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Prognostic significance of IDH 1 mutation in patients with glioblastoma multiforme

Inamullah Khan, Muhammad Waqas, Muhammad Shahzad Shamim

Abstract

Focus of brain tumour research is shifting towards tumour genesis and genetics, and possible development of individualized treatment plans. Genetic analysis shows recurrent mutation in isocitrate dehydrogenase (IDH1) gene in most Glioblastoma multiforme (GBM) cells. In this review we evaluated the prognostic significance of IDH 1 mutation on the basis of published evidence. Multiple retrospective clinical analyses correlate the presence of IDH1 mutation in GBM with good prognostic outcomes compared to wild-type IDH1. A systematic review reported similar results. Based on the review of current literature IDH1 mutation is an independent factor for longer overall survival (OS) and progression free survival (PFS) in GBM patients when compared to wild-type IDH1. The prognostic significance opens up new avenues for treatment.

Keywords: Glioblastoma multiforme, IDH1 mutation, overall survival, progression free survival

Introduction

Glioblastoma multiforme (GBM) is the commonest primary malignant brain tumour and carries poor prognosis despite recent advances in management.[1] A comprehensive genetic analysis of protein codes has found recurrent mutations in isocitrate dehydrogenase 1 (IDH1) gene in 12% of GBM.[2] IDH1 catalyzes the oxidative decarboxylation of isocitrate to ?-ketoglutarate which protects cells in situation of oxidative stress.[3] The recurrent somatic mutation involves codon 132 of IDH1 gene on chromosome 2q33 and is implicated in determining the prognosis.[2] Herein we have reviewed the evidence on the effect of IDH 1 mutation on the survival of patients with GBM.

Review of Evidence

Frequency of IDH1 mutation was first reported by Yan et al., in 2009 when they extracted DNA from primary brain tumour and xenografts, and from patient-matched

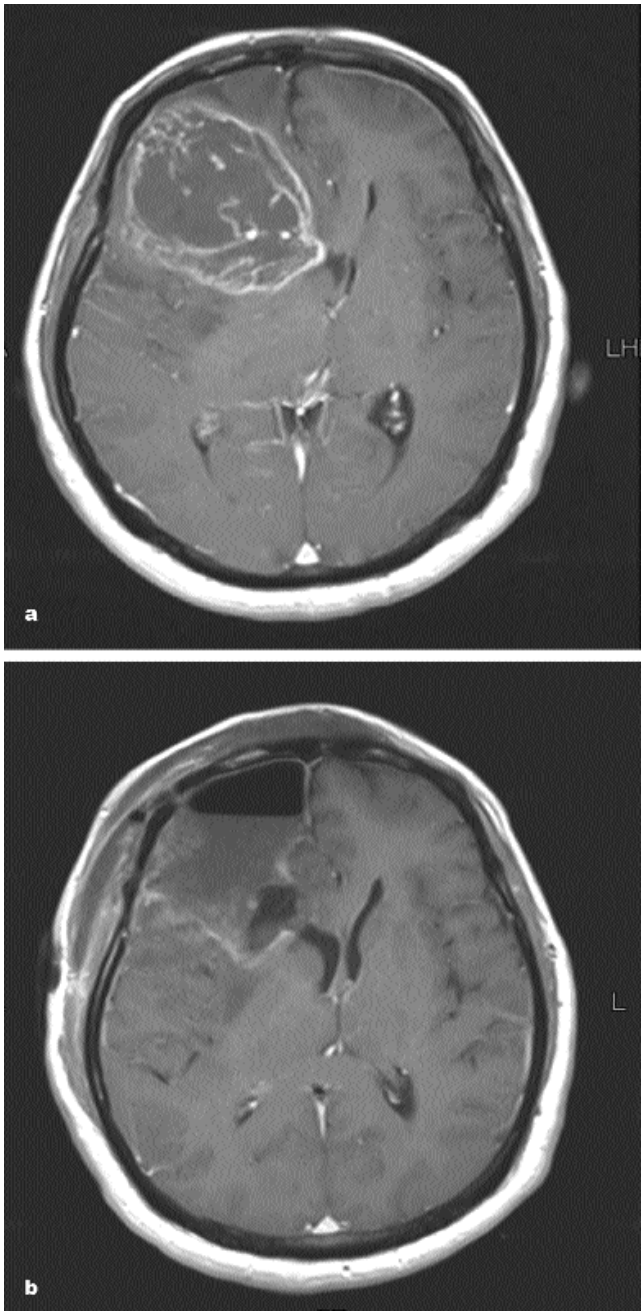

Figure-1: a) Pre-operative MRI TIWI with contrast showing the typical location of a GBM with IDH1 mutation. b) Post-operative MRI T1WI with contrast of the same patient showing gross total resection.

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normal blood lymphocytes.[4] The sequence of IDH1 gene was determined and mutation was reported in majority of the malignant gliomas. Bleeker et al., in 2010 used DNA samples from a set of frozen GBM specimens, and analyzed for enzyme activity and survival.[5] They reported a significant increase in overall survival for both primary and secondary GBM in patients with IDH1 mutation. After correction for age, Karnofsky Performance Status (KPS), extent of surgery, received dosage of radiotherapy, additional chemotherapy or treatment other than radiotherapy, mutational status of IDH1 was reported as an independent factor for OS.

In 2011 Song Tao et al.,[6] reported 69.6% IDH1 mutation in genomic DNA extracted from formalin-fixed and paraffin-embedded GBM. All clinical features of these patients were retrospectively analyzed and it was concluded that patients with IDH1 mutation had longer PFS (Hazards Regression HR = 0.110, P < 0.001).[6] In 2012, Yan et al.,[7] also reported significantly longer PFS for GBM patients with IDH1 mutation compared to wild-type IDH1. (497.0±267.8 days versus 342.3±261.6, p= 0.026). In 2013, Cheng et al.,[8] reported via a meta-analysis that the IDH1 mutation has a significant association with improved survival outcomes in GBM patients compared to wild-type IDH1 (HR= 0.45, 95% CI, 0.29-0.69, P <0.001). They included studies providing HR from multivariate analyses by adjusting for confounding factors that were more accurate than the unadjusted HR. The meta-analysis hence provides strong evidence for IDH1 mutation as an independent prognostic factor in improving survival in GBM patients.

In 2014, Polivka et al.,[9] assessed IDH1 mutation by RT-PCR (Reverse Transcriptase- Polymerase Chain Reaction) in GBM specimens and correlated it with the OS and PFS. They reported longer OS, (270 versus 130 days; P < 0.024) and PFS (136 versus 51 days; p< 0.021) in patients with IDH1 mutation compared to wild-type IDH1.

In 2016, Mandel et al.[10] analyzed their institutional data and found statistically significant improvement in median OS in patients with mutated IDH1 compared to wild-type IDH1 (83 versus 22 months; p < 0.0001). IDH1 mutation remained a significant prognostic marker in multivariate analysis (p 0.0005).

Conclusion

Review of evidence identifies the prognostic significance of IDH1 mutation in GBM. Multiple studies report IDH1 mutation as a significant, independent factor for predicting longer overall survival and progression free survival in patients with GBM. The information can help in treatment planning, prognostication and counseling, and also opens new avenues for research.

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