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Randomized phase II trial of chemoradiotherapy followed by either dose-dense or metronomic temozolomide for newly diagnosed glioblastoma.

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Abstract

PURPOSE: Alternative dosing schedules of temozolomide may improve survival in patients with newly diagnosed glioblastoma (GBM) by increasing the therapeutic index, overcoming common mechanisms of temozolomide resistance, or both. The goal of this randomized phase II study was to evaluate two different temozolomide regimens in the adjuvant treatment of newly diagnosed GBM.

PATIENTS AND METHODS: Adult patients with newly diagnosed GBM were randomly assigned to receive standard radiotherapy with concurrent daily temozolomide followed by six adjuvant cycles of either dose-dense (150 mg/m(2) days 1 to 7 and 15 to 21) or metronomic (50 mg/m(2) continuous daily) temozolomide. Maintenance doses of 13-cis-retinoic acid were then administered until tumor progression. The primary end point was overall survival (OS) at 1 year. Tumor tissue was assayed to determine O(6)-methylguanine-DNA methyltransferase (MGMT) promoter methylation status.

RESULTS: Eighty-five eligible patients were enrolled; 42 were randomly assigned to dose-dense and 43 to metronomic temozolomide. The 1-year survival rate was 80% for the dose-dense arm and 69% for the metronomic arm; median OS was 17.1 months (95% CI, 14.0 to 28.1 months) and 15.1 months (95% CI, 12.3 to 18.9 months), respectively. The most common toxicities were myelosuppression (leukopenia, neutropenia, and thrombocytopenia) and elevated liver enzymes. Pseudoprogression was observed in 37% of assessable patients and may have had an impact on estimates of progression-free survival (6.6 months in the dose-dense arm and 5.0 months in the metronomic arm).

CONCLUSION: Both dose-dense and metronomic temozolomide regimens were well tolerated with modest toxicity. The dose-dense regimen appears promising, with 1-year survival of 80%.

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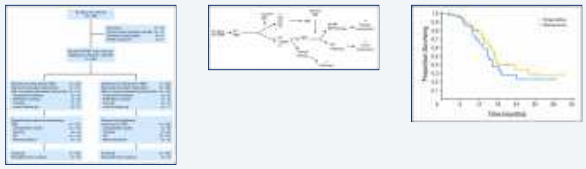

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