JOURNAL ARTICLE CORRECTED PROOF

The *IDH* paradox: Meta-analysis of alkylating chemotherapy in *IDH*-wild type and -mutant lower grade gliomas

, , , , , , , , , , , , , , , , , ✉, ✉

Neuro-Oncology, noae102, https://doi.org/10.1093/neuonc/noae102
Published: 29 June 2024 **Article history ▾**

Abstract

Background

IDH-wild type (-wt) status is a prerequisite for the diagnosis of glioblastoma (GBM); however, *IDH*-wt gliomas with low-grade or anaplastic morphology have historically been excluded from GBM trials and may represent a distinct prognostic entity. While alkylating agent chemotherapy improves overall survival (OS) and progression-free survival (PFS) for *IDH*-wt GBM and also *IDH*-mutant gliomas, irrespective of grade, the benefit for *IDH*-wt diffuse histologic lower-grade gliomas is unclear.

Methods

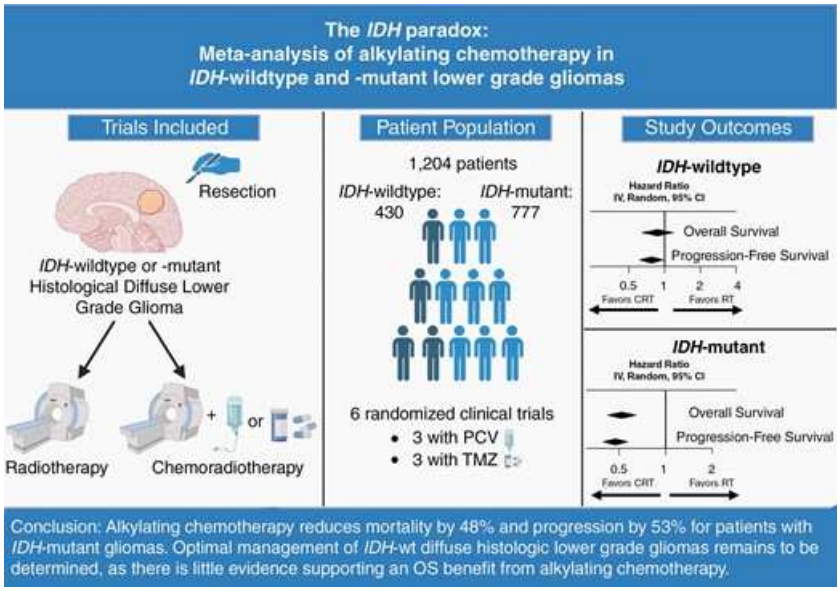
We performed a meta-analysis of randomized clinical trials for World Health Organization (WHO) grades 2–3 gliomas (2009 to present) to determine the effect of alkylating chemotherapy on *IDH*-wt and -mutant gliomas using a random-effects model with inverse-variance pooling.

Results

We identified 6 trials with 1204 patients (430 *IDH*-wt, 774 *IDH*-mutant) that evaluated alkylating chemoradiotherapy versus radiotherapy alone, allowing us to perform an analysis focused on the value of adding alkylating chemotherapy to radiotherapy. For patients with *IDH*-wt tumors, alkylating chemotherapy added to radiotherapy was associated with improved PFS (HR:0.77 [95% CI: 0.62–0.97], $P = .03$) but not OS (HR:0.87 [95% CI: 0.64–1.18], $P = .17$). For patients with *IDH*-mutant tumors, alkylating chemotherapy added to radiotherapy improved both OS (HR:0.52 [95% CI: 0.42–0.64], $P < .001$) and PFS (HR = 0.47 [95% CI: 0.39–0.57], $P < .001$) compared to radiotherapy alone. The magnitude of benefit was similar for *IDH*-mutant gliomas with or without 1p19q-codeletion.

Conclusions

Alkylating chemotherapy reduces mortality by 48% and progression by 53% for patients with *IDH*-mutant gliomas. Optimal management of *IDH*-wt diffuse histologic lower-grade gliomas remains to be determined, as there is little evidence supporting an OS benefit from alkylating chemotherapy.



Graphical Abstract

Keywords: alkylating chemotherapy, glioma, isocitrate-dehydrogenase, meta-analysis, radiotherapy

Issue Section: Metadata Analysis/Review