Date: September 2, 2008

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Question DIQ 3067: What is the optimal length of treatment with Temodar (temozolomide) for glioblastoma?

Background: Many doctors say to use temozolomide for 6 months only, some say 1 or 2 years, and some say it is okay to use as long as it is helping and the blood counts are okay. Is there an optimal treatment time?

Response:

Current clinical practice guidelines (last updated May 2006) recommend the use of temozolomide during radiotherapy and post-radiotherapy in adult patients with newly diagnosed glioblastoma multiforme. This can also be considered in younger patients, patients with anaplastic (grade III) astrocytoma, and patients with oligodendroglioma, although safety and survival data is poorly studied in these populations. The guidelines are not clear on a recommendation for how long temozolomide therapy should continue.[1] A literature review was done to evaluate the various lengths of temozolomide treatment in the clinical trials that led to the development of these guidelines.

A joint study by the European Organization for Research and Treatment of Cancer and the National Cancer Institute of Canada (EORTC/NCIC) published in 2005 evaluated temozolomide given concomitantly with and after radiation for the treatment of glioblastoma. Patients aged 18-70 with newly diagnosed gliomastoma were randomly assigned to receive either radiotherapy alone (control group) or radiotherapy plus continuous daily temozolomide (75 mg/m^2 body surface area per day) followed by six cycles of temozolomide therapy (150-200 mg/m^2 for 5 days during each 28-day cycle). [2]

In this study, treatment started 5 weeks after diagnosis on average. Interruptions due to toxicity occurred in only 3-4% of patients, and 85% of the intervention group completed both radiation and temozolomide therapy as planned. The main reason for not continuing temozolomide after radiation or quitting the regimen prematurely was disease progression; only 8% of patients discontinued due to toxicity. Overall, this study demonstrated a 37% relative risk of death reduction when temozolomide was used with and continued after radiation as compared to radiation alone. The average survival

benefit was 2.5 months (14.6 months for intervention group and 12.1 months in control), the two-year survival rate was 16.1% improved (26.5% in the intervention group compared to 10.4% with radiation alone), and the median progression-free survival was 1.9 months longer (6.9 months for intervention compared to 5.0 months in control).[2]

No grade 3 or 4 hematologic toxic effects were observed in the control group. During the first phase of concomitant temozolomide therapy, 19 patients (7%) had some type of hematologic toxic effect (neutropenia or thrombocytopenia). During the second phase of adjuvant temozolomide, 14% of patients experienced a hematologic toxic effect (grade 3 or 4 neutropenia or thrombocytopenia). The most common non-hematologic adverse event was moderate-to-severe fatigue (26% control group and 33% intervention group). At the cutoff date, 512 patients (94% of the control group and 85% of the intervention group) had disease progression. When disease progression occurred, further treatment was the physician's decision, and the response to second-line treatments were not recorded.[2]

This study demonstrated that temozolomide plus radiotherapy followed by six months of maintenance temozolomide significantly prolongs survival and should be used as first-line treatment. Patients with newly diagnosed glioblastoma treated with radiotherapy plus daily temozolomide followed by an additional six cycles of temozolomide showed 1- and 2- year survival rates of 61% and 27%, which was a statistically and clinically significant improvement from the conventional therapy of radiation alone.[2]

Following this, a survey of neuro-oncologists was conducted in 2007 to specifically evaluate the safety and survival of patients using temozolomide for longer periods of time. Fifty physicians presented a total of 128 patients with grade III or IV glioma who had received temozolomide for at least 12 months or 12 cycles (28 days each). These patients either received temozolomide on the standard 5-day regimen or according to the protocol of concomitant and adjuvant temozolomide from the EORTC/NICIC trial, but in all patients, temozolomide was continued beyond six cycles until patients experienced unacceptable toxicity or disease progression occurred.[3]

Overall toxicities of long-term temozolomide therapy were low. Major adverse events included grade III or grade IV thrombocytopenia (10%), leukopenia (7%), GI toxicity (5%), and infection (4%). Patients who received temozolomide first line had an average time to progression (TTP) of 14 months from diagnosis, and patients treated for recurrent disease had a median TTP of 15.5 months from start of temozolomide treatment. Survival data was available for 56 patients, and among these, the median overall survival was 35 months. The longest survival time of 58.5 months was in a patient receiving temozolomide as first-line treatment.[3]

In this study, patients with well-controlled disease and an overall survival of < 58.5 months, temozolomide did have an acceptable safety profile. Long-term therapy is feasible and tolerable in this patient population, and temozolomide should be considered as a safe option for continued use until unacceptable toxicity develops or disease progression occurs.[3]

Another retrospective analysis sought to evaluate the potential for benefit of long-term temozolomide therapy and the ideal length of treatment. They analyzed 36 patients with malignant gliomas (class III or IV) who received temozolomide, either alone or in combination, for at least 12 months. Progression-free survival (PFS) rates were compared between patients who received 12-18 cycles of temozolomide or stopped treatment in the absence of tumor progression and those who continued treatment until progression of disease or received temozolomide for 19 cycles or more. Mean PFS was 95 weeks for those receiving treatment for 12-18 cycles or discontinuing before signs of disease progression, and average PFS could not be obtained for the other group after a follow-up of 124 weeks. This was enough to prove a statistically significant difference between groups in favor of longer temozolomide treatment. This data suggests that patients can safely be treated with temozolomide for longer periods of time, and progression-free survival is likely to improve, especially in cases of recurrent high-grade gliomas.[4]

In conclusion, temozolomide is the currently recommended chemotherapy, along with surgery and radiation, for treatment of glioblastoma. Although the guidelines are unclear regarding an optimal length of time for treatment, it seems reasonable to continue temozolomide therapy on the 28-day cycle until disease progression is noted or toxicities occur. Long-term treatment, especially in high-grade gliomas, has resulted in a generally low risk of toxicity and significant improvements in terms of overall survival and progression-free survival.

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Resources:

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2. Stupp R, Mason WP, Van den Bent, MJ, Weller M, Fisher B, Taphoorn MJB, et al. Radiotherapy plus Concomitant and Adjuvant Temozolomide for Glioblastoma. N Engl J Med 2005;352:987-996.
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