

Radiotherapy plus adjuvant temozolomide for the treatment of glioblastoma—a paradigm shift

GLOSSARY

WHO GRADE IV ASTROCYTOMA

A high-grade brain tumor that forms from glial (supportive) tissue of the brain; also called glioblastoma multiforme

HAZARD RATIO (HR)

The relative likelihood of experiencing a particular event; an HR of 0.5 indicates that one group has half the risk of the other group

COX MULTIVARIATE MODEL

Statistical regression technique which takes into account the time interval to an outcome in relation to baseline characteristics (of a patient)

NITROSOUREAS

Any of several chemically related antineoplastic agents including carmustine, lomustine, semustine, and the antibiotic streptozocin

EPIGENETIC SILENCING

Inappropriate repression of gene expression caused by increased genomic heterochromatinization; epigenetic silencing of gene promoter regions can be caused by DNA methylation and histone deacetylation

Original article Stupp R *et al.* (2005) Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. *N Engl J Med* 352: 987–996

SYNOPSIS

KEYWORDS astrocytoma, glioblastoma, radiotherapy, survival, temozolomide

BACKGROUND

Most adults with glioblastoma die within 1–2 years of diagnosis. Standard care is currently surgical resection, when possible, with subsequent radiotherapy. Addition of chemotherapy could provide a small survival benefit. Following promising results from a pilot phase II trial of temozolomide plus radiotherapy, Stupp *et al.*'s larger study compared this same regimen with radiotherapy alone.

OBJECTIVE

To determine the efficacy and safety of radiotherapy plus temozolomide, in comparison with radiotherapy alone, in patients with newly diagnosed glioblastoma.

DESIGN AND INTERVENTION

Between August 2000 and March 2002, patients from 85 sites in 15 countries were enrolled in this randomized multicenter phase III trial. The age range was 18–70 years (median 56 years) and debulking surgery had been performed in 84% of patients. Inclusion criteria were newly diagnosed glioblastoma (WHO GRADE IV ASTROCYTOMA), a performance status of ≤ 2 , and adequate renal, hematologic, and hepatic function. Patients were randomly assigned to receive radiotherapy alone or radiotherapy plus temozolomide. Radiotherapy comprised fractionated focal irradiation (2 Gy per fraction, once daily, 5 days per week for 6 weeks; total dose 60 Gy). Concomitant temozolomide (75 mg/m² body surface area) was given 7 days per week during radiotherapy, for a maximum of 49 days. This was followed by up to six cycles of adjuvant temozolomide (150–200 mg/m²

body surface area for 5 days per 28-day cycle). Adjuvant chemotherapy was abandoned if there were hematologic toxic effects.

OUTCOME MEASURES

The primary endpoint was overall survival; secondary endpoints were progression-free survival, safety and quality of life. Toxic effects were recorded.

RESULTS

There was similarity between the baseline characteristics of the patients in the radiotherapy group ($n=286$) compared with those in the radiotherapy plus temozolomide group ($n=287$). At a median follow-up of 28 months, the group receiving radiotherapy plus temozolomide had a median survival time of 14.6 months (95% CI 13.2–16.8), compared with 12.1 months (95% CI 11.2–13.0) in the radiotherapy-alone group. Comparison of the intervention group with the control group revealed an unadjusted HAZARD RATIO for death of 0.63 (95% CI 0.52–0.75, $P<0.001$). When adjusted for potential confounding factors (COX MULTIVARIATE MODEL), the hazard ratio for death was essentially unchanged. A higher 2-year survival rate was found in the radiotherapy-plus-temozolomide group (26.5% [95% CI 21.2–31.7%]) than in the radiotherapy-alone group (10.4% [95% CI 6.8–14.1%]). Grade 3 or 4 hematologic toxic effects occurred in 7% of patients as a result of concomitant radiotherapy and temozolomide treatment.

CONCLUSION

The addition of temozolomide to radiotherapy significantly prolonged survival among patients with newly diagnosed glioblastoma. The authors recommend this chemotherapy plus radiotherapy regimen as the preferred standard treatment in this patient group, but recommend further studies and long-term monitoring of late toxic effects.

COMMENTARY

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Randomized trials have demonstrated that fractionated radiotherapy treatment confers a definite survival benefit on patients with glioblastoma. The benefits of 'adjuvant' chemotherapy have proven more difficult to document, however.¹ The results of nearly 30 randomized trials of post-radiation adjuvant chemotherapy have been inconclusive, because of underpowered studies and heterogeneity among the patient groups. Meta-analyses have therefore addressed these limitations, demonstrating that the addition of chemotherapy to radiotherapy results in a significant prolongation of median survival by approximately 2 months.^{2,3} Based on these and other data, the administration of single-agent NITROSOUREAS (carmustine or lomustine) following radiotherapy became the standard care for patients with glioblastoma in the US.

The trial by Stupp and co-workers is likely to change standard practice because it is the most markedly positive trial performed in patients with glioblastoma in the past 20 years. Nevertheless, the benefits seen in this trial were modest, with only a 2.5-month prolongation of median survival for patients treated with temozolomide and radiation compared with radiation alone. Interestingly, this was almost exactly the same benefit as was seen with nitrosoureas in the above meta-analyses. The 2-year survival in the patients treated with temozolomide and radiation (26.5%), however, was nearly double that seen in the meta-analyses (13%),^{2,3} suggesting that temozolomide might be more effective than nitrosoureas in a small subgroup of patients.

Based on the report by Hegi and co-workers,⁴ it is tempting to speculate that this hypothetical subgroup of long-term surviving patients might be those with methylation (and thus inactivation) of the O-6-methylguanine-DNA methyltransferase (*MGMT*) drug-resistance gene promoter. This seems unlikely, however, to account for the difference between temozolomide and nitrosoureas, because EPIGENETIC SILENCING of the *MGMT* gene has also been associated

with sensitivity to nitrosoureas in patients with glioblastoma. Therefore, whether the increased 2-year survivorship is in fact caused by temozolomide treatment, or is merely a statistical anomaly, awaits further studies. Until then, it seems reasonable to consider temozolomide to be the drug of choice for adjuvant therapy of glioblastoma, given its excellent tolerability, ease of administration and lack of known long-term toxicity compared with nitrosoureas. If legitimate clinical trials are not available to medically appropriate patients with glioblastoma, temozolomide and radiation should be offered as part of a standard initial treatment regimen, regardless of the methylation status of the tumor *MGMT* gene.

Patients who are most likely to benefit from temozolomide (i.e. those who have *MGMT* promoter methylation) must be definitively identified. Additionally, it will be important to define whether the benefit afforded by temozolomide is secondary to its daily administration with radiotherapy (i.e. radiosensitization), or the 6 months of post-radiation standard-dose temozolomide, or both. The resulting data will be crucial for the planning of future clinical trials with new and, it is hoped, even more active agents. Despite the survival benefits seen with temozolomide, we must still strive to improve this new standard of care, given that most of our patients still die within 2 years of diagnosis and almost no one is cured. Clearly, much more work needs to be done.

References

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Competing interests

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PRACTICE POINT

Temozolomide with fractionated radiotherapy confers a modest but significant survival advantage versus radiation alone in patients with glioblastoma and should be considered the new standard of care