

Prognostic Value of BRAF Mutation in Glioblastoma

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Abstract

With advances in molecular genetics, exploring targetable mutations for treating glioblastoma (GBM) patients, has become a centre of interest in modern day neuropathology. BRAF mutation has been extensively reported in several brain tumours. Recent studies report identification of BRAF mutation in GBM patients, especially isocitrate dehydrogenase wildtype glioblastomas (IDH-WT GBM), and its potential role in patient outcomes. Here we discuss the existing literature on the prognostic value of BRAF mutation in GBM.

Keywords: Glioblastoma, BRAF mutation, prognosis

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Introduction

In modern neuropathology, the analysis of molecular genetics has become an essential component, as it is important for diagnosis, treatment and prognosis of brain tumours.¹ Substantial research efforts focused on genomics coupled with expanding clinical molecular diagnostics have sparked interest in exploring targetable mutations in the management of GBM, the most common and aggressive variant of adult glioma.^{2,3} One such targetable mutation is the BRAF V600E mutation, which has important therapeutic implications. These mutations affect a specific region prone to mutation at amino acid position 600 and is characterised by the substitution of valine with glutamate (referred as BRAFV600E).³

The BRAFV600E mutation is believed to imitate phosphorylation of the activating amino acids T599 and S602, resulting in constitutive activation of the protein that affects cell proliferation, differentiation, and survival. Although this mutation is often linked with poor prognosis in certain gliomas, it is shown to correlate with better prognosis in cases of isocitrate dehydrogenase wildtype glioblastomas (GBM IDH-WT).⁴ BRAF belongs to RAS/RAF/MEK/ERK kinase pathway. Clinical trials are underway to evaluate the effectiveness of RAF-targeted therapy alone or in combination with radiation for the

treatment of low and high-grade BRAF-mutant gliomas. Therefore, identifying BRAF mutations in patients with GBM is of clinical significance as GBM patients may potentially benefit from BRAFV600E targeted therapy. Herein, we have reviewed prognosis of BRAF mutant GBM.

Review of Evidence

Chan et al., examined 578 cases of infiltrative gliomas over a period of 24 years.⁴ The overall BRAF-V600E mutation rate observed was 5.9% (34 out of 578) in this cohort which included 21 cases of IDH-WT GBM.⁴ BRAF mutation was seen to be associated with younger age and female gender. Univariate analysis showed that BRAF mutation in IDH-WT GBM was associated with significantly longer median overall survival of around 3.6 years compared to BRAF wild type in GBM with a median overall survival of 0.9 years.⁴

Dono et al., analyzed 372 patients with gliomas and reviewed outcomes of different cancer-associated genes in these patients.³ Among 372 gliomas, 249 were classified as GBM IDH-WT.⁴ Within the subset of 249 patients, only 8 (3.2%) cases exhibited BRAF mutations in GBM IDH-WT. In addition to this, all (2/2) patients with epithelioid-GBM (E-GBM) had BRAF mutant genes. Majority of patients with GBM IDH-WT underwent resection followed by temozolomide (TMZ) and radiotherapy according to the Stupp protocol. The median overall survival of patients with GBM IDH-WT with a BRAF mutation was 12.8 months which was lower than the median overall survival of 19.1 months for the remaining 241 GBM, IDH-WT (BRAF wild-type) cases in this database which led to the conclusion that that BRAF mutation in IDH-WT GBM may have a worse prognosis. This result contrasts with the previously mentioned study by Chan et al.⁴ This may be because this study was limited by a small sample size due to the rarity of BRAF-mutant infiltrating gliomas.³ In contrast to this, all E-GBM patients were alive at the time of submission of this study with a median overall survival of 12.1 months.

Korshunov et al., analyzed 64 (33 paediatric and 31 adult) patients who were initially diagnosed as E-GBM.⁵ All patients underwent gross total or subtotal resection followed by radiotherapy and chemotherapy with TMZ.⁵ During the follow-up period, 28 (60%) patients died with median overall survival of 23 months.⁵ Molecular analysis revealed that E-GBM can be distinguished into three tumour subtypes: pleomorphic xanthoastrocytomas (PXA)

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like tumours with favourable prognosis, IDH-WT GBM-like tumours with poor prognosis and RTK1 paediatric GBM-like tumours with intermediate outcomes.⁵ The good clinical outcome of E-GBM in the previous study might be because they had PXA-like subtype.

Wang et al., conducted a retrospective study over a period of 5 years to analyze clinical and pathological characteristics of 33 patients diagnosed with E-GBM.⁶ All these patients underwent either gross total or subtotal resection followed by chemotherapy, radiotherapy, or a combination of both.⁶ BRAF V600E mutation was identified in all 33 cases (100%). Their average survival period was of 13 months.⁶

Kaley et al., conducted a multi cohort, non-randomized VE-BASKET study.⁷ 24 patients with BRAF mutant gliomas were identified, among which GBM accounted for 25% (6/24) of the cases. All of these patients received 960mg of vemurafenib twice a day.⁷ Median overall survival for malignant diffuse glioma was 11.9 months.⁷ The study suggested that vemurafenib may benefit patients with BRAFV600 mutant gliomas including GBM subtypes. Thus, the study serves as a demonstration of the concept that BRAFV600 is a potentially targetable oncogene which may have a favourable prognosis.⁷

Wen et al., conducted a study that was part of the ROAR basket trial. They enrolled 206 patients with BRAF mutation positive rare cancers.⁸ Among the 45 patients with high grade gliomas (HGG), 31 patients had GBM. All patients received dabrafenib and trametinib. Median overall survival of patients with HGGs was 17.6 months, which is greater than in previously mentioned studies (~12 months). This shows the benefit of these chemotherapeutic agents as well the advantage of regular testing of BRAFV600E in glioma patients.

Conclusion

BRAF V600E mutations are increasingly being identified in GBM patients. Although, there is no conclusive evidence as yet that GBM patients with BRAF mutations have a favourable prognosis in comparison to BRAF wild-type patients with GBM, treatment targetted at specific BRAF mutant genes are being tested in clinical trials.

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