Epidemiologic and Molecular Prognostic Review of Glioblastoma

Jigisha P. Thakkar, Therese A. Dolecek, Craig Horbinski, Quinn T. Ostrom, Donita D. Lightner, Jill S. Barnholtz-Sloan, and John L. Villano

Abstract

Glioblastoma multiforme (GBM) is the most common and aggressive primary central nervous system malignancy with a median survival of 15 months. The average incidence rate of GBM is 3.19/100,000 population, and the median age of diagnosis is 64 years. Incidence is higher in men and individuals of white race and non-Hispanic ethnicity. Many genetic and environmental factors have been studied in GBM, but the majority are sporadic, and no risk factor accounting for a large proportion of GBMs has been identified. However, several favorable clinical prognostic factors are identified, including younger age at diagnosis, cerebellar location, high performance status, and maximal tumor resection. GBMs comprise of primary and secondary subtypes, which evolve through different genetic pathways, affect patients at different ages, and have differences in outcomes. We report the current epidemiology of GBM with new data from the Central Brain Tumor Registry of the United States 2006 to 2010 as well as demonstrate and discuss trends in incidence and survival. We also provide a concise review on molecular markers in GBM that have helped distinguish biologically similar subtypes of GBM and have prognostic and predictive value.

Introduction

Glioblastoma multiforme (GBM) is the most aggressive diffuse glioma of astrocytic lineage and corresponds to grade 4 based on WHO classification (1). GBM is the most common brain and central nervous system (CNS) malignancy, accounting for 45.2% of malignant primary brain and CNS tumors, 54% of all gliomas, and 16% of all primary brain and CNS tumors (2). GBM remains an incurable disease, with a median survival of 15 months (3, 4). Treatment is complex and initially consists of maximal safe surgical resection followed by radiotherapy (RT) with concurrent temozolomide (TMZ) chemotherapy followed by 6 cycles of maintenance TMZ (5).

GBMs comprise of primary and secondary subtypes, which evolve through different genetic pathways, affect patients at different ages, and have differences in outcomes (6). Primary (de novo) GBMs account for 80% of GBMs and occur in older patients (mean age, 62 years). Secondary GBMs develop from lower-grade astrocytoma or oligodendrogliomas and occur in younger patients (mean age, 45 years; refs. 6–9). The WHO recently added a rare subtype of GBM termed “with oligodendroglioma component” (GBM-O), defined as GBM having areas that resemble anaplastic oligodendroglioma with hallmark features of GBM, necrosis with or without microvascular proliferation (1).

Epidemiology

Incidence and risk factors

Based on the 2013 Central Brain Tumor Registry of the United States (CBTRUS) report, the average annual age-adjusted incidence rate (IR) of GBM is 3.19/100,000 population (2). This is the highest IR among brain and CNS tumors with malignant behavior followed by diffuse astrocytoma grade 2 (0.56/100,000), and malignant glioma not otherwise specified (0.46/100,000; ref. 2). Incidence is highest in the northeast and lowest in the south-central region of the United States (Fig. 1); however, these differences could reflect differences in cancer reporting by region (2). Many genetic and environmental factors have been studied in GBM but no risk factor that accounts for a large proportion of GBM has been identified and like many cancers are sporadic (10).

Age. GBM is primarily diagnosed at older ages with the median age of diagnosis of 64 years (2, 11). It is uncommon in children accounting only approximately 3% of all brain and CNS tumors reported among 0 to 19 year olds (2). The incidence continues to rise with increasing age, peaks at 64 years, and continues to rise with age in the older age groups.

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75 to 84 years of age and drops after 85 years (Fig. 2; ref. 2). With a growing and aging U.S. population, the number of cases is expected to increase (12).

**Gender.** Differences in incidence and death rates for specific cancers based on race and ethnic groups as well as gender, suggest potential identifiable biologic and environment based variables (13, 14). A higher incidence of GBM has been reported in men as compared with women (Fig. 2; refs. 2, 11, and 15–17). The IR of GBM is 1.6 times higher in males as compared with females (3.97 vs. 2.53; ref. 2) with a higher frequency of primary GBMs men (male-to-female ratio, 1:33) and secondary GBMs in women (male-to-female ratio, 0:65; 7).

**Race/ethnicity.** Whites have the highest incidence rates for GBM, followed by blacks, Asian/Pacific Islanders (API), and American Indian/Alaska Native (AI/AN; Fig. 3A; ref. 2). From 2006 to 2010, whites had 2 times higher IR as compared with blacks (3.45 vs. 1.67; Fig. 3A) and non-Hispanics had higher IR as compared with Hispanics (3.26 vs. 2.45; Fig. 3B; refs. 2 and 11).

Figure 1. Age-adjusted incidence rates of glioblastoma by region in the United States, CBTRUS Statistical Report, SEER 2006–2010. Rates are per 100,000 (2).
Site. GBMs are more commonly located in the supratentorial region (frontal, temporal, parietal, and occipital lobes), are rarely seen in the cerebellum, and are very rare in the spinal cord (18, 19). A Surveillance Epidemiology and End Results (SEER) population-based study (1973–2009) did find a difference in the behavior of GBM at these 2 locations (19). When compared with supratentorial location, cerebellar GBMs occurred in younger patients, occurred less commonly in whites and were smaller in size (19–21). Cerebellar GBM occurs rarely in adults, accounting for 0.4% to 3.4% of all GBMs (21). Patients with cerebellar GBM are significantly younger than those with supratentorial tumors (median age of 50–56 years in contrast to 62–64 years for patients with supratentorial GBM; ref. 21). A population-based study of the Los Angeles County reported that, GBM had the highest incidence for frontal lobe tumors and for tumors that involved 2 or more lobes (overlapping tumors), followed by tumors in the temporal and parietal lobes (11). The male-to-female ratio was elevated for each brain subsite except the posterior fossa; occipital lobe amongst these sites had the greatest ratio (11).

Summary of risk. Factors associated with GBM risk are prior therapeutic radiation, decreased susceptibility to allergy, immune factors and immune genes, as well as some single nucleotide polymorphisms (SNP) detected by genome wide association studies (GWAS; refs. 22–25). A lower risk of gliomas has been associated with allergies or atopic diseases (e.g., asthma, eczema, psoriasis) and the protective effect does not vary by major histologic subtypes of glioma or by histologic grade (26–28). In addition, short term (<10 years) use of anti-inflammatory medications is associated with a protective effect against GBM, especially among individuals with no history of asthma or allergies (29). GWAS have detected increased risk of high-grade glioma with inherited variation in a region containing cyclin-dependent kinase inhibitor 2B (CDKN2B) on Chromosome 9p21 and in 2 SNPs in regulator of telomere elongation helicase 1 (RTEL1; ref. 25). Other factors associated with GBM risk are high socioeconomic status (SES) and taller height (11, 30). The higher SES groups were up to 70% more likely to be diagnosed with GBM in the frontal lobes and they had higher IR for all tumor sites, except for posterior fossa tumors (11).

There is no substantial evidence of GBM association with life-style characteristics such as cigarette smoking, alcohol consumption, use of drugs of any kind, or dietary exposure to N-nitroso compounds (cured or smoked meat or fish; ref. 31). Inconsistent and nondefinitive results have been published regarding the risk of glioma with use of mobile phones (32–37).

Survival and prognostic factors

GBM has a poor prognosis with quite low relative survival estimates, only a few patients reaching long-term survival status of 2.5 years and less than 5% of patients survive 5 years postdiagnosis (Fig. 4A; refs. 2 and 38). The relative survival for the first year after diagnosis is 35% and it falls in the second year postdiagnosis (13.7%) and thereafter (ref. 2; Fig. 4A). A population-based study found that the first quarter of the second year (5th quarter) postdiagnosis is considered to be the peak incidence of mortality and the risk of death decreases to half of its rate at 2.5 years (38). Despite these unfavorable survival and mortality estimates, there exist reassuring data for conditional probability of survival in GBM (likelihood of surviving into the future based on previous survival; ref. 39). Patients surviving past 2 years from diagnosis have a relatively favorable conditional probability of survival into the future compared with newly diagnosed patients (39, 40).

GBM is an aggressive neoplasm, which has a median survival of 3 months if untreated (41, 42). Combined modality therapy with surgery, RT, and chemotherapy
has significantly improved survival of patients with GBM. Surgical intervention has decompressive and cytoreductive effects and there is increasing evidence of a significant survival advantage with complete resection (43, 44). Tumor fluorescence derived from 5-aminolevulinic acid enables more complete resections of contrast-enhancing tumor, leading to improved progression-free survival (PFS) in patients with malignant gliomas (45).

In 2004, the European Organization for Research and Treatment of Cancer (EORTC) group and National Cancer Institute of Canada Clinical Trials Group (NCIC) presented a phase III study demonstrating a significant improvement in 2-year overall survival (OS) from 10.4% with postoperative radiotherapy alone to 26.5% with postoperative combined radiotherapy plus TMZ and an improvement in median OS from 12.1 to 14.6 months (5). These results also translated into a survival benefit in a population-based cohort after introduction of TMZ in 2005 (3). In addition, a survival benefit was seen in each recursive partitioning analysis (RPA) class with combined modality therapy as compared with RT alone (46). The RPA classification is based on pretherapeutic prognostic factors that have a more powerful impact on survival than any adjuvant treatment (47). It helps determine a particular category of patients who will benefit most from newer therapeutic approaches. The RTOG RPA classification is based on age, Karnofsky Performance Status (KPS), and neurologic function; classes III and IV include anaplastic astrocytomas (AA) as well as GBM. The EORTC RPA classification is based on age, WHO performance status, and neurologic function determined by mini mental status exam; classes III and IV include only patients with GBM (46). The overall median survival and 2-year survival was highly statistically different after combined modality treatment (RT + TMZ) among the 3 prognostic EORTC RPA classes (classes III–V; ref. 46). The survival benefit of combined treatment as compared with RT alone was highest in RPA class III, advantage in class IV remained highly significant, and small difference of borderline significance was found in class V (46).

Several variables affect the prognosis of patients with GBM, including age, preoperative performance status, tumor location, preoperative imaging characteristics of the tumor, and extent of resection (7, 44, 47). Site. The prognosis of cerebellar GBMs with respect to their supratentorial counterparts has been unclear.
However, age-associated differences in survival are apparent at a younger age in cerebellar as compared with supratentorial GBMs (40 years vs. 60 years; refs. 19–21). Among supratentorial GBMs, frontal lobe tumors have better survival as compared with other sites (51, 52).

**Gender.** The relative survival in both men and women is the highest at 1 year (36.7% and 32.8%, respectively), it declines steeply in the second year (13.7% in both genders) and gradually thereafter, with a very low 5-year survival rate (4.7% and 4.6%, respectively; Fig. 4B; ref. 2). Men have a significant survival advantage than women in the first-year postdiagnosis but the difference is not significant thereafter (2).

**Race.** Population-based studies do not demonstrate a race-based disparity in GBM survival (53–57). No significant differences in GBM survival have been observed among whites and blacks; however, Asian Pacific Islanders have a significantly better survival rates than both whites and blacks at all time points (Fig. 4C; ref. 2). In our recent population-based study, we studied interrelations between race, surgery received, and survival of patients with GBM who were not treated with initial RT (57). We did not find race-based differences in outcomes among these patients with GBM receiving different surgical interventions (57). The limited influence of therapy on GBM may be responsible in part for this result (55). There is also a possibility that biologic factors influencing GBM outcomes could be similar across races (57).

**Age.** Age of 50 years has been identified as an appropriate cutoff age for the clinical subdivision of patients with GBM into prognostically relevant subsets (7). In multivariate analysis of OS risk factors increasing age is associated with shortened survival (Fig. 5; ref. 2). Patients ages 70 to 74 years and those >75 have a significantly higher risk of death than those 65–69 years (58). Poorer survival in the older age group has been attributed to comorbidities as well as decreased ability to withstand neurological insults caused by the tumor itself, surgery, and/or adjuvant therapy (47, 59, 60). In addition, aggressive tumors in older patients have been attributed to resistance genes and tumors with different molecular profiles (61–63).

**Miscellaneous factors.** Various other factors, including SES and marital status, could be associated with GBM survival differences. Marital status had a beneficial effect on survival in a SEER-based population study, where unmarried patients with supratentorial GBM presented with larger tumors, were less likely to undergo both surgical resection and postoperative RT, and had a shorter survival after diagnosis when compared with married patients (64).

Effects of SES on survival have been examined by studying the primary payer for care (Medicare, Medicaid, self-pay, or private insurance) as predictor of in-hospital mortality (65). Compared with Medicare patients, Medicaid patients had higher mortality (58). For patients with GBM with dual eligibility in Medicare and Medicaid were much less likely to report radiation claims than those with Medicare alone (58). Higher chemotherapy claims were reported in patients with a median annual income >35,000 than those with <25,000 (58). Those who reported radiation or chemotherapy claims had a significantly lower risk for death than those who did not (58).

**Disparities in Healthcare**

In our recent SEER population-based study, we did not find an obvious racial difference in receipt of RT for patients with GBM (57). However, another SEER
population-based study investigating the influence of regional health system resources on the surgical management of GBM and receipt of postoperative RT found that younger, married patients in health service areas (HSA) with higher median incomes were significantly more likely to receive both gross total resection and postoperative RT (66). For every $10,000 increase in the median income of a HSA, a patient’s likelihood of receiving gross resection increased by 7% and postoperative RT receipt by 6.3% (66). Their findings indicated that it may not be the density of individual radiation oncologists, but rather the prevalence of radiation oncology centers that influences postoperative RT receipt, suggesting a dominant role of hospital-level infrastructure over individual providers for addressing disparities in GBM management (66). It is possible that the large variations in treatment of GBM may be related less to access to neuro-oncology services, but a larger apprehension of physicians to attempt aggressive surgery and RT for patients with less favorable prognosis (66).

A significant percentage of patients with GBM (27.3%) do not receive RT in the initial round of therapy and majority of these are elderly patients (65 years and older; refs. 57 and 67). Similar trends are seen in other SEER-based population studies for breast and lung cancer where lower rates of RT with increased age were observed (68, 69). Underuse of RT in a large number of elderly patients with GBM could be attributed increased risk of cognitive side-effects associated with RT (67, 70). However, recent data do show benefit of RT in the elderly population (71).

**Prognostic molecular markers in GBM**

Various molecular markers are associated with varying grades of glioma (Fig. 6). All GBMs are WHO grade 4 but exhibit significant genetic heterogeneity and tumor subtypes with genetic alterations exist within this larger homogeneous histologic category that carry prognostic significance (6, 72). Various prognostic markers have been identified in GBM, including methylation status of the gene promoter for O6-methylguanine-DNA methyltransferase (MGMT), isocitrate dehydrogenase enzyme 1/2 (IDH1/2) mutation, epidermal growth factor receptor (EGFR) overexpression and amplification, glioma-CpG island methylator phenotype (G-CIMP), tumor protein (TP53) mutation, and genetic losses of chromosomes.

Primary GBMs show EGFR overexpression, phosphatase and tensin homolog gene (PTEN) mutations, loss of heterozygosity (LOH) 10q, p16 deletions, less frequently mouse double-minute 2 (MDM2) amplification, high frequency of telomerase reverse transcriptase (hTERT) promoter mutations, and absence of IDH1 mutation (9, 73). The hallmark of secondary GBMs is TP53, α-thalassemia/mental retardation syndrome X-linked (ATRX) and IDH1 mutations. In addition, they show LOH 10q (7–9). GBM-O occurs in younger patients and often contains TP53 mutations, IDH1 mutation, and lack of EGFR amplification (6, 74). They have been reported to have longer survival as compared with other GBMs, have a lower frequency of PTEN deletions, and genetic heterogeneity (75–79).

There is a complex interaction between age and genetic alterations that result in variation of clinical outcomes in different age groups (72, 80, 81). Patients with GBM age <50 years have molecularly and clinically distinct disease and age 40 years seems to be a more appropriate cutoff point for their further prognostic subdivision (82). Patient age <40 years is strongly associated with a favorable prognosis whereas ≥40 years shows markers associated with shorter survival (wild-type IDH1/2, EGFR amplification, loss of 9p, loss of 10q, and gain of chromosome 19; ref. 82).

**MGMT status**

TMZ is an alkylating agent that functions by transferring alkyl groups to guanine bases causing DNA damage and cellular death. Failure to repair alkylation results in apoptosis. MGMT is a DNA repair protein that removes alkyl groups from the O6 position of guanine in DNA, making cells resistant to the alkylating agent TMZ (83, 84). Methylation causes MGMT silencing that interferes with DNA repair and increases TMZ sensitivity whereas an unmethylated promoter for MGMT results in active gene expression and high levels of the repair enzyme that results in chemotherapy resistance (85, 86).

The MGMT promoter is methylated in approximately 50% of newly diagnosed GBMs (87–89). MGMT methylation is associated with IDH1/2 mutant tumors because of which it is more common in secondary as compared with primary GBM (75% vs. 36% respectively; refs. 86, 90, 91). MGMT promoter methylation has prognostic and predictive significance in patients with GBM with better OS irrespective of treatment choices (84, 92, 93). In addition, it is associated with better response to TMZ as well as RT and improves PFS and OS with combined treatment approach (TMZ + RT) than either treatment modality alone (77, 84, 92, 94, 95).
IDH mutation

IDH1/2 mutations are far more common in grades 2 and 3 astrocytomas and oligodendrogliomas compared with GBMs and over 90% of the mutations involve IDH1 (74, 96–99). The effects of IDH1/2 mutations on gliomagenesis are greater than inhibition of their wild-type counterparts, and more likely represent a true gain-of-function genetic change (100). IDH1-R132H point mutated enzyme (mutation in IDH1 at R132) prefers binding to α-ketoglutarate and reduces it to D-2-hydroxyglutarate (100). The levels of this oncometabolite are 10- to 100-fold higher in mutant gliomas than their wild-type counterparts (100).

IDH mutations tend to occur in younger adults (20- to 60-year range; refs. 101–104). The relative frequency of IDH1 tumors rises sharply in the third decade of life and decreases in the fifth decade (105). IDH1-mutated high-grade gliomas arise by transformation from lower-grade gliomas and have distinguishing radiographic, histologic, and transcriptional features (frontal location and lesser extent of contrast enhancement and necrosis) that are consistent with a less aggressive clinical course (105). They are a selective molecular marker of secondary GBMs and distinguish them from primary GBMs (86, 97, 101). IDH1-mutated high-grade gliomas have a more favorable prognosis than the ones without IDH1 mutation and the sequence from more favorable to poorer outcome is: AA with IDH1 mutation, GBM with IDH1 mutation, AA without IDH1 mutation, and GBM without IDH1 mutation (97, 106).

G-CIMP

Analysis of the GBM DNA methylation array data generated by The Cancer Genome Atlas Research Network (TCGA) identified G-CIMP, a DNA methylation phenotype present in ~10% of GBM (107). This phenotype is strongly associated with IDH1 mutation and proneural tumor subtype, and is rare in primary GBM (5%-8%). There is a significant OS advantage of patients with G-CIMP, proneural tumor subtype and IDH1 mutation (107–109).

EGFR

EGFR is a transmembrane tyrosine kinase on chromosome 7p12 whose downstream signaling pathways modulate a wide range of cellular activities, including growth, migration, and survival (110). In GBMs, EGFR signaling promotes cell division, tumor invasiveness, and resistance to RT and chemotherapy (111–113). EGFR activity is enhanced by upregulation of EGFR protein expression, inhibition/deletion of downstream pathway inhibitors, constitutively active EGFR (EGFRVIII), and EGFR amplification (114, 115). EGFR amplification results in overexpression of EGFR (116–118). Alteration of the EGFR gene, results in overexpression of varied mutations, including the most common mutation, EGFRVIII (variant III), as well as wild-type EGFR (EGFRwt; refs. 119–121). EGFRVIII (variant III) is the most common mutation among EGFR amplified GBMs and has been described in approximately 60% to 70% of these tumors (120, 122). EGFRVIII overexpression was found to be a strong predictor of poor prognosis in presence of EGFR amplification (123).

About 40% of all GBMs have EGFR amplification, and it is more common in primary as compared with secondary GBMs (7–9, 124, 125). There is experimental evidence that EGFR amplification may result in a less favorable prognosis; however, clinical studies are inconclusive (72, 117, 118). Some have shown the degree of EGFR amplification to impact survival with higher levels associated with longer median survival whereas others have found it to be differentially prognostic with age (115, 126). EGFR overexpression was associated with worse prognosis in younger patients and better prognosis in older patients (41, 72, 127). Data also suggest the existence of a complex relationship of survival in GBM with the patient’s age, p53, and EGFR amplification. Poorer survival was noted in younger patients whose tumors overexpressed EGFR but had normal p53 immunohistochemistry (72). In addition, lower levels of amplification correlated with worse response to TMZ-containing adjuvant therapeutic regimens compared with GBMs with high amplification or none at all (126).

TP53 mutation

Mutation of the TP53 gene has been found in 60% to 70% of secondary GBMs, 25% to 30% of primary GBMs, and occurs more frequently in younger patients (9). Studies of TP53 mutations as a prognostic marker have not been definitive (72, 128, 129).

ATRX mutation

Mutations in ATRX have been identified in multiple tumor types and seem to cause alternative lengthening of telomeres (ALT), a presumed precursor to genomic instability (130, 131). ATRX alterations are present mainly in tumors of an astrocytic lineage and are specific to astrocytic tumors carrying IDH1/2 and TP53 mutations (132). They are more common in secondary as compared with primary GBMs (132, 133).

ATRX is frequently mutated in grade 2 and 3 astrocytomas (71%), oligoastrocytomas (68%), and secondary GBMs (57%), but is infrequent in primary (4%) and pediatric GBMs (20%) as well as pure oligodendrogial tumors (14%; ref. 133). ATRX mutations are associated with ALTs phenotype among GBMs (133, 134). They cluster with IDH1 and TP53 mutations in secondary GBMs (133).

In a prospective cohort of patients with astrocytic tumors, those harboring ATRX loss had a significantly better prognosis than the ones that expressed ATRX and had IDH mutation (135). Jiao and colleagues described the prognostic molecular classification of gliomas and based on 3 gene signatures (133). The I-A signature was defined by alterations in ATRX and IDH; with ALT and TP53 mutations. These tumors were grade 2 and 3 astrocytomas and secondary GBMs, were often diagnosed in the fourth decade of life, and had a median survival of 51 months (133). LCF signature was defined by IDH mutations and by alterations in either capicua transcriptional repressor...
(CIC), far upstream element (FUSE) binding protein 1 (FUBP1) and/or 1p/19q, rarely displayed ALT. These tumors typically had an oligodendrogial component and were often diagnosed in the fifth decade of life with a median survival of 96 months (133). I-X signature was defined by lack of IDH1 or ATRX mutations. I-X tumors are a genetically heterogeneous group, associated with poor patient survival 13 months, advanced patient age, and are similar to primary GBMs (133, 134).

**TERT**

TERT is involved in telomere maintenance, which is essential for actively growing cells. TERT mutation is one of the most frequent genetic alterations in primary adult GBMs and is significantly higher in these tumors as compared with secondary adult or any pediatric GBMs (73, 136). In GBMs, TERT mutations are significantly correlated with EGFR amplification but have an inverse correlation with IDH and TP53 mutations (73, 136). Although TERT mutations have yet to be directly compared with ATRX mutations, it is highly probable that the 2 are mutually exclusive. GBMs with TERT mutation have a shorter survival than those without TERT mutations (136). However, when adjusted for GBM subtype (primary and secondary), they do not have a significant impact on survival (136).

**Genetic losses of chromosomes**

**Losses on chromosome 10.** Some of the most frequent genetic alterations in GBMs are genetic losses on chromosome 10 (80%–90%), occurring either as loss of the entire chromosome or as loss of only the long or short arms (9). Phosphatase and tensin (PTEN), located at 10q23.3, was the first tumor suppressor gene identified on chromosome 10 and is mutated in 20% to 40% of GBMs and almost exclusively in primary GBM (7, 137). Prognostic role of 10q deletion in GBM are controversial, with some studies suggesting 10q loss as an indicator of poor outcome whereas others did not report a significant role as prognostic factor (127, 129, 138, 139).

**1p/19q status.** 1p/19q deletions (loss of the short arm of chromosome 1 and the long arm of chromosome 19) predict response to chemotherapy and better prognosis in anaplastic oligodendrogliomas (140). However, it has no utility in histologically unequivocal GBMs (141).

**Conclusion**

Although many studies have investigated the basis of incidence differences by gender, age, race, and risk factors for GBM, many of these studies had inconclusive findings. Although ionizing RT increases risk and allergies decrease risk, these factors do not account for a large proportion of GBMs. Hence, further studies are warranted to untangle the complexities of GBM etiology.

Advances have been made in development of prognostic tools and identifying molecular markers that help predict prognosis and response to therapy. Progress in investigating the molecular biology has led to identification of GBM subsets that are biologically similar, are more susceptible to standard therapy, and have a better prognosis. Efforts to establish the role of IDH1 and MGMT in predicting therapeutic response is ongoing. Understanding the role of IDH1/2 mutations in promoting gliomagenesis, its effect on prognosis, and targeting IDH1/2 mutations in novel therapies holds promise to make advances in preventive and treatment strategies (86).

In summary, GBM represents a molecularly heterogeneous disease with numerous subclassifications. The field has invested significant resources on this characterization and is now poised to advance therapies specific to the genetic abnormalities of each subtype. The success of mTOR pathway inhibition for subependymal giant-cell astrocytomas and the possibility of identifying a subtype of GBM sensitive to upfront treatment with bevacizumab are examples, but we need much more (142, 143). The complex molecular changes associated with GBM will likely make personalized therapy challenging and although clinical advances in GBM are rare, we are in a new era in cancer biology. Whether an immune-based therapy or treating multiple targets will provide the breakthroughs is yet unknown, but we expect meaningful clinical advances to occur—and soon.

**Disclosure of Potential Conflicts of Interest**

No potential conflicts of interest were disclosed.

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