RTOG 0525: A randomized phase III trial comparing standard adjuvant temozolomide (TMZ) with a dose-dense (dd) schedule in newly diagnosed glioblastoma (GBM).


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Abstract Disclosures

Abstract

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Background: Radiotherapy with concomitant and adjuvant TMZ (TMZ/RT→TMZ) is the standard of care for newly diagnosed GBM. MGMT methylation status may be an important determinant of treatment response. Compared with the standard adjuvant TMZ, dd TMZ results in prolonged depletion of MGMT in blood mononuclear cells and possibly in tumor. This trial determined if intensified TMZ improves survival (OS) or progression free survival (PFS).

Methods: This phase III trial was conducted by the RTOG, EORTC and NCCTG. Neurologically stable patients with adequate tissue for prospective MGMT analysis were randomized to Arm 1: standard TMZ (150-200 mg/m² x 5 d) or Arm 2: dd TMZ (75-100 mg/m² x 21 d) q 4 wks for 6-12 cycles. Symptom, QOL and neurocognitive testing was performed in a subset of patients. The primary endpoint was OS. Secondary analyses evaluated impact of MGMT status. Eligibility criteria included age > 18 yrs, KPS ≥ 60, and tissue block with > 1 cm² tumor.

Results: A total of 833 patients were randomized from a total of 1173 registered. Inadequate tissue (n=144) and early disease progression (n =56) were the most frequent reasons for non-randomization. No statistical difference was observed between Arms 1 and 2 for median OS (16.6, 14.9 mo, p = 0.63), or median PFS (5.5, 6.7 mo, p = 0.06), or by methylation status. MGMT methylation was associated with improved OS (21.2, 14 mo, p < 0.0001), PFS (8.7, 5.7 mo, p < 0.0001) and response (p = 0.012). Cox modeling showed that MGMT status and RPA class were significant predictors of OS while the treatment arm and radiation technique (EORTC vs. RTOG) were not. There was increased grade ≥ 3 toxicity in Arm 2 (19%, 27%, p = 0.008); mostly lymphopenia and fatigue.

Conclusions: This study did not demonstrate improved efficacy for dd TMZ for newly diagnosed GBM regardless of methylation status. However, it confirmed the prognostic significance of MGMT methylation in GBM. Additionally, it demonstrated the feasibility of tumor tissue collection, molecular stratification and collection of patient outcomes in a large transatlantic intergroup trial and established this as a viable clinical trial paradigm. Supported by NCI U10 CA 21661 and U10 CA37422.

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