ABSTRACT

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Systematic Review of Epigenetic Therapies for Treatment of IDH-mutant Glioma.

Govindarajan V, Shah AH, Di L, Rivas S, Suter R, Eichberg DG, Luther E, Lu V, Morell AA, Ivan ME, Komotar RJ, Ayad N, De La Fuente M.

PURPOSE: Isocitrate dehydrogenase mutations (IDH) are present in 70% of WHO grade II and III gliomas. IDH mutation induces accumulation of the onco-metabolite 2-hydroxyglutarate (2-HG). Therefore, therapies targeting reversal of epigenetic dysregulation in gliomas have been suggested. However, the utility of epigenetic treatments in gliomas remains unclear. Here, we present the first clinical systematic review of epigenetic therapies in treatment of IDH-mutant gliomas, and highlight their safety and efficacy.

METHODS: We conducted a systematic search of electronic databases from 2000-January 2021 following PRISMA guidelines. Articles were screened to include clinical usage of epigenetic therapies in case reports, prospective case series or clinical trials. Primary and secondary outcomes included safety/tolerability of epigenetic therapies and progression free survival (PFS)/Overall survival (OS) respectively.

RESULTS: 133 patients across 8 clinical studies were included in our analysis. IDH inhibitors appear to have the best safety profile, with an overall grade 3/grade 4 adverse event rate of 9%. Response rates to IDH mutant inhibitors were highest in non-enhancing gliomas (stable disease achieved in 55% of patients). In contrast, HDAC inhibitors demonstrate a lower safety profile with single-study adverse events as high as 28%.

CONCLUSION: IDH inhibitors appear promising given their benign toxicity profile and ease of monitoring. HDAC inhibitors appear to have a narrow therapeutic index, as lower concentrations do not appear effective, while increased doses can produce severe immunosuppressive effects. Preliminary data suggests that epigenetic therapies are generally well-tolerated, and may control disease in certain patient groups, such as those with non-enhancing lesions.

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