Radiotherapy plus Concomitant and Adjuvant Temozolomide for Glioblastoma

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Introduction

- Glioblastoma multiforme is the most common primary malignant brain tumor in adults and carries a median survival of less than 1 year.
- The current standard of care consists of surgical resection followed by radiotherapy.
- Although carmustine is commonly prescribed in the United States, no randomized phase III trial of nitrosourea-based chemotherapy has demonstrated a survival benefit compared to radiation alone.
- Temozolomide has demonstrated activity in the treatment of recurrent glioma, and a pilot phase II trial of concomitant temozolomide and radiation therapy followed by adjuvant temozolomide showed promising results.
- The EORTC and NCIC therefore initiated a randomized, multicenter, phase III trial to compare concomitant and adjuvant temozolomide with radiation alone.

Methods

- Eligible patients included those aged 18 to 70 years with newly diagnosed and histologically confirmed glioblastoma multiforme, and a WHO performance status of 2 or less.
- Those patients on corticosteroids were eligible only if the dose was stable or decreasing for at least 14 days prior to randomization.
- Study participants were stratified according to WHO performance status, whether or not they had undergone a debulking surgical procedure, and treatment center.
- Radiation consisted of 2 Gy daily fractions (Monday through Friday) for a total dose of 60 Gy delivered to the gross tumor volume with a 2 to 3 cm margin.
- Concomitant temozolomide was given 7 days a week at a dose of 75 mg per square meter body surface area.
- Adjuvant temozolomide was given for 5 days, followed by a 23-day break, and then was continued for up to six cycles. The first cycle began 4 weeks after the end of radiation treatment at a dose of 150 mg per square meter body surface area; subsequent doses were increased to 200 mg per square meter body surface area, provided there were no hematologic toxic effects.
- Tumor progression was defined as: an increase in tumor size by 25 percent, the appearance of new lesions, or an increased need for corticosteroids.
- The primary end point was overall survival, and secondary end points were progression-free survival, safety, and quality of life
- Analyses were conducted on an intention-to-treat basis, and the study was powered at 80 percent at a 5 percent significance level to detect a 33 percent increase in median survival.

Results

- 573 patients from 85 institutions in 15 countries were randomized between August 2000 and March 2002
- The median age was 56 years
- 84 percent of patients underwent debulking surgery
- Median follow-up was 28 months
- Slightly more patients in the radiotherapy alone group were receiving corticosteroids at the time of randomization
- There was a significant benefit in the temozolomide group with respect to median survival (14.6 months vs. 12.1 months), median progression-free survival (6.9 months vs. 5.0 months), and 2-year overall survival (26.5% vs. 10.4%)
- The hazard ratio for death was 0.63 ($p<0.001$) and for death or disease progression was 0.54 ($p<0.001$) in the temozolomide group versus the radiation alone group
- During concomitant temozolomide treatment, grade 3 or 4 neutropenia was demonstrated in 4 percent of patients, and grade 3 or 4 thrombocytopenia in 7 percent of patients
- During adjuvant temozolomide therapy, 4 percent of patients had grade 3 or 4 neutropenia, and 11 percent had grade 3 or 4 thrombocytopenia
- Severe infections during the radiation period occurred in 2 percent of patients in the radiotherapy alone arm and in 3 percent of patients in the temozolomide arm; severe infections during the adjuvant temozolomide period occurred in 5 percent of patients in the temozolomide arm

Author’s Conclusions

- The addition of temozolomide chemotherapy to radiation for treatment of glioblastoma multiforme significantly prolongs survival, with a median increase of 2.5 months and a relative reduction in mortality of 37 percent.
- There was a clinically meaningful increase (by factor of 2.5) in the 2-year survival rate among patients treated with both radiation and temozolomide.
- The outcome for patients in the control arm compares favorably with earlier trials.

Clinical Implications

- Concomitant and adjuvant temozolomide chemotherapy added to radiation treatment provides a statistically significant and clinically meaningful survival advantage compared to radiation alone, with a modest increase in treatment toxicity.
- This treatment regimen represents the new standard of care in the treatment of glioblastoma multiforme.