One week on/one week off: A novel active regimen of temozolomide for recurrent glioblastoma

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Neurology 2004;62;2113-2115
DOI 10.1212/01.WNL.0000127617.89363.84

One week on/one week off: A novel active regimen of temozolomide for recurrent glioblastoma

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Abstract—Twenty-one patients with recurrent or progressive glioblastoma were enrolled in a prospective phase II trial to determine the safety and efficacy of a 1-week on/1-week off regimen of temozolomide administered at 150 mg/m^2 on days 1 to 7 and days 15 to 21 of 28-day treatment cycles. Two patients achieved a partial response (10%), and 17 patients (81%) had stable disease. The median progression-free survival was 5 months. The progression-free survival at 6 months was 48%.

NEUROLOGY 2004;62:2113–2115

The primary treatment of patients with glioblastoma produces median survival times in the range of 12 months.[1] Salvage therapies may add a median of 4 to 6 months. Using different salvage therapies, there was an overall response rate, comprising complete and partial remissions,[2] of 9%.[3]

Temozolomide (Schering Plough Pharmaceuticals, Kenilworth, NJ) at 150 to 200 mg/m^2 on the first 5 days of 28-day cycles was superior to procarbazine for the management of recurrent glioblastoma in adults and produced an overall response rate of 5.4% and a progression-free survival rate at 6 months of 21%.[4]

A 1-week on/1-week off schedule of temozolomide at 150 mg/m^2 is feasible and permits a 2.1-fold greater drug exposure than the conventional schedule of 5 days every 28 days.[5] This schedule was evaluated to determine overall response rates and progression-free survival in patients with recurrent glioblastoma.

Patients and methods. This prospective nonrandomized phase II study was activated on December 11, 2001 and closed to accrual on July 15, 2003 (Tübingen Ethics Committee approval 211/01). The objective was to determine the safety and efficacy of a 1-week on/1-week off regimen of temozolomide for the treatment of patients with recurrent or progressive glioblastoma. The primary endpoint was progression-free survival at 6 months. Secondary endpoints included response rate and median progression-free survival and overall survival at 12 months.

Inclusion criteria were similar to other studies with a previous histologic diagnosis of supratentorial glioblastoma, previous radiotherapy without or with one regimen or more of nontemozolomide chemotherapy, recurrence or progression on cranial CT (CCT) or MRI, and a Karnofsky performance status (KPS) of ≥60.[6,7] Temozolomide was administered orally at 150 mg/m^2 on days 1 to 7 and days 15 to 21 of 28-day cycles for at most 12 × 28 days. The start of each new cycle required that all hematologic toxicity from the previous cycle had resolved to grade 2 or less and that all nonhematologic toxicity had recovered to grade 0 or 1. If recovery had not occurred by day 28, the subsequent course of temozolomide was delayed until these criteria were met. No dose escalations were allowed. Leukopenia $<2 \times 10^9$/L or thrombopenia $<75 \times 10^9$/L led to dose reductions of 25 mg/m^2 for the next week. The requirement for a reduction by 75 mg/m^2 resulted in the withdrawal from the study. Re-escalations in steps of 25 mg/m^2 were allowed when the lowest counts for leukocytes were $>2 \times 10^9$/L and for platelets $>75 \times 10^9$/L for two subsequent weeks.

Monitoring of toxicity, and safety and concomitant therapy was as usual. During the trial the patients had a CCT or MRI at 2-monthly intervals (e.g., before every second cycle). The status was assessed as complete response, partial response, stable disease, or progressive disease by one of the authors (W.K.).[2] Remissions are defined as complete reduction (complete response), >50% reduction (partial response), or >25% increase (progressive disease) of contrast-enhancing lesions. Stable disease is defined by <50% reduction and ≤25% increase of contrast-enhancing lesions.[2] Progression-free survival with temozolomide and overall survival were calculated from the date recurrent or progressive tumor was diagnosed.

The proportion of patients free from progression at 6 months in the study used for comparison was 21%.[4] We wanted to test whether a 1-week on/1-week off regimen of temozolomide resulted in an improvement of >0.2. We concluded that 21 patients in a single-arm study would give us acceptable error rates for testing our hypothesis and acceptable precision for estimation. To declare success, 10 successful treatments (patients alive and progression free at 6 months) of 21 patients (target, at least 43%) were needed. We performed a two-sided Fisher's exact test to test for significance of the outcome in our study compared with the standard regimen.[4]

Results. *Patients and treatment.* Twenty-eight patients with recurrent or progressive glioblastoma were assessed for eligibility. Five patients did not meet the inclusion criteria; one patient refused to participate; and one patient did not receive the first treatment although he agreed to enter the study. Clinical and demographic features of the remaining 21 patients are listed in table 1. Of seven patients with a second resection, six had a resection immediately before the temozolomide regimen, but only one patient entered the study without MRI-assessable residual tumor. Fourteen patients were treated at first relapse, and seven patients were treated at second relapse.

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Received September 8, 2003. Accepted in final form January 29, 04.

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Table 1 *Patient characteristics*

Characteristics	Patients, n	Patients, %
Age, y		
21–40	4	19
41–60	15	71
>60	2	10
Sex		
F	7	33
M	14	67
Karnofsky performance status		
60–80	5	24
90–100	16	76
Prior surgical interventions, n		
1	14	67
2	7	33
Prior radiotherapy	21	100
Prior nitrosourea-based chemotherapy regimens, n		
0	12	57
1	8	38
2	1	5
Median time from diagnosis, weeks	39	

The total number of cycles in the 1-week on/1-week off regimen was 99. The median number of cycles per patient was five. Three patients (14%) received only one cycle; another four patients (19%) completed only two cycles. Four patients (19%) completed more than eight cycles. All 21 patients were assessable for toxicity, response, and survival.

Toxicity. Toxicity was recorded for all eligible patients using the World Health Organization recommendations for grading of acute and subacute toxicity. Temozolomide was generally well tolerated, and the main toxicities seen were hematologic (table 2). There were no deep venous thromboses or other organ toxicities during the temozolomide treatment. Temozolomide did not induce relevant nausea or constipation. Follow-up evaluation after temozolomide treatment either clinically or by neuroimaging did not indicate neurotoxicity of this regimen.

Table 2 *Toxicity*

Toxicity	Grade 3, n	Grade 4, n
Anemia	0	1
Leukopenia	1	1
Granulocytopenia	0	1
Infection, neutropenic	0	1
Thrombocytopenia	3	3
Nausea alone	2	0
Vomiting	0	0
Deep venous thrombosis	0	0
Fatigue	4	0
Total	10	7

Table 3 *Survival*

Response and survival data	Temozolomide, one week on/ one week off	Conventional temozolomide regimen[4]	Historical database[3]
Patients, n	21	112	375
Overall response rate (complete + partial response), %	9.5	5.4	6
Progression-free survival at 6 mo, % (95% CI)	48 (33–63)*	21	21
Median progression-free survival, weeks (95% CI)	21 (16–26)	13	10
Overall survival at 12 mo %	81	No data	55

* $p = 0.026$, historical comparison[4].

Response and survival. There were no complete responses, but there were two partial responses, resulting in an overall response rate of 9.5%. Another 17 patients (81%) showed stable disease at least from study entry to the first control scan 2 months later. Only two patients (9.5%) showed progressive tumor growth during the first 8 weeks of therapy. The median progression-free survival was 21 weeks. Ten patients (48%) were free from progression at 6 months (table 3). The overall survival at 12 months was 81%. Six of the 18 patients who have failed to respond to this temozolomide regimen to date have received further chemotherapy, mostly nitrosourea based. The t-test for the impact of previous chemotherapy on median progression-free survival revealed no significant difference ($p = 0.056$).

Discussion. The progression-free survival rate with the standard regimen of temozolomide (150 to 200 mg/m^2 × 5 days in 28-day cycles) was 21%.[4] Promising efforts to improve on that figure include the combination of temozolomide with the matrix metalloproteinase inhibitor marimastat or with 13-cis-retinoic acid, producing progression-free survival rates at 6 months for recurrent glioblastoma of 39% and 32%, respectively.[6,7]

The median progression-free survival, the progression-free survival rate at 6 months, and the overall response rate achieved in the current study (see table 3) compare well with the larger randomized multicenter trial using the conventional temozolomide regimen that involved an intent to treat analysis[4] or a historical database of phase II trials for recurrent glioblastoma.[3] Our results resemble those obtained with recent approaches of temozolomide-based combination chemotherapy.[6,7] Of note, there was a rather high proportion of chemonaive patients (57%) in our trial, which might have contributed to the favorable results of our trial. Conversely, seven patients were treated at their second relapse, not their first. The total dose of temozolomide in the 1-week on/1-week off regimen is theoretically increased 2.1-fold over the total dose in the conventional regimen. Assuming that no dose re-

duction is necessary in a conventional regimen, the total amount of temozolomide applied over 99 cycles in our trial corresponded to a 1.95-fold dose escalation. This dose escalation did not result in enhanced myelotoxicity compared with the conventional regimen.[4] Thus, the 1-week on/1-week off regimen of temozolomide is a feasible and effective salvage therapy with modest toxicity that should be evaluated in a larger randomized phase II trial.

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