and sunitinib,[140] have shown minimal activity, and suggest that VEGF monotherapy may have a limited role in an unselected population.

BRAF V600E activating mutations are present in approximately 6% of glioblastomas,[141] with a predominance in the epithelioid glioblastoma histologic variant. Preliminary data from studies of vemurafenib indicated modest activity in *BRAF* V600E–mutant glioblastoma.[142] Combination BRAF/MEK inhibition with dabrafenib and trametinib, however, may be more promising.[143]

The incidence of gene fusions is increasingly recognized in glioblastoma, occurring in up to 50% of tumors,[144] with targetable fusions involving a tyrosine kinase domain in approximately 10%.[145] These predominantly include *FGFR*, *MET*, and *NTRK* fusions, with rare instances of *EGFR*, *ROS1*, and *PDGFRA* fusions.[145-147] NTRK TKIs, such as larotrectinib and entrectinib, have already received tumor-agnostic FDA approval for patients with solid tumors harboring *NTRK* fusions, based on impressive response rates in early basket trials.[148,149] There were patients with glioblastoma on those trials, and subgroup analyses suggested a benefit from NTRK inhibitors in these patients.[150,151] There are also numerous FGFR TKIs in development, and there are documented cases of response.[152]

Although many trials of targeted therapies to date have not demonstrated significant efficacy, better enrichment strategies using precision biomarkers will increase the chances of future success. An enhanced understanding of the underlying molecular biology will also guide combination approaches. Innovative and novel clinical trial design is needed to improve our ability to evaluate many of these novel targeted therapies.

Conclusions

The multimodality approach to glioblastoma remains the cornerstone of the therapeutic approach in the newly diagnosed setting. A multitude of novel therapies have exhibited promising signs of efficacy in the recurrent or relapsed setting to achieve more durable responses in patients with this aggressive cancer. Ultimately, this must be combined with improved supportive and palliative care to not only improve survival outcomes but also to enhance the quality of life for both patients and caregivers. ■

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