

Temozolomide Versus Procarbazine, Lomustine, and Vincristine in Recurrent High-Grade Glioma

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ABSTRACT

Purpose

Temozolomide (TMZ) is an alkylating agent licensed for treatment of high-grade glioma (HGG). No prospective comparison with nitrosourea-based chemotherapy exists. We report, to our knowledge, the first randomized trial of procarbazine, lomustine, and vincristine (PCV) versus TMZ in chemotherapy-naïve patients with recurrent HGG.

Patients and Methods

Four hundred forty-seven patients were randomly assigned to PCV (224 patients) or TMZ (sub-random assignment: TMZ-5 [200 mg/m² for 5 days, 112 patients] or TMZ-21 [100 mg/m² for 21 days, 111 patients]) for up to 9 months or until progression. The primary outcomes were survival (PCV v TMZ) and 12-week progression-free survival (PFS; TMZ-5 v TMZ-21). This study is registered as ISRCTN83176944.

Results

Percentages of patients completing 9 months of treatment in the PCV, TMZ-5, and TMZ-21 arms were 17%, 26%, and 13%, respectively. Major toxicity was similar across all three groups. With a median follow-up time of 12 months and 382 deaths, there was no clear survival benefit when comparing PCV with TMZ (hazard ratio [HR], 0.91; 95% CI, 0.74 to 1.11; *P* = .350). For TMZ-5 versus TMZ-21, 12-week PFS rates were similar (63.6% and 65.7%, respectively; *P* = .745), but TMZ-5 improved overall PFS (HR, 1.38; 95% CI, 1.05 to 1.82; *P* = .023), survival (HR, 1.32; 95% CI, 0.99 to 1.75; *P* = .056), and global quality of life (49% v 19% improved > 10 points at 6 months, respectively; *P* = .005).

Conclusion

Although TMZ (both arms combined) did not show a clear benefit compared with PCV, comparison of the TMZ schedules demonstrated that the 21-day schedule was inferior to the 5-day schedule in this setting. This challenges the current understanding of increasing TMZ dose-intensity by prolonged scheduling.

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INTRODUCTION

Astrocytic tumors of WHO grade 3 (anaplastic astrocytoma [AA]) and 4 (glioblastoma multiforme [GBM]) are the most common primary brain tumors in adults. The prognosis after surgical resection and conventional radiotherapy is poor, with a median survival of 9 to 12 months for GBM and 36 months for AA.^{1,2}

Standard treatment for recurrent high-grade gliomas (HGGs) before temozolomide (TMZ) was nitrosourea-based chemotherapy. Response rates ranged from 8% to 27%.³⁻⁵ Since its introduction, TMZ has been used in patients with recurrent HGG because it is well tolerated, has good oral bioavailability, and is convenient to administer as an outpatient regimen.⁶ A study in 162 patients with

recurrent AA reported a progression-free survival (PFS) rate of 46% at 6 months, median PFS time of 5.4 months, and median survival time of 13.6 months. In a randomized phase II study of 225 patients with relapsed GBM comparing TMZ versus procarbazine as the reference arm, TMZ improved 6-month PFS (21% v 8%, respectively; *P* = .008) and median PFS (12.4 v 8.3 weeks, respectively; *P* = .006).⁷ In a single-arm phase II study, the 6-month PFS in 138 patients with GBM was 18%.⁸ These findings formed the basis for accelerated approval of TMZ by the US Food and Drug Administration in 1999.⁹ More recently, TMZ showed improved survival in patients with newly diagnosed GBM when administered concomitantly with radiotherapy and adjuvantly.² This is the standard of care in this group of patients.

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Clinical Trials repository link available on JCO.org.

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Although clinical trials have shown TMZ to be active in AA and GBM at relapse, no randomized comparison with (standard) nitrosourea-based chemotherapy had been performed. Such a trial was considered necessary to determine the most appropriate first-line chemotherapy at first recurrence. This trial was designed before the introduction of TMZ in primary therapy of GBM to compare TMZ with an accepted standard regimen of procarbazine, lomustine, and vincristine (PCV).

The standard TMZ regimen, a 5-day schedule of 150 to 200 mg/m²/d, repeated every 28 days (TMZ-5),⁶ is based on preclinical and phase I clinical studies showing schedule dependency.^{10,11} TMZ and procarbazine form *O*-methylguanine DNA lesions, causing DNA strand breaks and apoptotic cell death in mismatch repair proficient cells.^{6,12} The DNA repair protein, *O*⁶-methylguanine-DNA-methyltransferase (MGMT), can repair these adducts and reduce cytotoxic efficacy.¹³ Because tumor sensitization is a consequence of MGMT depletion, improved response to treatment has been postulated with more protracted TMZ dosing and consequently more prolonged MGMT depletion.¹⁴ Because the optimal TMZ schedule had yet to be established, we also examined whether a 21-day TMZ schedule of 100 mg/m²/d (TMZ-21) is superior to the standard TMZ-5.

PATIENTS AND METHODS

All participating institutions obtained local ethics approval and written informed consent from all patients.

Patients

Eligible patients were adults of either sex with histologically verified AA, GBM, gemistocytic astrocytoma, oligoastrocytomas, or gliosarcomas (WHO grade 3 or 4 at diagnosis, relapse, or transformation) who had undergone primary treatment including radiotherapy completed more than 2 months before random assignment, had a life expectancy of ≥ 1 month, and were fit for chemotherapy with adequate hepatic, renal, and hematologic function. Evidence of first progression was confirmed by evaluable enhancing recurrent tumor on contrast-enhanced magnetic resonance imaging/computed tomography within the 2 weeks before start of treatment. Patients who had received chemotherapy, radiosurgery, or brachytherapy for glioma were excluded, but debulking at relapse was permissible. Patients with WHO performance status (PS) of 4, active pregnancy, or oligodendroglioma histology were excluded.

Treatment

Random assignment was performed by telephone call to the Medical Research Council Clinical Trials Unit. Patients were allocated to either PCV or TMZ, with patients assigned to TMZ further randomly assigned to TMZ-5 or TMZ-21. Treatment allocation used minimization with stratification factors of center, tumor grade (3 or 4 or high grade unspecified), and PS (0 or 1 v 2 or 3) across all three groups.

PCV was administered every 6 weeks for up to six cycles or until progression and comprised procarbazine (100 mg/m²) on days 1 through 10, lomustine (100 mg/m²), and intravenous vincristine (1.5 mg/m² capped at 2 mg) on day 1. TMZ was administered orally (TMZ-5 200 mg/m² and TMZ-21 100 mg/m²) repeated every 28 days for up to nine cycles or until progression. Dose modifications for all treatments were specified in the protocol according to clinical evidence of grade ≥ 3 toxicity in the previous cycle and blood counts. Pneumocystis pneumonia prophylaxis was not mandatory. Formal assessment of clinical and radiologic progression, neurologic status, and PS was performed every 12 weeks. Criteria for clinical progression included the presence of any one of the following: neurologic deterioration (based on 12-point neurologic assessment), decline of ≥ 1 point in PS, increased corticosteroid requirements for more than 2 weeks where causes other than progression had been ruled out, or increased symptoms of raised intracranial pressure. Imaging

(using the same contrast-enhanced imaging method as the baseline scan) was repeated on clinical progression wherever possible; scans were also performed at baseline and at 12 and 24 weeks, with progressive disease defined as a $\geq 25\%$ increase in two-dimensional tumor size. Quality of life (QOL) was measured using the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire C30 (version 3.0) with brain tumor module at baseline and at 12 and 24 weeks.

Study Measures and Statistical Analyses

The primary comparison on which the study was powered was TMZ (both schedules combined) versus PCV. With 380 deaths from approximately 500 patients randomly assigned over 3 to 4 years, the study had 80% power to detect a 2-month increase in median survival (hazard ratio [HR], 0.75) and 90% power to detect a 3-month increase (HR, 0.67), with a two-sided significance level of $P = .05$. We assumed that at least two thirds of patients had GBM (grade 4), giving 80% power to detect a similar difference in survival in a planned subgroup analysis of such patients. Secondary outcomes included PFS and QOL.

Comparison between TMZ schedules was a secondary analysis, with sample size dictated by the primary comparison; the primary outcome was PFS rate at 12 weeks with PFS time, survival time, toxicity rates, and QOL as secondary outcomes. The analysis strategy allowed for direct comparison of the individual TMZ arms with PCV only where the TMZ-5 versus TMZ-21 comparison yielded a $P < .05$. Within this conditional analysis approach, the significance values for the paired comparisons are presented without adjustment.

Survival was calculated from date of random assignment to death, and PFS was calculated from date of random assignment to first event (ie, progression confirmed either radiologically or clinically if scan not performed or death). Event-free patients were censored on the date last seen. Kaplan-Meier curves were compared using the log-rank test. Treatment HRs were calculated using the Cox regression model. In comparisons against PCV, HRs less than 1 indicate benefit with TMZ. In comparisons of the TMZ schedules, HRs less than 1 indicate benefit with TMZ-21. A χ^2 test for interaction was performed to investigate heterogeneity of treatment effect across baseline characteristics. All P values stated with tests of significance are two-sided.

For the QOL data, mean scores at baseline and 12 and 24 weeks are reported for each treatment arm, along with the proportion of patients reporting a moderate improvement (defined as a 10-point change) from baseline to 12 weeks and baseline to 24 weeks.

An independent data monitoring committee met annually to review accrual, safety, and efficacy. At each review, continuation of the trial was recommended until the required 380 deaths were observed. A formal stopping rule was not specified.

Independent central reviews of pathology (eligibility and tumor grade) and radiology (evidence of progression at 12 and 24 weeks) were conducted. Sensitivity analyses were performed to assess the impact on the primary results of differences between data obtained locally and through independent review.

RESULTS

From June 2003 to January 2008, 447 patients were randomly assigned from 36 centers in the United Kingdom (PCV, $n = 224$; TMZ-5, $n = 112$; TMZ-21, $n = 111$; Fig 1). Baseline characteristics were similar across all three groups (Table 1).

Treatment

Allocated treatment was started in more than 98% of patients in each group. The percentages of patients completing the full 9 months of treatment in PCV, TMZ-5, and TMZ-21 arms were 17.0%, 25.9%, and 12.6%, respectively; including all patients still on treatment, the median number of cycles received was two, five, and four cycles, respectively. When censoring patients still on treatment at the last day of the cycle (ie, day 42 for PCV patients and day 28 for TMZ patients),

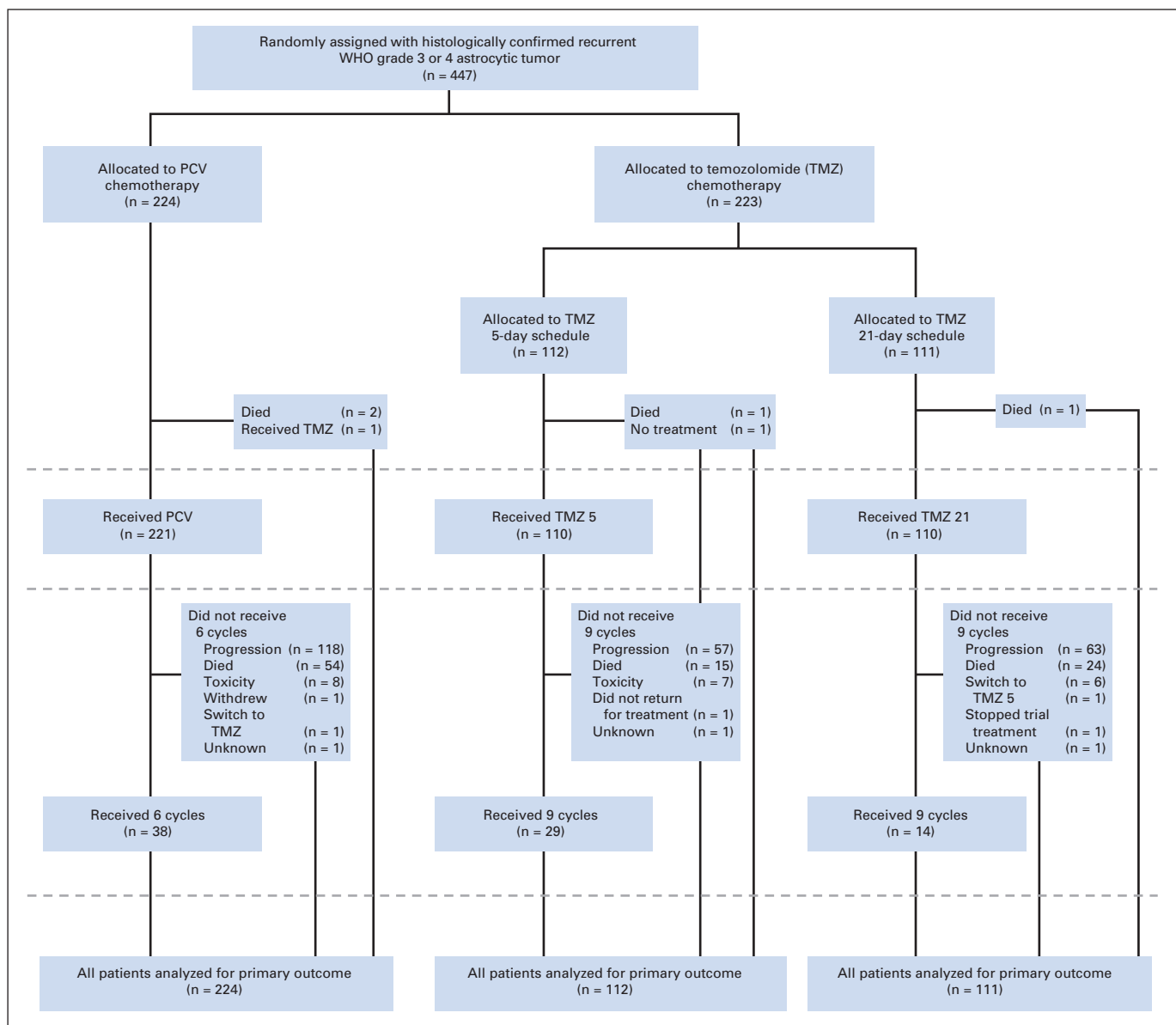


Fig 1. CONSORT diagram. PCV, procarbazine, lomustine, and vincristine; TMZ 5, 5-day schedule of TMZ; TMZ 21, 21-day schedule of TMZ.

the median number of cycles received was four, six, and five cycles relating to a median time on treatment of 5.5, 5.8, and 4.8 months for PCV, TMZ-5, and TMZ-21, respectively. The percentages of patients with no modification or delay in any cycle were 62.8% for PCV, 47.3% for TMZ-5, and 60.9% for TMZ-21; the corresponding percentages of cycles with no modifications or delays were 71.2%, 72.9%, and 84.6%, respectively. Of 156 PCV patients receiving treatment on progression, 53 (34%) received TMZ, and 45 (27%) of 164 TMZ patients received PCV.

Toxicity

The proportions of patients with at least one grade 3 or greater hematologic toxicity over the whole treatment period (Table 2) were 16.4%, 18.9%, and 14.0% for PCV, TMZ-5, and TMZ-21, respectively (P = .63). To allow for the longer treatment duration seen in the TMZ-5 group and avoid any potential biases as a result of a higher

cumulative dose seen in this group, toxicity experienced only during the first 12 weeks of treatment was compared. This showed similar patterns but with lower absolute rates; the percentages of patients with at least one grade 3 or greater hematologic toxicity within the first 12 weeks of treatment were 9.2%, 14.3%, and 10.3% for PCV, TMZ-5, and TMZ-21, respectively (P = .40).

Efficacy

Overall survival and PFS for PCV versus TMZ. At the time of analysis, 382 patients had died (189 on PCV and 193 on TMZ, with 95 on TMZ-5 and 98 on TMZ-21). Median follow-up time of survivors was 10.5 months for PCV and 14.0 months for TMZ. Main outcomes are listed in Tables 3 and 4. Median survival was 6.7 and 7.2 months for PCV and TMZ, respectively (HR, 0.91; 95% CI, 0.74 to 1.11; P = .35; Fig 2A). Median PFS was 3.6 months for PCV and 4.7 months for TMZ (HR, 0.89; 95% CI, 0.73 to 1.08; P = .23;

Table 1. Patient Demographic and Clinical Characteristics

Characteristic	PCV (n = 224)		TMZ-5 (n = 112)		TMZ-21 (n = 111)		All TMZ (n = 223)	
	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%
Sex								
Male	146	65.2	72	64.3	70	63.1	142	63.7
Female	78	34.8	40	35.7	41	36.9	81	36.3
Age at random assignment, years								
Median	53		53		53		53	
IQR	43-60		41-59		41-60		41-60	
WHO tumor grade								
Grade 3	51	22.8	26	23.2	26	23.4	52	23.3
Grade 4	166	74.1	83	74.1	83	74.8	166	74.4
High grade (unspecified)	7	3.1	3	2.7	2	1.8	5	2.2
Central review histology								
Astrocytoma	23	13.5	15	15.8	15	16.7	30	16.3
Glioblastoma	139	81.8	72	75.8	66	73.3	138	75.6
Oligoglioma	4	2.4	2	2.1	3	3.3	5	2.7
Oligoastrocytoma	2	1.2	2	2.1	4	4.4	6	3.3
Gliosarcoma	1	0.6	1	1.1	1	1.1	2	1.1
Ineligible	1	0.6	3	3.2	1	1.1	4	2.2
No specimen available for central review	54		17		21		38	
WHO performance status								
Normally active	34	15.2	24	21.4	21	18.9	45	20.2
Restricted strenuous	108	48.2	46	41.1	51	46.0	97	43.5
Self-care no work	63	28.1	28	25.0	27	24.3	55	24.7
Limited self-care	19	8.5	14	12.5	12	10.8	26	11.7
Type of initial surgery								
Total resection	30	13.5	19	17.0	12	10.8	31	13.9
Subtotal resection/debulking	135	60.5	64	57.1	69	62.2	133	59.6
Biopsy	58	26.0	29	25.9	30	27.0	59	26.0
Missing	1		0		0		0	
Further debulking surgery since initial diagnosis								
No	202	90.2	98	87.5	98	88.3	196	87.9
Yes	22	9.8	14	12.5	13	11.7	27	12.1
Radiotherapy, Gy								
< 55	64	28.6	27	24.1	23	20.7	50	22.4
≥ 55	159	71.0	85	75.9	87	77.7	172	77.1
Missing	1		0		1		1	
Time from initial diagnosis to start of treatment, months								
Median	9.4		10.9		9.8		10.4	
IQR	7.1-14.5		7.4-21.0		7.0-18.2		7.2-19.6	
Time from end of radiotherapy to trial entry, months								
Median	6.9		7.9		7.0		7.4	
IQR	4.5-12.1		4.9-18.5		4.5-14.6		4.7-16.4	

Abbreviations: PCV, procarbazine, lomustine, and vincristine; TMZ, temozolomide; TMZ-5, 5-day schedule of temozolomide; TMZ-21, 21-day schedule of temozolomide; IQR, interquartile range.

Fig 2B). The central pathology review found only five patients ineligible, and sensitivity analyses excluding these patients did not change the primary conclusions.

There was no clear evidence of heterogeneity of treatment effect with respect to survival according to tumor grade (heterogeneity, $P = .484$; grade 4 [GBM]: HR, 0.95; 95% CI, 0.75 to 1.19; and grade 3: HR, 0.79; 95% CI, 0.50 to 1.25). In addition, there was no evidence of heterogeneity according to other baseline characteristics (ie, age group, WHO PS, and sex; Fig 3).

Overall survival and PFS for TMZ-5 versus TMZ-21. PFS at 12 weeks was 63.6% for TMZ-5 and 65.7% for TMZ-21 ($P = .745$), with similar results when incorporating the data from the independent

radiologic review (data not shown). Median PFS was 5.0 months for TMZ-5 and 4.2 months for TMZ-21 (HR, 1.38; 95% CI, 1.04 to 1.82; $P = .023$; Fig 2D). Therefore, in keeping with the analysis plan, a direct comparison of the PCV arm with the individual TMZ arms was made for PFS. Median PFS was 3.6 months for PCV, 5.0 months for TMZ-5, and 4.2 months for TMZ-21, with 6-month PFS rates of 34.5%, 46.9%, and 36.2%, respectively. A significant difference was found for PCV versus TMZ-5 in terms of PFS (HR, 0.78; 95% CI, 0.62 to 0.99; $P = .038$) but not for PCV versus TMZ-21 (HR, 1.04; 95% CI, 0.82 to 1.32; $P = .759$).

In the TMZ-5 and TMZ-21 arms, 95 and 98 deaths were reported, respectively. The survival HR was 1.32 in favor of TMZ-5

Table 2. Grade 3 or 4 Worst Toxicity for Entire Treatment Period

Toxicity	PCV (n = 221)		TMZ-5 (n = 110)		TMZ-21 (n = 110)	
	No. of Patients	%	No. of Patients	%	No. of Patients	%
Nausea	9	4.1	2	1.8	7	6.4
Vomiting	8	3.7	6	5.4	7	6.4
Neuropathy, motor	21	9.5	16	14.5	15	13.6
Neuropathy, sensory	5	2.3	10	9.1	5	4.5
Skin rash	3	1.4	1	0.9	3	4.5
Hemoglobin	4	1.9	1	0.9	1	0.9
Platelets	16	7.2	17	15.5	11	10.0
WBC toxicity	19	8.6	9	8.2	9	8.2
Neutrophil toxicity	18	8.1	11	10.0	7	6.4
ALT	14	6.4	1	0.9	1	0.9
AST	4	1.8	1	0.9	0	0.0

Abbreviations: PCV, procarbazine, lomustine, and vincristine; TMZ-5, 5-day schedule of temozolomide; TMZ-21, 21-day schedule of temozolomide.

(95% CI, 0.99 to 1.75; $P = .056$), with median survival of 8.5 months for TMZ-5 and 6.6 months for TMZ-21 (Fig 2C). The a priori criteria for comparing PCV with the individual TMZ arms were not met with respect to survival but are included at the request of referees (PCV ν TMZ-5: HR, 0.80; 95% CI, 0.63 to 1.03; PCV ν TMZ-21: HR, 1.04; 95% CI, 0.81 to 1.33).

QOL

The percentages of patients surviving and progression free who completed the QOL questionnaires were 93.5% and 93.5% at baseline, 65.1% and 74.2% 12 weeks after random assignment, and 51.6% and 68.2% 24 weeks after random assignment, respectively. The mean global QOL scores and the percentages of patients improving by ≥ 10 points are listed in Table 5. Although no clear differences were seen at 12 weeks, at 24 weeks, the mean QOL scores were 51.9 for PCV versus 59.8 for TMZ ($P = .038$) and 64.3 for TMZ-5 versus 54.4 for TMZ-21 ($P = .036$), with a significant difference also seen between PCV and TMZ-5 (51.9 ν 64.3, respectively; $P = .006$). The percentage of patients with a ≥ 10 -point improvement from baseline to 24 weeks was more marked in the TMZ-5 group (TMZ-5 ν TMZ-21: 49% ν 19%, respectively; $P = .005$; and PCV ν TMZ-5: 23% ν 49%, respectively; $P = .007$).

Table 3. Progression-Free and Overall Survival

Comparison	HR	95% CI	P	Median Survival (months)
Progression-free survival				
PCV ν TMZ	0.89	0.73 to 1.08	.229	3.6 ν 4.7
PCV ν TMZ-5	0.78	0.62 to 0.99	.038	3.6 ν 5.0
PCV ν TMZ-21	1.04	0.82 to 1.32	.759	3.6 ν 4.2
TMZ-5 ν TMZ-21	1.38	1.04 to 1.82	.023	5.0 ν 4.2
Overall survival				
PCV ν TMZ	0.91	0.74 to 1.11	.350	6.7 ν 7.2
TMZ-5 ν TMZ-21	1.32	0.99 to 1.75	.056	8.5 ν 6.6

Abbreviations: HR, hazard ratio; PCV, procarbazine, lomustine, and vincristine; TMZ, temozolomide; TMZ-5, 5-day schedule of temozolomide; TMZ-21, 21-day schedule of temozolomide.

DISCUSSION

This trial did not demonstrate a clear survival or PFS benefit for TMZ (both arms combined) over PCV. For PCV and the combined TMZ arms, the median survival times were 6.7 and 7.2 months, respectively ($P = .350$), and the median PFS times were 3.6 and 4.7 months, respectively ($P = .229$); these results were comparable with other studies.^{7,9} Although a comparison of the two TMZ schedules demonstrated no clear differences with respect to 12-week PFS or survival, TMZ-5 was superior to TMZ-21 with respect to overall PFS ($P = .023$) and also showed a 2-month increase in median survival ($P = .056$). A comparison of TMZ-5 with the PCV regimen showed that TMZ-5 improved PFS ($P = .038$). Survival was not significantly prolonged, but QOL changes during the first 6 months favored TMZ-5 (Table 5).

Lomustine, TMZ, and procarbazine are agents forming cytotoxic O^6 -alkylguanine DNA lesions, which can be repaired by MGMT in an autoinactivating stoichiometric reaction.¹³ Thus, MGMT is depleted by its action, and further repair requires synthesis of new protein.¹³ On the basis of progressive depletion in peripheral blood mononuclear cells (PBMCs), it was suggested that the schedule-dependent antitumor activity of TMZ is a result of cumulative depletion of MGMT,¹⁵ and it was hypothesized that treatment efficacy may increase with more protracted TMZ dosing. Although several alternative dose-dense TMZ regimens have been investigated,^{16,17} we selected the TMZ-21 schedule. This combined the potential benefit of dose-intensification with the assumed prolonged MGMT depletion.¹⁴ Tissue samples have been collected and are currently undergoing detailed analysis for MGMT status using pyrosequencing, generating percent methylation at each of 16 CpGs. Methylation status was assessable in 61% of patients (PCV, 58%; TMZ-5, 64%; TMZ-21, 63%). Mean percent methylation across all CpGs appeared balanced across the arms (PCV, 29.5%; TMZ-5, 26.7%; TMZ-21, 30.5%). Full results will be reported in a separate publication.

The inferior efficacy of the TMZ-21 arm was not a result of early discontinuation after excessive toxicity (percentage of cycles with no modifications or delays was 73% for TMZ-5 and 85% for TMZ-21). This is in line with observations with a similar agent, dacarbazine, which demonstrated dose-dependent MGMT modulation with more extensive and prolonged MGMT inactivation in PBMCs when a higher dose was used.¹⁸ In pharmacokinetic terms, it may be the real drug exposure achieved with a higher daily dose, rather than higher area under the curve, that is the principal determinant of cytotoxicity. Indeed, the actual amount of O^6 -methylguanine accumulated in DNA and persisting through two rounds of DNA replication, after MGMT depletion, is likely to be the critical factor in both effects.¹⁹ If so, our study suggests that prolonged treatment with lower doses of TMZ has achieved this less effectively than the same dose over a shorter period, suggesting that the 100 mg/m² daily dose was suboptimal for therapy and success is more likely to come from a ≥ 200 mg/m² daily dose schedule such as a 7-day-on, 7-day-off treatment strategy.¹⁴ No increased \geq grade 3 myelosuppression was seen in patients treated with TMZ-21 compared with TMZ-5, suggesting that hematologic toxicity may at least in part be considered as a good surrogate of MGMT-modulating activity for future studies. In addition, reduced TMZ concentrations may also lead to lower concentration available in the CNS as a result of reduced brain penetration.

Table 4. First Progression-Free Survival Event

Event	PCV		TMZ-5		TMZ-21	
	No. of First Events	%	No. of First Events	%	No. of First Events	%
Clinical and radiologic progression	71	34.5	32	31.7	32	30.2
Radiologic progression only	27	13.1	11	10.9	13	12.3
Clinical progression, no scan	49	23.8	33	32.6	28	26.4
Death, no prior reported progression	59	28.6	25	24.8	33	31.1

Abbreviations: PCV, procarbazine, lomustine, and vincristine; TMZ-5, 5-day schedule of temozolomide; TMZ-21, 21-day schedule of temozolomide.

It must also be considered that MGMT activity measured in PBMCs may not be an accurate marker of MGMT activity in the glioma tumor.²⁰ Furthermore, although MGMT is considered the principal repair mechanism of DNA damage induced by these alkylating agents, it is also recognized that other DNA repair processes such as base excision repair are also active. Thus, depletion of MGMT may not be the primary determinant of resistance with protracted dosing regimens.

Potential limitations of this trial primarily relate to the assessment of PFS. The scheduled time points for neurologic imaging were at baseline and 12 and 24 weeks; thereafter, scans were performed as per normal practice outside of the trial. This may lead to inaccurate assessment of the time of progression, although we note that more than half the PFS events had occurred by 24 weeks and that only approximately 10% of first events were radiologic progressions only (Table 4). The trial is unblinded, and patients were

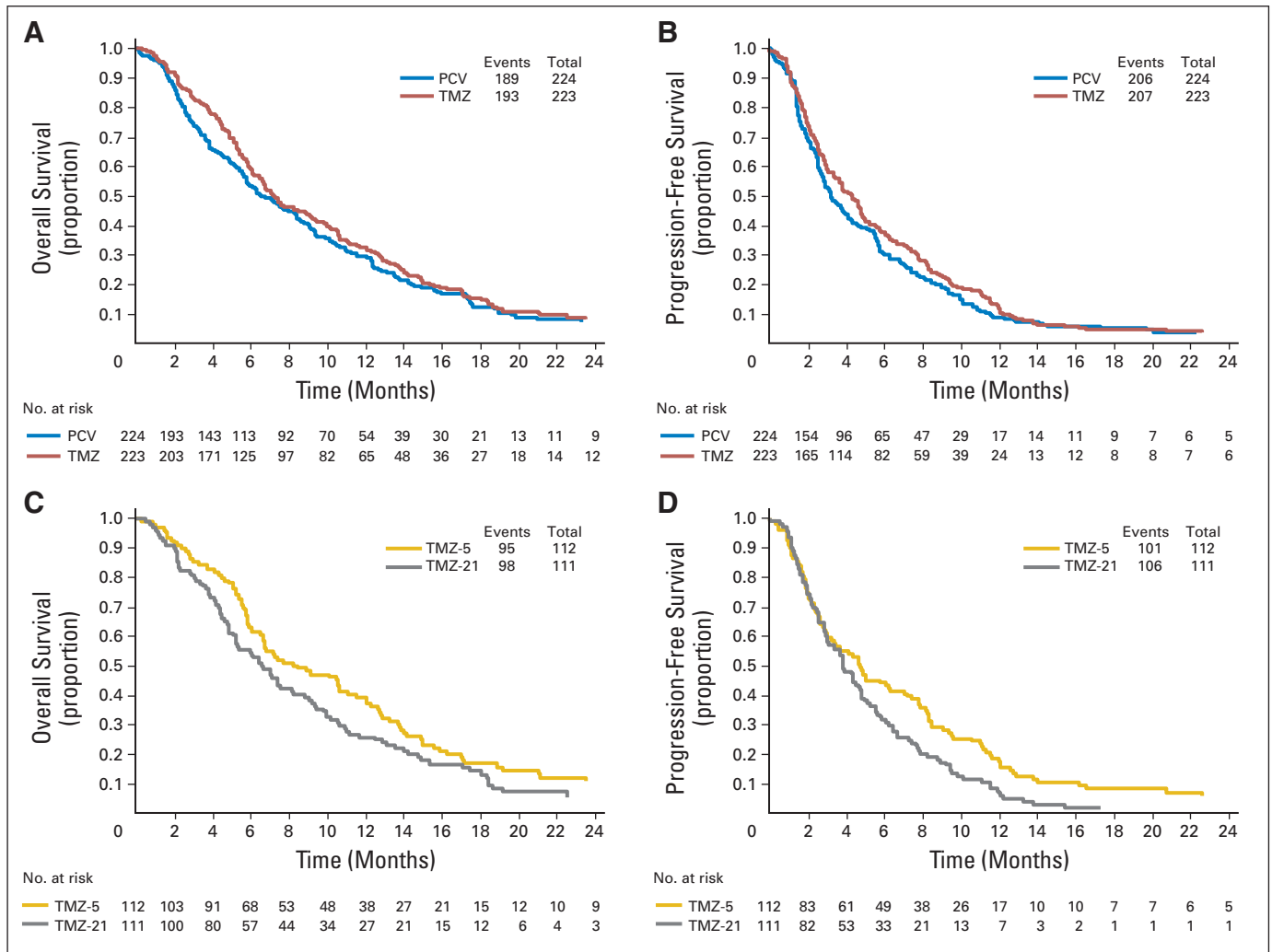


Fig 2. Kaplan-Meier plots for overall survival (OS) and progression-free survival (PFS). (A) OS for procarbazine, lomustine, and vincristine (PCV) versus temozolomide (TMZ). (B) PFS for PCV versus TMZ. (C) OS for 5-day schedule of TMZ (TMZ-5) versus 21-day schedule of TMZ (TMZ-21). (D) PFS for TMZ-5 versus TMZ-21.

Temozolomide Versus PCV in Recurrent High-Grade Glioma

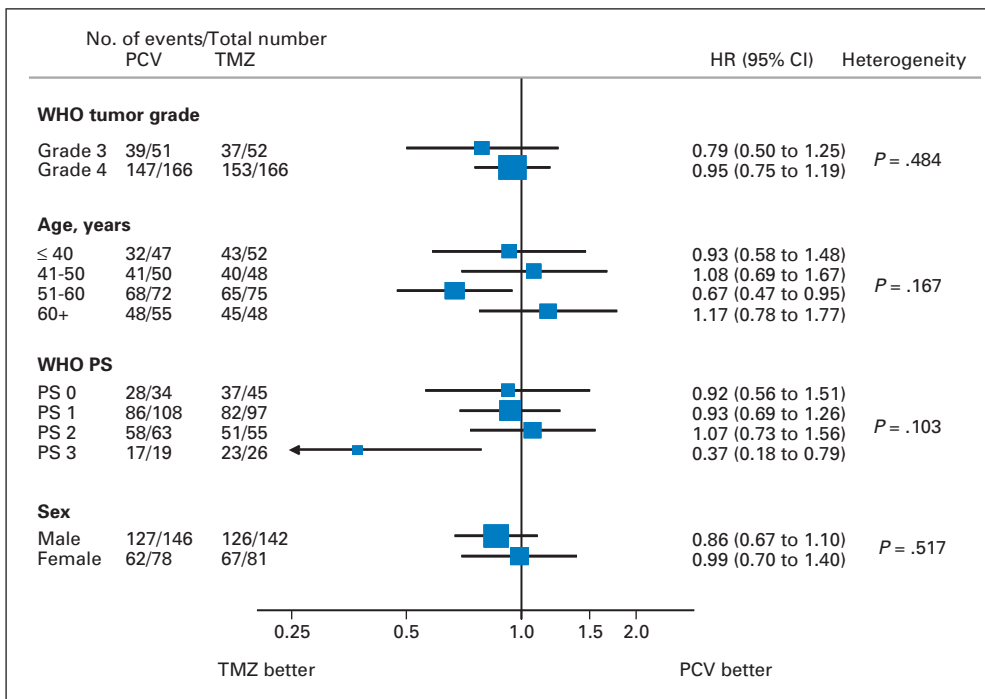


Fig 3. Test for heterogeneity of treatment effect in terms of overall survival according to the baseline characteristics of the patients. PCV, procarbazine, lomustine, and vincristine; TMZ, temozolomide; HR, hazard ratio; PS, performance status.

able to move to TMZ after progression on PCV; however, trial conclusions with respect to PFS were confirmed by the analysis of an independent scan review. For practical reasons, QOL assessments were conducted only at baseline and 12 and 24 weeks and hence provide a snapshot of QOL at these time points, which may miss interim changes.

This study was designed before commencement of the EORTC/National Cancer Institute of Canada trial testing the role of concomitant and adjuvant TMZ and implemented before the results were known.² Although the results are not directly applicable to the population of patients with primary GBM currently receiving concomitant and adjuvant TMZ, the issue of comparing two chemotherapy regimens is of general interest in the disease group, and a significant group of patients receive radiotherapy alone. These include elderly/unfit patients unsuitable for radical treatment at initial diagnosis and patients with grade 3 astrocytomas, for whom the role of concurrent and/or adjuvant TMZ versus radiotherapy alone is being assessed in the intergroup Concurrent and Adjuvant Temozolomide Chemother-

apy in Non-1p/19q Deleted Anaplastic Glioma (CATNON) trial. The Radiation Therapy Oncology Group 0525/EORTC trial, which recruited more than 1,100 newly diagnosed patients with GBM, comparing the same standard 5-day and 21-day maintenance TMZ regimens, will provide further information on TMZ scheduling in the primary setting.

This trial, which is, to our knowledge, the largest randomized trial in chemotherapy-naive patients with recurrent HGG, did not demonstrate a clear survival benefit in the planned comparison of TMZ (both arms combined) over PCV; however, TMZ-21 was not superior to TMZ-5 and, in fact, seems to be inferior for PFS, overall survival, and short-term QOL. This questions the basis of increasing TMZ dose-intensity by using a low-dose daily schedule. Either the 5-day TMZ dosing schedule of 200 mg/m²/d or PCV can be recommended as the current standard of care for chemotherapy-naive patients with recurrent malignant glioma when crossover is possible, although TMZ-5 is associated with better initial PFS. Future TMZ trials should examine schedules using higher daily

Table 5. QOL

QOL Assessment	PCV			TMZ-5			TMZ-21		
	No. of Patients	Global Mean Score	Improvement (%)*	No. of Patients	Global Mean Score	Improvement (%)*	No. of Patients	Global Mean Score	Improvement (%)*
Baseline	211	53.2	—	103	54.6	—	101	53.9	—
12 weeks	101	53.7	27†	77	59.1	32†	60	53.9	27†
24 weeks	54	51.9	23‡	46	64.3	49‡	38	54.4	19‡

Abbreviations: QOL, quality of life; PCV, procarbazine, lomustine, and vincristine; TMZ-5, 5-day schedule of temozolomide; TMZ-21, 21-day schedule of temozolomide.

*Percentage of patients with a ≥ 10-point increase in global health score.

†Percentage of patients who have improved from baseline to 12 weeks (PCV, n = 95; TMZ-5, n = 71; TMZ-21, n = 56).

‡Percentage of patients who have improved from baseline to 24 weeks (PCV, n = 53; TMZ-5, n = 45; TMZ-21, n = 37).

doses ≥ 200 mg/m²/d with intensification to achieve higher peak, rather than area under the curve, concentrations.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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