Isocitrate Dehydrogenase (IDH) Mutation and Methyl-Guanine Methyl Transferase (MGMT) Promoter Methylation Status as Independent Glioblastoma Biomarkers

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Background

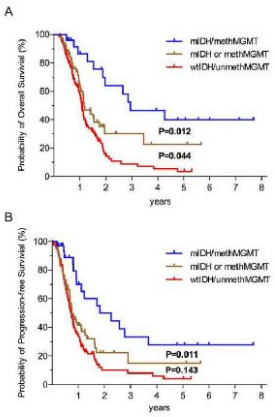
Two molecular biomarkers of significant interest for glioblastoma involve isocitrate dehydrogenase (IDH) mutations and O6-methylguanine-DNA methyltransferase (MGMT) promoter methylation. IDHs are enzymes that catalyze the decarboxylation of isocitrate to a-ketoglutarate . There are three isoforms of IDHs, termed IDH1, 2, and 3. Nearly all IDH mutations in glioblastomas involve substitution of R132 of IDH1, though rare mutations in R172 of IDH2 are also reported. IDH mutations in glioblastoma simultaneously result in the loss of native enzymatic activity as well as conferred novel activity in the production of 2 hydroxyglutarate (2HG). These enzymatic alterations ultimate trigger epigenetic changes 11 that defined the Glioma CpG Island Methylation phenotype (G-CIMP), a phenotype that is associated with improved prognosis.

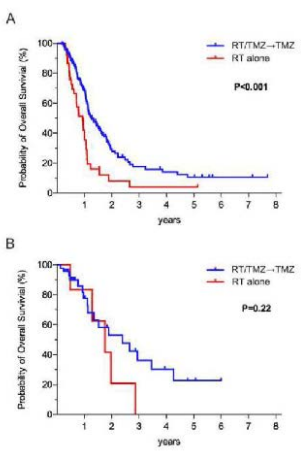
Another important biomarker in glioblastoma involves MGMT promoter methylation(methMGMT). MGMT encodes an evolutionarily conserved DNA repair enzyme responsible for detoxifying TMZ induced DNA damages. Clinically, high MGMT mRNA and protein expression has been associated with therapeutic resistance to DNA alkylating agents in a number of cancers. A major mechanism of MGMT regulation involves methylation of CpG islands in the promoter region. Methylation of these regions suppresses MGMT transcription. mMGMT has been associated with favorable response to temozolomide in glioblastoma patients by two RCTs, including NOA -8 23, and the Nordic Trial. Interestingly, the EROTC-NCIC demonstrated that MGMT promoter methylation additionally carried prognostic value in patients who did not receive TMZ.

It remains unclear whether mIDH and methMGMT present overlapping or independent clinical information as biomarkers. We analyzed our prospective CGGA registry to address this question.

Methods

We investigated the association between methMGMT and mIDH with progression free survival (PFS) and overall survival (OS) in a prospectively collected molecular registry of 274 glioblastoma patients.





Results

For glioblastoma patients who underwent concurrent Temozolomide and Radiation Therapy (TMZ+RT), OS and PFS was most favorable for those with tumors harboring both mIDH and methMGMT (median OS (mOS): 35.8 mo, median PFS (mPFS):27.5 mo); patients afflicted glioblastomas with either mIDH or methMGMT exhibited intermediate OS and PFS (mOS: 36 and 17.1 mo; mPFS: 12.2 mo and 9.9 mo, respectively); poorest OS and PFS was observed in wild type IDH1 (wtIDH1) glioblastomas that were MGMT promoter unmethylated (mOS: 15 mo, mPFS: 9.7 mo). For patients with wtIDH glioblastomas, TMZ+RT was associated with improved OS and PFS relative to patients treated with RT (OS: 15.4 mo v 9.6 mo; PFS: 9.9 mo v 6.5 mo).

Conclusions

Our study demonstrates that IDH and MGMT promoter methylation status independently associate with favorable outcome in TMZ+RT treated glioblastoma patients. However, these biomarkers differentially impact clinical TMZ response.

Learning Objectives

1) Understanding the prognostic value of isocitrate dehydrogenase (IDH1) mutations and Methyl-Guanine Methyl Transferase (MGMT) promoter methylation

2) Understanding the influence of IDH1 mutation and MGMT promoter methylation on temozolomide response

3) Understanding the therapeutic strategies against IDH1 mutated glioblastomas

References

1. Hegi ME, Diserens AC, Gorlia T, et al. MGMT gene silencing and benefit from temozolomide in glioblastoma. N Engl J Med 2005; 352(10): 997-1003.