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Phase II Trial of Temozolomide Plus O6-Benzylguanine in Adults With Recurrent, Temozolomide-Resistant Malignant Glioma.

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PURPOSE: This phase II trial was designed to define the role of O(6)-benzylguanine (O(6)-BG) in restoring temozolomide sensitivity in patients with recurrent or progressive, temozolomide-resistant malignant glioma and to evaluate the safety of administering O(6)-BG in combination with temozolomide. PATIENTS AND METHODS: Patients were accrued into two independent strata on the basis of histology: glioblastoma multiforme (GBM) and anaplastic glioma. Both temozolomide and O(6)-BG were administered on day 1 of a 28-day treatment cycle. Patients were administered a 1-hour O(6)-BG infusion at a dose of 120 mg/m(2) followed immediately by a 48-hour infusion at a dose of 30 mg/m(2)/d. Temozolomide was administered orally within 60 minutes of the end of the 1-hour O(6)-BG infusion at a dose of 472 mg/m(2). The primary end point was objective response rate. Secondary end points included progression-free survival, overall survival, and safety. RESULTS: Sixty-six of 67 patients who enrolled were treated with temozolomide and O(6)-BG. One of 34 patients (3%) with GBM (95% CI, 0.1% to 15%) and five of 32 assessable patients (16%) with anaplastic glioma (95% CI, 5% to 33%) were responders. The most commonly reported adverse events were grade 4 hematologic events experienced in 48% of the patients. CONCLUSION: O(6)-BG when added to a 1-day dosing regimen of temozolomide was able to restore temozolomide sensitivity in patients with temozolomide-resistant anaplastic glioma, but there seemed to be no significant restoration of temozolomide sensitivity in patients with temozolomide-resistant GBM.

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