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Phase II trial of continuous low-dose temozolomide for patients with recurrent malignant glioma.

Omuro A, Chan TA, Abrey LE, Khasraw M, Reiner AS, Kaley TJ, Deangelis LM, Lassman AB, Nolan CP, Gavrilovic IT, Hormigo A, Salvant C, Heguy A, Kaufman A, Huse JT, Panageas KS, Hottinger AF, Mellinghoff I.

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Abstract

BACKGROUND: In this phase II trial, we investigated the efficacy of a metronomic temozolomide schedule in the treatment of recurrent malignant gliomas (MGs).

METHODS: Eligible patients received daily temozolomide (50 mg/m2) continuously until progression. The primary endpoint was progression-free survival rate at 6 months in the glioblastoma cohort (N = 37). In an exploratory analysis, 10 additional recurrent grade III MG patients were enrolled. Correlative studies included evaluation of 76 frequent mutations in glioblastoma (iPLEX assay, Sequenom) aiming at establishing the frequency of potentially "drugable" mutations in patients entering recurrent MG clinical trials.

RESULTS: Among glioblastoma patients, median age was 56 y; median Karnofsky performance score (KPS) was 80; 62% of patients had been treated for ≥2 recurrences, including 49% of patients having failed bevacizumab. Treatment was well tolerated; clinical benefit (complete response + partial response + stable disease) was seen in 10 (36%) patients. Progression-free survival rate at 6 months was 19% and median overall survival was 7 months. Patients with previous bevacizumab exposure survived significantly less than bevacizumab-naive patients (median overall survival: 4.3 mo vs 13 mo; hazard ratio = 3.2; P = .001), but those patients had lower KPS (P = .04) and higher number of recurrences (P < .0001). Mutations were found in 13 of the 38 MGs tested, including mutations of EGFR (N = 10), IDH1 (N = 5), and ERBB2 (N = 1).

CONCLUSIONS: In spite of a heavily pretreated population, including nearly half of patients having failed bevacizumab, the primary endpoint was met, suggesting that this regimen deserves further investigation. Results in bevacizumab-naive patients seemed particularly favorable, while results in bevacizumab-failing patients highlight the need to develop further treatment strategies for advanced MG. Clinical trials.gov identifier NCT00498927 (available at http://clinicaltrials.gov/ct2/show/NCT00498927).

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