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Glioblastoma Multiforme and Genetic Mutations: The Issue Is Not Over Yet. An Overview of the Current Literature

Nicola Montemurro[1,2]

[1] Unit of Neurosurgery, "Di Venere" City Hospital, ASL Bari, Bari, Italy
[2] Department of Basic Medical Sciences, Neurosciences and Sensory Organs, University of Bari Aldo Moro, Bari, Italy

Address for correspondence Nicola Montemurro, MD, "Di Venere" City Hospital, ASL Bari - Unit of Neurosurgery, Via Ospedale Di Venere, 1 Bari 70131, Italy (e-mail: montemurronic@hotmail.com).

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Abstract

Background and Objective Glioblastoma multiforme (GBM) is still a deadly disease with a poor prognosis and high mortality, despite the discovery of new biomarkers and new innovative targeted therapies. The role of genetic mutations in GBM is still not at all clear; however, molecular markers are an integral part of tumor assessment in modern neuro-oncology.

Material and Methods We performed a Medline search for the key words "glioblastoma," "glioblastoma multiforme," and "genetic" or "genetics" from 1990 to the present, finding an exponential increase in the number of published articles, especially in the past 7 years.

Results The understanding of molecular subtypes of gliomas recently led to a revision of the World Health Organization classification criteria for these tumors, introducing the concept of primary and secondary GBMs based on genetic alterations and gene or protein expression profiles. Some of these genetic alterations are currently believed to have clinical significance and are more related to secondary GBMs: TP53 mutations, detectable in the early stages of secondary GBM (found in 65%), isocitrate dehydrogenase 1/2 mutations (50% of secondary GBMs), and also O6-methylguanine-DNA methyltransferase promoter methylation (75% of secondary GBMs).

Conclusion From the introduction of the first standard of care (SOC) established in 2005 in patients with a new diagnosis of GBM, a great number of trials have been conducted to improve the actual SOC, but the real turning point has never been achieved or is yet to come. Surgical gross total resection, with at least one more reoperation, radiation therapy plus concomitant and adjuvant temozolomide chemotherapy currently remains the current SOC for patients with GBM.

Keywords
- glioblastoma multiforme
- prognostic biomarker
- genetics
- isocitrate dehydrogenase 1/2
- O6-methylguanine-DNA methyltransferase (MGMT)

Introduction

Glioblastomas multiforme (GBMs) are the most common malignant tumors of the central nervous system, accounting for 12 to 15% of all intracranial tumors, with an annual incidence of 5 per 100,000 people and ~ 17,000 new cases diagnosed each year.[1] The incidence of GBMs increases with age, peaking between 75 and 84 years. GBMs have a poor prognosis, and the 5-year survival is < 10%. Diffuse gliomas are highly invasive. Thus curative surgical resection can never be achieved, which leads to recurrence. The median overall survival (OS) from diagnosis was 14 months versus 22 months in patients who did not undergo second surgery and those with surgery at recurrence, whereas the median survival from the time of second surgery was ~ 9.7 months.[2–5]

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GBMs can be classified into primary (accoun90–95%ting for of all GBMs), more common among older adults, and secondary GBMs, which evolve from low-grade gliomas (LGGs) or anaplastic astrocytomas (AAs) over the years, which are more common among young people.[6] GBM is still a deadly disease with a poor prognosis and high mortality, despite the discovery of new biomarkers. Some of these need validation to be used in the clinical routine, such as advances in technologies, for example genomics, epigenomics, transcriptomics, and new innovative targeted therapies. The role of genetic mutations in GBMs is still unclear; however, molecular markers are an integral part of tumor assessment in modern neuro-oncology, helping clinicians make therapeutic and clinical decisions for their patients with GBM.[7]

Materials and Methods

We performed a Medline search for the key words "glioblastoma," "glioblastoma multiforme" and "genetic" or "genetics" from 1990 to the present to identify the most recent advances in the genomics of GBMs and summarize genetic review articles, clinical studies in patients with primary or secondary GBM, and validated or not yet validated biomarkers that may affect patients' outcome.

Results

More than 9,500 studies were found using Ovid Medline databases, an exponential increase in the number of published articles, especially in the past 7 years, that discuss potential genetics perspectives in patients with GBMs (►**Fig. 1**). Recent studies were eligible for inclusion if they were not single cases, reported original data on genetic mutations about GBMs, and were targeted therapies and reviews (►**Fig. 2**). Our digital search was supplemented by examining the reference lists of the selected studies, analyzing the most important.

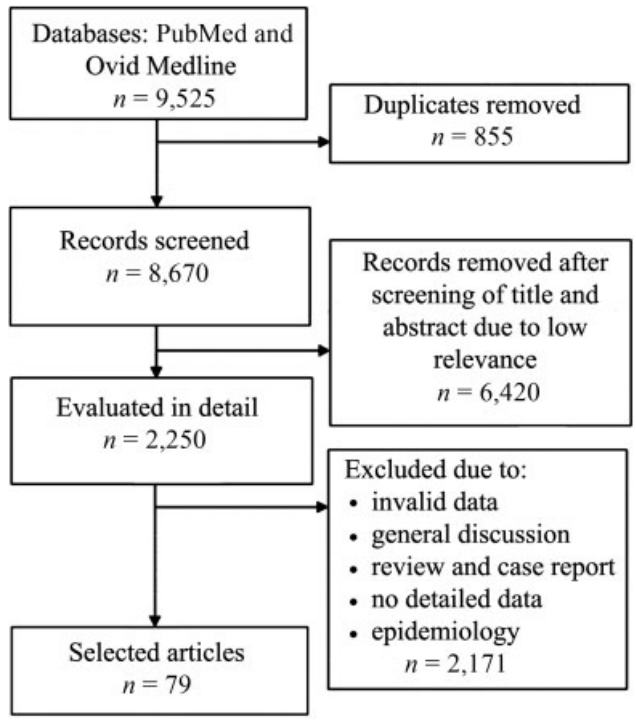

Fig. 2 Flow diagram of study selection of the current literature.

Discussion

GBM was one of the first tumors profiled by The Cancer Genome Atlas Network, using molecular parameters in addition to histology to define many tumor entities.[8] The understanding of molecular subtypes of GBMs and other grades of gliomas recently led to a revision of the World Health Organization (WHO) diagnostic and classification criteria for these tumors.[9] The 2016 WHO classification divides gliomas into LGGs and GBMs per histology. LGGs are further divided into isocitrate dehydrogenase (IDH) 1/2 wild-type or mutant and further classified if there is a

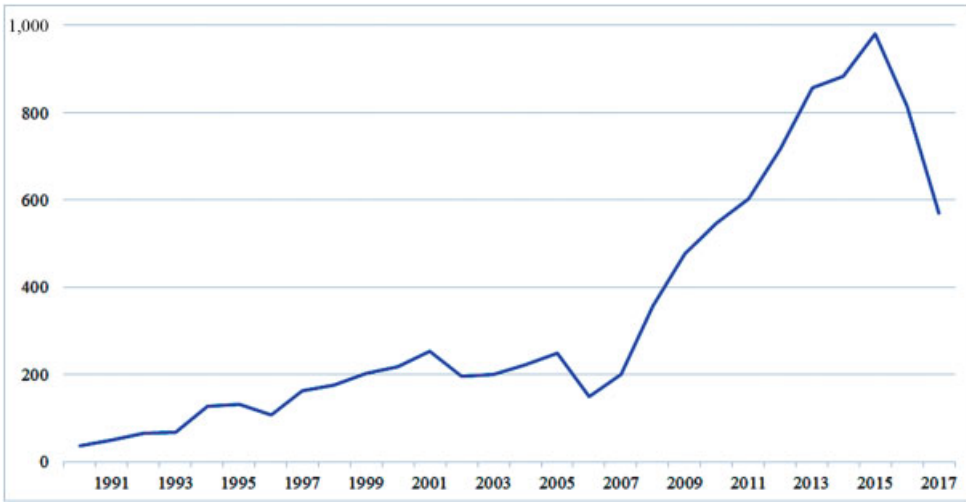

Fig. 1 Diagram showing exponential increase in the number of published articles debating primary and secondary glioblastomas and both genetic alterations and gene expression profiles.

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complete deletion of both the short arm of chromosome 1 and the long arm of chromosome 19 (1p/19q codeletion) (oligodendroglioma) or intact 1p/19q loci (diffuse astrocytoma). GBMs are divided into IDH wild-type (primary or de novo GBMs) and IDH mutant (secondary GBMs).[9–11] This new classification merges classical histologic classification, grading, immunohistochemical, and molecular genetic data, allowing a better characterization of gliomas.

Most (~ 90%) of GBMs are primary tumors. They are highly invasive neoplasms, more common in older patients, and arise in the absence of prior disease. Secondary GBMs are much less common, develop from LGGs or AAs, and are associated with a better prognosis. Primary and secondary GBMs are histologically indistinguishable, but they develop from different genetic precursors and show different genetic alterations that permit differentiation. Patients with secondary GBMs were found to be significantly younger than those with primary GBMs.[12] With respect to anatomical localization, Li et al reported secondary GBMs are more commonly located in the frontal lobe (68%), whereas the frontal and temporal lobes were the most typically involved sites in both primary and secondary GBMs.[12]

In primary GBMs, the most frequent genetic alterations observed are loss of heterozygosity (LOH) at 10q (65% of cases), amplification or mutation of epidermal growth factor receptor (EGFR) (22–40%), amplification of platelet-derived growth factor receptor (PDGFR) (7%), tumor protein 53 (TP53) mutation (28–31%), *cyclin-dependent kinase inhibitor 2 A/B* (*CDKN2A/B*) deletion (31%), phosphatase and tensin homolog (PTEN) mutation or deletion (24–30%), IDH1/2 mutation (5%), telomerase reverse transcriptase (TERT) promoter (10%), O6-methylguanine-DNA methyltransferase (MGMT) promoter methylation (36%), loss of expression of the *retinoblastoma gene* (*RB1*) (2%), phosphatidylinositol-4,5-bisphosphate 3-kinase A (PIK3CA) (1%), *murine double minute 2* (*MDM2*) (7–12%), neurofibromatosis type 1 (NF1) deletion or mutations (11%), and glioma-associated *oncogene homolog 1* (*GLI1*) (5–22%).[8,13–21]

In secondary GBMs, the most frequent genetic alteration observed are TP53 mutation (65% of cases), LOH at 22q (70–80%), LOH 19q (40–50%), IDH1/2 mutation (45–50%), MGMT promoter methylation (75%), *CDKN2A/B* deletion, PDGFR gene amplification (7%) 1p/19q codeletion (15–20%), and EGFR (5–7%).[16,17,20,22–26]

Secondary GBMs

Although some genetic aberrations are more frequently expressed in both secondary and primary GBMs, and both subgroups are capable with time of undergoing further malignant degeneration, their role appears to be predominantly related to one of them. Some of them are currently considered clinically significant and are more related to secondary GBMs: TP53 mutations, detectable in the early stages of secondary GBM (found in 65% versus 28% of primary GBMs); IDH1/2 mutations (50% of secondary versus 5% of primary GBMs); and also MGMT promoter methylation (75% of secondary GBMs versus 36% of primary GBMs).[17,27]

TP53 mutation is predominantly related to secondary GBMs, suggesting that TP53 mutation is a specific and stereotyped event in secondary GBM oncology, whereas TP53 mutation in primary GBM is potentially a consequence of widespread genomic instability. In 2008, Parsons et al first reported recurrent mutations in the IDH1/2 genes in patients with gliomas.[28] Subsequent studies identified IDH1 mutations in 45 to 50% of patients with grade II/III gliomas and secondary GBMs.[22,23,25,29] These patients with IDH mutation showed a better prognosis in every grade of glioma and different disease characteristics relative to patients with a glioma with wild-type IDH.[30–32] IDH1/2 mutations were identified by WHO as a critical biomarker in the classification of gliomas and the most reliable marker of secondary GBMs than any other pathologic criterion to differentiate primary from secondary GBMs, whereas an IDH wild type in grade II/III gliomas showed an OS rate more similar to that of GBMs.[9,26,28,30,33]

Nobusawa et al reported a small subgroup of patients with primary GBM and IDH mutation (3.4%) who were younger than other patients and who had TP53 mutations and absence of EGFR amplification (features of the secondary GBMs), suggesting cases of rapidly progressive secondary GBMs, rather than a true primary GBM.[34] For the same reason, a histologic AA with an IDH wild type is now considered a GBM, and a GBM with IDH1 mutation and 1p/19q codeletion is considered an anaplastic oligodendroglioma (AO) in determining patient survival.[35] Studies reported that IDH1 mutation occurs before other mutations, whereas TP53 and α thalassemia/mental retardation syndrome X-linked (ATRX) mutations occur in the setting of development of an AA, and a 1p/19q codeletion occurs in the setting of the development of an AO.[26,29]

ATRX mutation, playing a role in chromatin modulation and maintenance of telomeres, represents a prognostic factor in gliomas. About 50% of MGMT promoter methylation occurs in secondary GBMs, which are more sensitive to chemoradiotherapy, increasing OS when surgery is followed by temozolomide (TMZ) concurrently with radiation therapy.[36–38] Since 2008, several studies have reported an increase in overall survival from 30 to 40 months in patients with GBMs or AAs with IDH1 mutation versus those without this mutation.[16,28,39–41] This survival benefit was also identified in patients with grade II gliomas, showing an increase in OS of 7 years in patients with IDH1 mutation versus patients without this mutation.[39] The best prognosis was found in patients with IDH1/2 mutant and 1p/19q codeleted tumors, whereas patients with IDH1/2 wild-type gliomas and glioblastoma-like genomic alterations (loss on chromosome arm 10q and TERT promoter mutation) tended to have the worst outcome.[15,42] Intermediate survival was seen in patients with IDH1/2 mutant but 1p/19q intact or in patients with IDH1/2 wild-type gliomas with glioblastoma-like genomic alterations.[42] Similarly, ATRX mutation with IDH1/2 wild type is a marker of grade II/III gliomas and secondary GBMs and associated with more favorable outcomes.[43]

Primary GBMs

Genetic aberrations that are more common in primary GBMs are EGFR, *CDKN2A/B* deletion, PTEN mutation or deletion,

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PDGFR, TP53 mutation, and TERT promoter.[8,14,16–18,21] EGFR and its most common EGFR-activating mutant variant (EGFRvIII) are tyrosine kinase growth factor receptors and associated with high-grade malignancy, poor prognosis, and shorter OS. The amplification of the *EGFR* gene has high incidence in all gliomas, and it is found in 40 to 50% of primary GBMs.[19] Currently, EGFR status can be used to predict patient response to EGFR-targeted therapies.

CDKN2A/B deletions, found in both primary and secondary GBMs, are more common in primary GBMs.[17,26] After TP53 mutation, *PTEN* is the second most commonly mutated tumor suppressor gene in all tumors. *PTEN,* found in the advanced stages of disease in primary GBM, is central in inhibiting cell proliferation and regulating the ability of cells in migration and invasion.[44,45] *PTEN* mutation rates in primary GBMs and in AAs are 26 to 34% and 18%, respectively. Patients with a *PTEN* mutation tend to have a poor prognosis. The contribution of TERT mutation to tumor aggressiveness is not clear because this mutation, detected in 46% of all GBMs, was found in both primary and secondary tumors and associated with a shorter OS.[46]

The prognostic effect of TERT mutations, according to Labussière et al, may depend on the context because they reported that in LGGs without IDH mutations, TERT mutation is a negative prognostic factor, but in IDH-mutated LGGs, TERT mutation is a positive prognostic factor.[47,48] Eckel-Passow et al reported that gliomas with only TERT mutations are primary GBMs, and patients with GBMs with only TERT mutations have a high prevalence of loss of chromosome 4 and acquired PIK3CA mutations and tend to have the poorest prognosis.[25]

Recent research reported the important role of the expression of vascular endothelial growth factor (VEGF), a common genetic alteration in GBMs, detected in 58.9% of cases, which contributes to the angiogenesis of tumors, as does the X-linked inhibitor of apoptosis (XIAP)-associated factor (XAF) 1, a tumor suppressor that is a precise indicator of IDH1 mutations in grade III gliomas.[49,50] Although mutations in certain cancer genes, such as B-Raf (BRAF) and RAS genes, have rarely been observed in GBMs, mutations in the PIK3CA and PIK3R1 genes, although rare, have been described.[8] BRAF is seen more frequently in pleomorphic xanthoastrocytomas (50–60%), in pilocytic astrocytomas ($<$ 10%), and in gangliogliomas (20–75%).[51,52]

Verhaak et al and other studies analyzing somatic mutations and gene expression identified four transcriptional subtypes of GBMs: classic, proneural, neural, and mesenchymal.[8,21,51,53,54] The classic category showed a greater preponderance of EGFR amplification and CDKN2A alterations, decreased rates of TP53 mutation, loss of chromosome 10, and amplification of chromosome 7 and mitogen-activated protein kinase.[53] The proneural category is associated with PDGFR amplification, IDH1 and TP53 mutations, and activation of the phosphatidylinositol 3-kinase (PI3K). Patients with proneural subtypes GBMs were younger, responded better to therapy, and had a prolonged OS.[53] The neural subtype was associated with a variety of neuron markers and closest to the normal brain, whereas the mesenchymal subtype was found to have a greater degree of NF1 mutations and alterations of PTEN and a greater degree of necrosis histologically.[53]

Although primary GBMs could be of any subtype and mutations, secondary GBMs are more linked with the proneural subtype,[53] predominantly associated with IDH1/2 mutations. This subtype was further subclassified as either CpG island methylator phenotype + (CIMP +) or CIMP− (of which the CIMP+ shows a better prognosis and is associated with longer survival).[21,33] Turcan et al demonstrated that the IDH1 mutation alone is capable of remodeling the genomic methylation profile of the tumor, thus promoting the CIMP+ profile.[55]

Chemotherapy, Immunotherapy, and Targeted Therapy

From the introduction of the first standard of care (SOC) established by Stupp and colleagues in 2005 in patients with new diagnosis of GBM, a great number of trials have been conducted to improve the actual SOC, but the real turning point has never been achieved or, more optimistically, is yet to come.[56–66] MGMT promoter methylation is used as a predictive biomarker of response to TMZ and associated with a better response to it and a better OS in MGMT methylated patients compared with MGMT unmethylated GBM patients.[67,68] Although it is difficult to withhold an approved chemotherapy from MGMT unmethylated patients with primary or secondary GBMs, at recurrence there is no evidence for treating unmethylated patients with TMZ at any dose or schedule.[67]

In a multivariate analysis on 180 patients, Azoulay et al[69] reported that repeat surgery and MGMT promoter methylation were independent prognostic factors that positively affect survival. In contrast, Franceschi et al,[70] in a multivariate analysis of 232 patients, showed that resurgery did not affect survival, whereas MGMT methylation were significantly correlated with OS, reporting that the median time between the first and second surgery was significantly longer in patients with methylated MGMT than in patients with unmethylated MGMT (19.3 versus 13 months). Similarly, mutations in IDH1/2 and TP53 are used as a strong predictive marker for response to chemotherapy in patients with GBMs.[21] However, these last few years have represented a challenge for neuro-oncologists, who try to improve the OS in patients with GBMs, intensifying the dose or prolonging the exposure to TMZ, adding integrin-inhibitor cilengitide or anti-VEGF antibody bevacizumab.[58–60,62,65] In any case, combination therapies require management of toxicities, therapeutic response monitoring, and drug interactions. Tyrosine kinase inhibitors drugs like gefitinib, erlotinib, and cetuximab have been tested for use in GBMs; however, they have not been proven effective for monotherapy.[64,66]

The brain has long been considered an immune-privileged site precluding potent immune responses, but the failure of conventional chemotherapy has led to a consideration of immunotherapy (brain tumor vaccines, immune checkpoint blockade, monoclonal antibodies, radiolabeled antibodies injected directly into the tumor, recombinant interleukin-2 and lymphokine activated killer cells, recombinant immunotoxins specific for EGFR) as a promising strategy.[71] Targeting the mutation EGFRvIII using vaccine alone or in combination with tyrosine kinases inhibitors and TMZ reduced tumor development in xenograft models, but a more recent phase III clinical trial using this approach showed no survival benefit;

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nor did other studies using specific targets toward EGFR that also showed disappointing results.[63,71–74]

Immunosuppression is one of the primary reasons for a poor prognosis in GBM. Reduction in T-cell mediated immune response is due to coinhibitory receptors on T cells known as immune checkpoint molecules. Blocking such immune checkpoint molecules, such as cytotoxic T-lymphocyte antigen 4 (CTLA-4) and programmed death 1 (PD-1), tumor regression and promotion of long-term survival can be induced.[75,76] The combination of anti-PD-1 antibodies and radiotherapy doubled median survival and enhanced long-term survival in 15 to 40% of GBM mice.[77] With improvement in diagnostic imaging and methods of delivery, gene therapy may be used in conjunction with surgery, chemotherapy/radiotherapy, or in cases of recurrences following excision as well as chemotherapy-resistant tumors, but at this time no gene therapy for GBM has yet been approved in the United States or Europe.[78] Second surgery, chemotherapy given at recurrence, target therapy, and radiotherapy led to a prolongation of the median OS to 18 to 20 months in the most recent trials.[2,61] Future research should focus on identifying synergistic interactions between chemotherapy, radiotherapy, and immunotherapy to maximize the antitumor potential of individual treatment approaches.

Conclusions

These molecular approaches to GBMs revolutionized the understanding of the pathophysiology of gliomas, pathologic classification of tumors, and therapeutic approaches, even if all these genetic classifications do not routinely influence treatment choices.[79] It is possible that further GBM subclassifications will lead toward individualized treatments for distinct molecular subtypes. GBM patient samples taken during the first tumor resection and after first-line chemotherapy, done during second tumor resection for recurrent GBMs, can be useful to understand the changes occurring in gene and protein expression, to improve pharmacologic research, and to establish the most effective pharmacotherapy for the single patient. At the present time, surgical gross total resection, with at least one more reoperation, radiation therapy plus concomitant and adjuvant TMZ chemotherapy remains the current SOC for patients with GBM. Ultimately, the goal would be an individualized approach to implement a personalized medicine for this deadly disease.

Conflict of Interest
None declared.

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