Prolonged Administration of Adjuvant Temozolomide Improves Survival in Adult Patients with Glioblastoma

AMÉLIE DARLIX[1,8], CÉDRIC BAUMANN[2], VÉRONIQUE LORGIS[3,8], FRANÇOIS GHIRINGHELLI[3,8], MARIE BLONSKI[1,8], BRUNO CHAUFFERT[4,8], SONIA ZOUAOUI[5,6], CATHERINE PINELLI[7,8], FABIEN RECH[7,8], PATRICK BEAUCHESNE[1,8] and LUC TAILLANDIER[1,8]

[1]*Neuro-oncology Unit, Department of Neurology, University Hospital, Nancy, France;*
[2]*Department of Clinical Epidemiology and Evaluation, University Hospital, Nancy, France;*
[3]*Department of Medical Oncology, Georges François Leclerc Cancer Center, Dijon, France;*
[4]*Department of Medical Oncology, University Hospital, Amiens, France;*
[5]*French Brain Tumor DataBase, Hérault Tumors Registry, Regional Cancer Institute Val d'Aurelle, Montpellier, France;*
[6]*Department of Neurosurgery, University Hospital, Montpellier, France;*
[7]*Department of Neurosurgery, University Hospital, Nancy, France;*
[8]*NENO Groupe de Neurooncologie du Nord Est, Nancy, France*

Abstract. *Background: Radiotherapy with concomitant and adjuvant temozolomide (six cycles) is the standard treatment after surgery in glioblastoma patients. Few studies have assessed the impact of additional cycles of temozolomide on survival. Patients and Methods: We conducted a bi-centric retrospective study comparing survival and toxicity according to the number of cycles of adjuvant temozolomide. Results: Fifty-eight patients were included. All patients received radiotherapy with concomitant temozolomide. Thirty-eight patients received six cycles, while 20 received nine or more (median=14) cycles. The risk of recurrence was significantly higher in the group receiving six cycles compared to the other group. Prolonged treatment improved progression-free survival (p=0.03) and overall survival (p=0.01) in multivariate analysis without a significant increase in toxicity. Conclusion: Prolonged administration of temozolomide seems to improve progression-free and overall survival, without increased toxicity. Prospective studies in larger populations are needed to better-define the population to whom it can be proposed and its optimal duration.*

Correspondence to: Dr. Amélie Darlix, Neuro-oncology Unit, Department of Neurology, Centre Hospitalier Universitaire, 29 Avenue du Maréchal Lattre de Tassigny, Nancy, 54035 Cedex, France. Tel: +33 383851688, Fax: +33 383851914, e-mail: a.darlix@gmail.com

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Glioblastoma (GBM) is the most common primary malignant brain tumor in adults. It has a poor prognosis despite surgery, radiation therapy (RT) and chemotherapy (1). RT with concomitant temozolomide (TMZ) followed by six cycles of adjuvant TMZ is the standard treatment after surgical resection or biopsy in patients with a good performance status. In the phase III trial conducted by the European Organization for Research and Treatment of Cancer and the National Cancer Institute of Canada, patients who underwent this regimen after resection had a median survival of 14.6 months (12.1 months for RT alone) and 9.8% of them were still alive after five years compared to 1.9% in the group treated with radiation-therapy only (2, 3). In this trial, adjuvant TMZ was stopped after six cycles, but its optimal duration remains uncertain. There is a certain rationale for additional cycles of TMZ if a residual disease is observed on imaging. This strategy could delay recurrence (4) but there are few data concerning its impact on survival (5-7). However some physicians propose treatment maintenance when magnetic resonance imaging (MRI) shows residual tumor despite clinical stability, and if the treatment has been well-tolerated to that point. Moreover, some guidelines suggest this strategy could be considered in patients with a partial response or with continuing radiological improvement at the end of the sixth cycle (8).

TMZ can be responsible for toxicities such as myelosuppression, and significant thrombocytopenia is observed in 12-20% of patients (9). The feasibility and safety of prolonged treatment has been investigated in several studies that suggest no significant increase in toxicity (5, 10, 11).

We aimed to compare the risk of recurrence and the survival between patients for whom adjuvant TMZ was stopped after six cycles and those for whom it was prolonged, and to investigate the toxicity of additional cycles of TMZ.

Patients and Methods

We conducted a bi-centric observational retrospective study in two French neuro-oncological centers: Dijon and Nancy.

Patients were included if they fulfilled the following criteria: age ≥18 years, histological diagnosis of WHO grade IV glioma between January 1st 2007 and December 31st 2010, stable disease on clinical and radiological levels after the sixth cycle of TMZ. Exclusion criteria were: treatment with carmustine wafers, treatment other than the standard Stupp regimen, inclusion in a clinical trial, treatment discontinuation (tumor progression, death, or toxicity), lost to follow-up, receiving seven or eight TMZ cycles (comparing them with those who received six cycles of adjuvant TMZ did not seem relevant).

Patients underwent surgical resection or biopsy followed by RT with concomitant TMZ (75 mg/m^2/day) and six or more cycles of adjuvant TMZ (five days every 28 days, 150 to 200 mg/m^2/day), based on the decision of the neuro-oncologist in charge of the patient. Patients who received six cycles of adjuvant TMZ are referred to as the 6C group hereafter, while the group receiving at least nine cycles are referred to as the 9C group.

Pre-treatment data [age at diagnosis, gender, Karnofsky performance status (KPS) at diagnosis, corticoid treatment and anti-epileptic drug intake] were collected for each patient. Clinical (KPS, corticoid treatment and anti-epileptic drug intake) and radiological (MRI with contrast enhancement) evaluation was performed after surgery, after RT with concomitant TMZ, and after completing the first six cycles of adjuvant TMZ. Patients were then evaluated (clinical and MRI status) every three months. MRI with contrast enhancement was performed at clinical progression. Tumor progression was defined on MRI with the MacDonald criteria (12). MRIs were not reviewed. The interpretation of the radiologist and the neuro-oncologist in charge of the patient was used. Data were collected until February, 29th 2012.

Statistical analysis. Baseline patient characteristics are described using the mean, standard deviation, median and range for continuous variables, percentages for categorical variables, and were compared between groups of patients using the Chi-square and Mann-Whitney tests. Overall survival (OS) and progression-free survival (PFS) were defined from the day of the pathological diagnosis. Progression was defined as the day when the MRI showing progression or recurrence was performed. Univariate survival analysis was performed using the Kaplan Meier method and the log-rank test. Factors associated with a value of $p<0.05$ were included in a multivariate Cox regression model. Statistical analysis was performed using the Statistical Application System v9.3 software (SAS Institute Inc., Cary, North Carolina, USA).

Results

Patients' characteristics. The clinical files of 448 patients were reviewed at both centers (Dijon: n=139; Nancy: n=309). Among them, 390 were not included in the study (Figure 1). Among the 58 patients included, 38 were males (65.5%) and 20 were females (34.5%). The sex ratio was 1.90. Median age and KPS at diagnosis were 58.2 (18.7-76.0) years and 80 (20-100), respectively. Neuropathological examination found 57 GBMs and one gliosarcoma. Due to the period of inclusion, O^6-methyguanine-DNA methyl-transferase (MGMT) promoter methylation status was not available. The characteristics of patients' treatments are summarized in Table I. Surgery consisted of tumor resection for 48 patients (82%). Thirty-five patients had a gross total resection. All patients received RT with concomitant TMZ. The median delay between surgery and radiochemotherapy was 41 days (range 17-116). The median total dose of RT was 60 Gy (range 55-66). Adjuvant TMZ was started four weeks after the end of radiochemotherapy (median 31 days, range 23-77) and continued for at least six cycles. Thirty-eight patients (Dijon: n=8; Nancy: n=30) received six cycles of adjuvant TMZ (mean dose=315±61 mg/day) and were then followed-up. Twenty patients (Dijon: n=8; Nancy: n=12) received nine or more cycles of adjuvant TMZ (mean dose=338±63 mg/day), with a median of 14 cycles (range 9-26). Twenty-five (43.1%) patients received bevacizumab as a treatment of the first, second or third tumor recurrence, while 33 patients did not. None of the patients received enzyme-inducer antiepileptic drugs. At tumor progression or recurrence, six patients underwent a new surgery (with carmustine wafers for one patient) (Table I). Seven patients were treated with radiation therapy, 19 with chemotherapy and seven with best supportive care. There was no significant difference between groups regarding gender, age, KPS at diagnosis or at the end of the first six cycles of TMZ, initial treatment (surgery, radiochemotherapy), and dose of adjuvant TMZ (Table II). Ten patients (50.0%) in the 9C group were taking corticosteroids at the end of the sixth cycle of TMZ, while only eight patients (21.6%) in the 6C group did. Patients in the 6C group received a higher dose of RT (59.7±1.9 Gy *versus* 58.3±3.1 Gy, $p=0.04$) and were at a higher risk of toxicity during radiochemotherapy (toxicity observed in 60.5% of patients *versus* 30.0%, $p=0.02$).

Treatment delivery, safety and tolerability. Toxicity was observed in 29 patients (50%) during radiochemotherapy. Four patients had a grade 3-4 haematological toxicity (two thrombocytopenias, one leukopenia with neutropenia and one anemia). Other toxicities consisted of grade 1-2 hematological, skin, gastrointestinal toxicity or asthenia. There was no case of pneumocystis observed. Patients in the 6C group had a higher risk of toxicity during radiochemotherapy ($p=0.02$) but three out of the four grade 3-4 hematological toxicities were observed in the 9C group (one thrombocytopenia, one anemia and one leukopenia in the 9C group *versus* one thrombocytopenia in the 6C group). Twenty-two patients presented toxicity during adjuvant TMZ: 14 patients (36.8%) in the 6C group and eight patients (40.0%) in the 9C group. Three patients in the 6C group

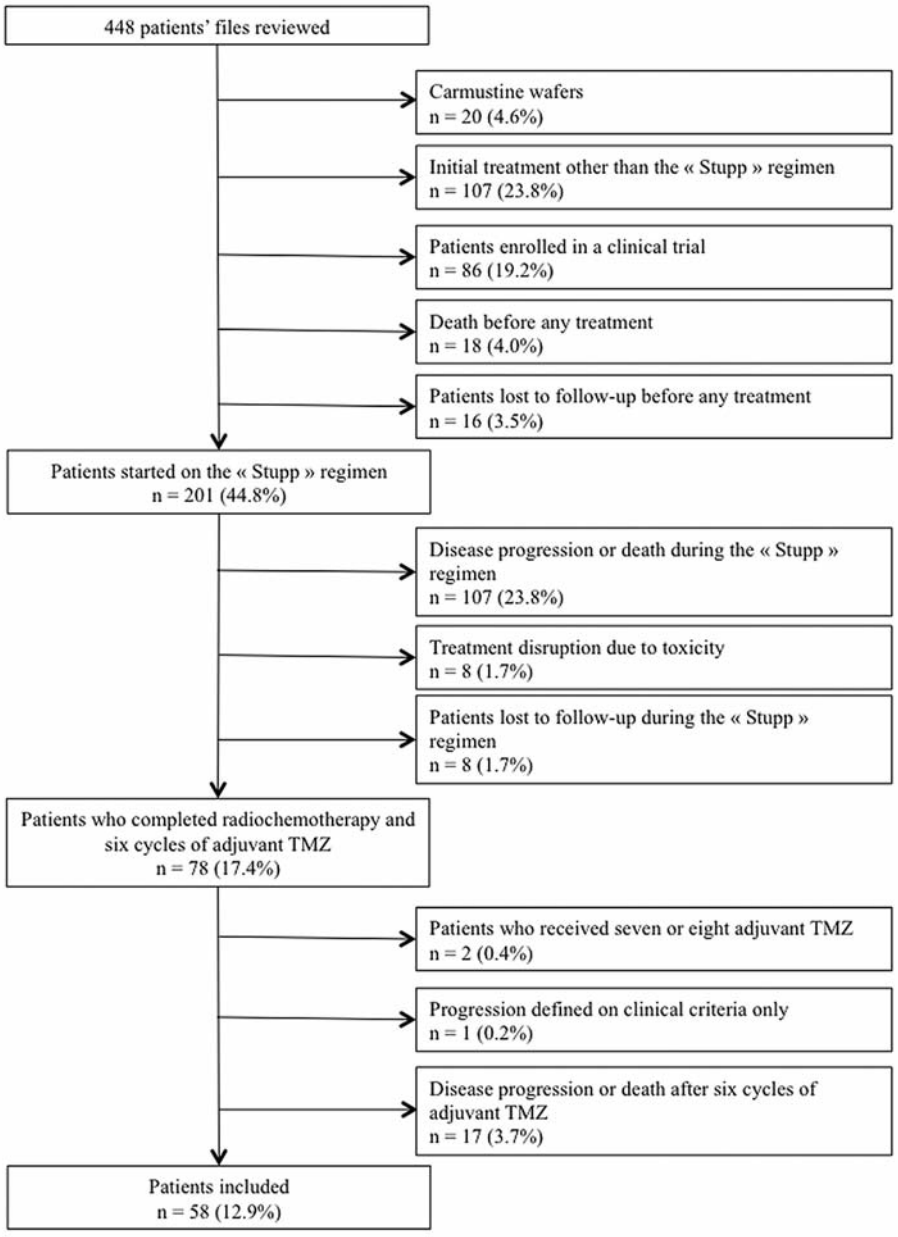

Figure 1. *Description of patients not included in the study.*

presented grade 3-4 toxicity (two thrombocytopenias, one asthenia), as did two patients in the 9C group. In that group, one patient presented thrombocytopenia grade 3 after the first cycle of adjuvant TMZ. Thus only one patient presented with severe toxicity (lymphopenia grade 4) during the additional cycles of TMZ (after the eighth), with no clinical consequence. No other grade 3 or 4 toxicity, secondary leukemia or myelodysplastic syndrome was observed in either group. A decrease of the TMZ dose was necessary because of hematological toxicity in 16 patients (nine patients in the 6C group and seven patients in the 9C group). In the 9C group, this decrease was made after the sixth cycle for two patients only (at the nineth and twelfth cycles).

Survival analysis. During the period of follow-up, 33 patients died at a median interval of 28.8 (range=11.4-55.9) months. In the 6C group, 26 patients died (68.4%) at a median interval of 28.2 (range=11.4-52.1) months, while seven patients (35.0%) died in the 9C group (p=0.01), at a median interval of 30.0 (range=15.1-55.9) months. The median OS

Table I. *Characteristics of patients' treatments (initial treatment and treatment at first recurrence).*

Treatment	N (%)/median (range)
Initial treatment:	
Number of patients	58
Surgery	
Number of patients	58 (100)
Biopsy	10 (17.2)
Resection:	48 (82.8)
Gross total resection	35 (60.3)
Partial resection	10 (17.2)
Unknown	3 (5.2)
Chemoradiotherapy	
Number of patients	58 (100)
Delay between surgery and radiochemotherapy in days, median (range)	41 (17-116)
Total dose of radiation therapy in Gy, median (range) n=52	60 (55-66)
Duration of the radiation therapy in days, median (range)	43 (30-59)
Adjuvant TMZ	
Number of patients	58 (100)
Delay between radiochemotherapy and first cycle of adjuvant TMZ in days, median (range)	31 (23-77)
Number of adjuvant TMZ cycles:	
6	38 (65.5)
9 or more	20 (34.5)
9 to 11	4
12 to 14	7
15 to 17	5
18 to 20	0
21 to 23	2
24 to 26	2
Dose of adjuvant TMZ in mg/day, median (range)	340 (160-400)
At first recurrence:	
Number of patients	39
Surgery:	6 (15.4)
Alone	5 (12.8)
With carmustine wafers	1 (2.5)
Radiation therapy	7 (17.9)
Chemotherapy	19 (48.7)
Bevacizumab (alone or in association)	8 (20.5)
TMZ	8 (20.5)
Fotemustine	2 (5.1)
PCV	1 (2.5)
Best supportive care	7 (17.9)

TMZ: Temozolomide; PCV: procarbazine, lomustine and vincristine.

12, 18, 24 and 36 months after diagnosis for all 58 patients was 96.5%, 87.5%, 69.4% and 30.6%, respectively. The survival in the 6C group compared to the 9C group was 94% and 100% at 12 months, 84% and 93% at 18 months, 65% and 76% at 24 months, 22% and 48% at 36 months, respectively. In multivariate analysis, OS was significantly higher in the 9C group [hazard ratio=3.22, 95% confidence interval (CI)=1.30-8.00]. A corticosteroid intake at the end of the sixth cycle of TMZ was associated with a higher risk of death in univariate (HR=2.40, 95% CI=1.10-5.24; p=0.02) and multivariate analyses (HR=3.88, 95% CI=1.66-9.09; p=0.001) (Figure 2).

During the period of follow-up, 39 patients (67.2%) presented with a tumor recurrence at a median interval of 19.0 (range=10.4-55.9) months: 30 patients (78.9%) in the 6C group, at a median interval of 18.0 (range=10.4-35.1) months, and nine patients (45.0%) in the 9C group (p=0.008), at a median interval of 28.4 (range=12.8-43.2) months. The mean delay between the end of the sixth cycle of TMZ and recurrence was 8.4 (±5.7) months (n=27) in the 6C group and 12.1 (±9.9) months (n=9) in the 9C group. PFS analysis was performed on data for 55 patients only because the date of recurrence was unknown for three patients. The PFS in the 6C group compared to the 9C group was 82.9% *versus* 100% at 12 months, 52.5% *versus* 73.3% at 18 months, 25.7% *versus* 65.9% at 24 months and 11.0% *versus* 43.5% at 36 months, respectively. The median PFS was 28.4 months in the 9C group. Patients in the 6C group had a significantly higher risk of recurrence compared to the 9C group (HR=2.25, 95% CI=1.05-4.82; p=0.03) in univariate analysis (multivariate analysis was not performed since all the variables tested with Log-rang test were associated with a p>0.05) (Figure 3). This difference in PFS was still significant when the analysis was performed on all 58 patients, including the three patients with an unknown date of recurrence and considering them as censored.

The difference between groups concerning the dose of RT (p=0.04) and the toxicity of radiochemotherapy (p=0.02) had no impact on OS (p=0.51 and p=0.48, respectively) or PFS (p=0.49 and p=0.56, respectively).

Discussion

The Stupp regimen remains the standard treatment in patients with GBM with a good performance status. However, in our study, only few of our patients completed the full protocol. Two-hundred-and-one patients out of the 448 reviewed (44.9%) were started on the Stupp regimen after surgery. A bi-centric retrospective study on glioma patients found similar results, with 45.7% of patients treated with this regimen after surgery (13). In our series, 107 (23.8%) patients had tumor progression or died during radiochemotherapy or adjuvant TMZ. The treatment was stopped because of toxicity in eight patients. Eight patients were lost to follow-up during the initial treatment. Only 38.8% of patients completed the full protocol (n=78). Among them, 17 patients had a tumor progression after the first six cycles of adjuvant TMZ, while only 61 (30.3%) patients were considered in response at that time (three of them were excluded from the study because

Table II. *Description of patients' baseline characteristics and comparison between groups.*

Characteristic	6C group N=38 (65.5%) N (%)/median (range)/ mean (SD)	9C group N=20 (34.5%) N (%)/median (range)/ mean (SD)	*p*-value*
Gender			
Female	10 (26.3)	10 (50.0)	0.07
Male	28 (73.7)	10 (50.0)	
Mean age at diagnosis in years	56.3±12.6 (n=38)	52.6±15.0 (n=20)	0.32
Median KPS at diagnosis	80 (20-100) (n=35)	76,7±18,1 (n=18)	0.59
Median KPS after six cycles of TMZ	90 (60-100) (n=37)	90 (60-100) (n=20)	0.68
Mean delay between surgery and radiochemotherapy (days)	43.6±21.5 (n=38)	46.3±11.9 (n=20)	0.60
Mean delay between radiochemotherapy and adjuvant TMZ (days)	34.4±11.5 (n=38)	31.4±8.5 (n=20)	0.31
Surgery:			0.06
Biopsy	4 (10.5)	6 (30.0)	
Resection:	34 (89.5)	14 (70.0)	0.14
Gross total	26 (83.9)	9 (64.3)	
Partial	5 (16.1)	5 (35.7)	
Bevacizumab at progression/recurrence:			0.36
No	20 (52.6)	13 (65.0)	
Yes	18 (47.4)	7 (35.0)	
Mean total dose of radiation therapy (Gy)	59.7±1.9 (n=34)	58.3±3.1 (n=18)	0.04
Mean dose of adjuvant TMZ (mg/d)	314.6±60.8 (n=37)	338.8±62.0 (n=16)	0.19
Corticosteroid intake after six cycles of TMZ:			0.02
No	29 (78.4)	10 (50.0)	
Yes	8 (21.6)	10 (50.0)	
Mean dose (prednisone-equivalent)	9.6±24.0 (n=37)	21.3±31.1 (n=20)	0.12
Enzyme-inducer antiepileptic drug intake	0 (0.0%)	0 (0.0%)	

SD: Standard deviation; KPS: Karnofsky performance status; TMZ: temozolomide. **p*-value of Chi-square test for categorical variables, and Man Whitney for continous variables.

they received seven or eight adjuvant TMZ). Our results are consistent with the existing data. In the EORTC-NCIC 2005 trial, only 36.5% (105/287) of patients who started on radiochemotherapy completed the scheduled plan (2). In recent studies, 40.3% to 42% of patients completed six cycles of adjuvant TMZ (14, 15).

In the study published by Hau *et al*., patients receiving TMZ as a first-line treatment (median number of cycles=13) had a median PFS of 14 months (5). In our study the median PFS was 28.4 months in the 9C group. In a retrospective study investigating 114 patients with GBM treated with radiochemotherapy followed by adjuvant TMZ until progression or toxicity, 55 patients received six cycles or fewer and 59 received more than six cycles (6). There was a significant correlation between the number of adjuvant TMZ cycles and both the PFS and the OS. In a phase II randomized multicentric trial, patients with GBM who were progression-free after the standard Stupp regimen were randomized (Baurain J., unpublished data): 21 patients underwent additional TMZ cycles until progression, while patients in the other group were simply followed-up. Interim analysis showed a six-month PFS of 70% and 57%, respectively, suggesting a potential benefit of additional cycles of TMZ. A recent retrospective study on 52 patients with GBM found a significant increase in PFS and OS (median survival=24.6 months *versus* 16.5 months, $p=0.03$) for patients treated with more than six cycles of adjuvant TMZ (median number of cycles=11) compared with those treated with six cycles (7). However a phase II trial investigating the addition of bevacizumab to the Stupp regimen showed there to be no difference in survival for patients who received more than six adjuvant cycles compared to those who received six cycles (16).

Patients in our series, regardless of the treatment group, seem to have a good prognosis, with 69.4% alive 24 months after diagnosis compared with 27.2% in the RT-TMZ arm of the EORTC-NCIC trial (2). In both cases, most patients underwent tumour resection (82.8% and 83.0%, respectively). However resection was complete in only 39% of patients in the RT-TMZ arm compared to 60.3% in our series, which could partly explain the better prognosis. Moreover, we selected patients who not only completed the full Stupp regimen but were considered at least stable at the end of the sixth cycle, whereas 63.5% of patients did not complete the full regimen in the 2005 trial (with 35% of them never starting on adjuvant TMZ).

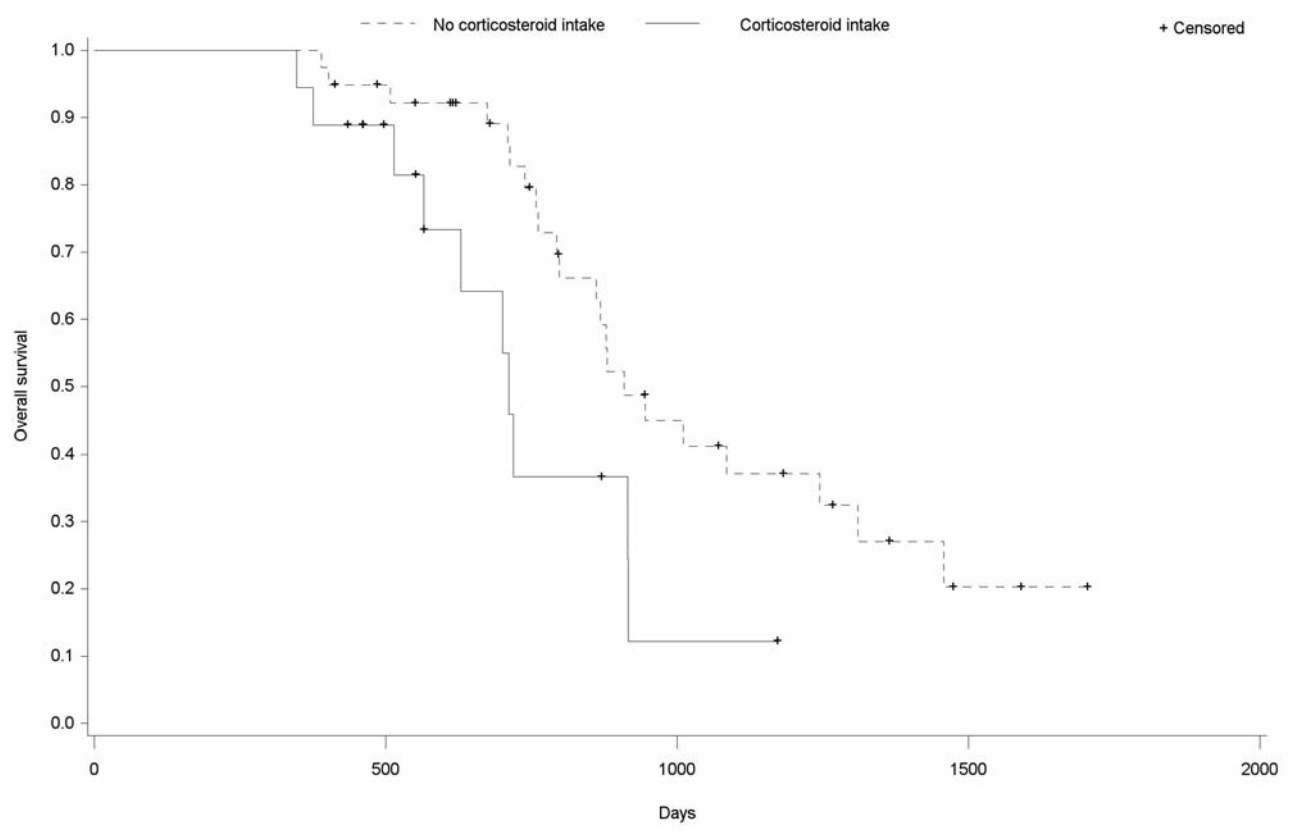

Figure 2. *Overall survival according to the corticosteroid intake at the end of the sixth cycle of adjuvant temozolomide.*

Only one patient presented with grade 4 toxicity (lymphopenia) during the prolonged treatment with TMZ (after the eighth cycle) with no clinical consequence. Hau *et al*. investigated the feasibility of prolonged adjuvant TMZ in newly-diagnosed or recurrent high-grade glioma treated with at least 12 cycles, *via* a questionnaire sent to neuro-oncologists (5). They showed that the additional cycles were well-tolerated (few grade 3-4 toxicities). In a retrospective study based on a prospective cohort of 46 patients with GBM treated with prolonged TMZ, no treatment disruption for toxicity was registered (11). Three patients have been reported who underwent prolonged treatment with TMZ up to 90 months for recurrence of a low-grade or high-grade glioma, with no significant toxicity (10). Severe hematological toxicity seems to most often occur in early treatment with TMZ, as suggested in a recent study (17).

Interestingly, patients in the 9C group were more often treated with corticosteroids at the end of the sixth cycle of TMZ than those in the 6C group. An explanation could be that patients in that group were more likely to have residual disease on the MRI performed at the end of the sixth cycle. We showed that corticosteroid intake after six cycles of TMZ had a significant impact on OS, with patients treated with corticosteroids having a higher risk of death. Patients in the 9C group, even though they were more often treated with corticosteroids after the first six cycles of TMZ, were found to have a better OS, suggesting a strong effect of the number of TMZ cycles on survival.

Our results have to be interpreted with great caution since our study is retrospective, not randomized (possible selection bias) and has a small number of patients. Conclusions on OS are difficult to draw since patients had different treatments at recurrence. MRIs were also not reviewed, which is another limitation of our study. It would be interesting to know if the patients for whom treatment maintenance was decided all had a residual disease after the first six cycles of TMZ. To date, no study has investigated this strategy in this specific population of patients. Patients with residual tumor are probably those for whom prolonged treatment should be proposed, but no study has yet investigated this strategy in this population.

We were not able to compare survival according to the *MGMT* methylation status, which is predictive of the response to TMZ and a favorable prognostic factor in GBM (18). It should be included in the multivariate model in future studies.

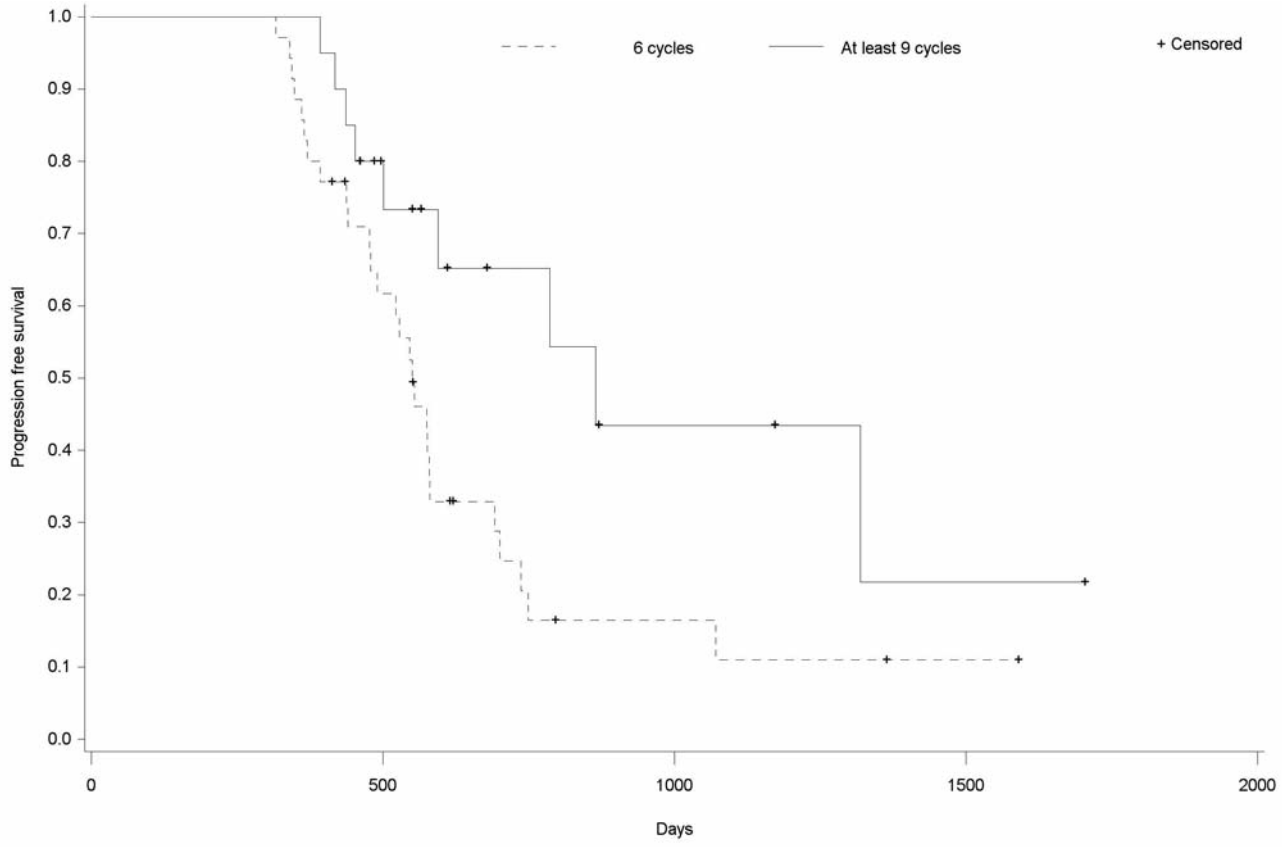

Figure 3. *Progression-free survival according to the number of cycles of adjuvant temozolomide.*

Conclusion

Prolonged administration of TMZ after radiochemotherapy in patients with GBM is feasible and seems to be well- tolerated. There is a growing number of data, including the present study, which suggests a benefit of this strategy on PFS and OS. Further prospective studies in larger populations of patients are needed to assess the potential benefit of this strategy and to better define the population to whom it can be proposed (presence of a residual tumor on MRI, good tolerance of TMZ, MGMT methylation status) and its optimal duration.

References

1 Ricard D, Idbaih A, Ducray F, Lahutte M, Hoang-Xuan K and Delattre JY: Primary brain tumours in adults. Lancet *379*: 1984-1996, 2012.

2 Stupp R, Mason WP, van den Bent MJ, Weller M, Fisher B, Taphoorn MJB, Belanger K, Brandes AA, Marosi C, Bogdahn U, Curschmann J, Janzer RC, Ludwin SK, Gorlia T, Allgeier A, Lacombe D, Cairncross JG, Eisenhauer E and Mirimanoff RO: Radiotherapy plus Concomitant and Adjuvant Temozolomide for Glioblastoma. N Engl J Med *352*: 987-996, 2005.

3 Stupp R, Hegi ME, Mason WP, van den Bent M, Taphoorn MJB, Janzer RC, Ludwin, Allgeier A, Fisher B, Belanger K, Hau P, Brandes AA, Gijtenbeek, Marosi K, Vecht CJ, Mokhtari K, Wesseling P, Villa S, Eisenhauer E, Gorlia T, Weller M, Lacombe D, Cairncross JG and Mirimanoff RO: Effects of radiotherapy with concomitant and adjuvant temozolomide *versus* radiotherapy alone on survival in glioblastoma in a randomised phase III study: 5-Year analysis of the EORTC-NCIC trial. Lancet Oncol *10*: 459-466, 2009.

4 Holdhoff M, Grossman SA: Controversies in the Adjuvant Therapy of High-Grade Gliomas. Oncologist *16*: 351-358, 2011.

5 Hau P, Koch D, Hundsberger T, Marg E, Bauer B, Rudolph R, Rauch M, Brenner A, Rieckmann P, Schuth J, Jauch T, Koch and Bogdahn U: Safety and feasibility of long-term temozolomide treatment in patients with high-grade glioma. Neurology *68*: 688-690, 2007.

6 Seiz M, Krafft U, Freyschlag CF, Weiss C, Schmieder K, Lohr F, Wenz F, Thomé C and Tuettenberg: Long-term adjuvant administration of temozolomide in patients with glioblastoma multiforme: Experience of a single institution. J Cancer Res Clin Oncol *136*: 1691-1695, 2010.

7 Roldán Urgoiti GB, Singh AD and Easaw JC: Extended adjuvant temozolomide for treatment of newly diagnosed glioblastoma multiforme. J Neurooncol *108*: 173-177, 2012.

8 Mason WP, Del Maestro R, Eisenstat D, Forsyth P, Fulton D, Laperrière N, Macdonald D, Perry J and Thiessen B: Canadian recommendations for the treatment of glioblastoma multiforme. Curr Oncol *14*: 110-117, 2007.

9 Gerber DE, Grossman SA, Zeltzman M, Parisi MA and Kleinberg L: The impact of thrombocytopenia from temozolomide and radiation in newly diagnosed adults with high-grade gliomas. Neuro Oncol *9*: 47-52, 2007.

10 Khasraw M, Bell D, Wheeler H: Long-term use of temozolomide: Could you use temozolomide safely for life in gliomas? J Clin Neurosci *16*: 854-855, 2009.

11 Malkoun N, Chargari C, Forest F, Fotso MJ, Cartier L, Auberdiac P, Thorin J, Pacaut C, Peoc'h M, Nuti C, Schmitt and Magné N: Prolonged temozolomide for treatment of glioblastoma: Preliminary clinical result and prognostic value of p53 overexpression. J Neurooncol *106*: 127-133, 2012.

12 Macdonald DR, Cascino TL, Schold SC Jr. and Cairncross JG: Response criteria for phase II studies of supratentorial malignant glioma. J Clin Oncol *8*: 1277-1280, 1990.

13 Delion M, Moraru C, Almayrac F, Von Langsdorff D, Paquis P and Menei P: Glioblastoma incident studies from May 2006 to May 2007 in Angers and Nice, France. Neurochirurgie *56*: 499-502, 2010.

14 Jeon HJ, Kong DS, Park KB, Lee JI, Park K, Kim JH, Kim ST, Lim DH, Kim WS and Nam DH: Clinical outcome of concomitant chemoradiotherapy followed by adjuvant temozolomide therapy for glioblastomas: Single-center experience. Clin Neurol Neurosurg *111*: 679-682, 2009.

15 van Genugten JAB, Leffers P, Baumert BG, Tjon-a-Fat H and Twijnstra A: Effectiveness of temozolomide for primary glioblastoma multiforme in routine clinical practice. J Neurooncol *96*: 249-257, 2010.

16 Vredenburgh JJ, Desjardins A, Reardon DA, Peters KB, Herndon JE, Marcello J, Kirkpatrick JP, Sampson JH, Bailey L, Threatt S, Friedman AH, Bigner DD and Friedman HS: The addition of bevacizumab to standard radiation therapy and temozolomide followed by bevacizumab, temozolomide, and irinotecan for newly diagnosed glioblastoma. Clin Cancer Res *17*: 4119-4124, 2011.

17 Villano JL, Letarte N, Yu JM, Abdur S and Bressler L: Hematologic adverse events associated with temozolomide. Cancer Chemother Pharmacol *69*: 107-113, 2012.

18 Hegi ME, Diserens AC, Gorlia T, Hamou MF, de Tribolet N, Weller M, Kros JM, Hainfellner JA, Mason W, Mariani L, Bromberg JEC, Hau P, Mirimanoff RO, Cairncross JG, Janzer RC and Stupp R: MGMT Gene Silencing and Benefit from Temozolomide in Glioblastoma. N Engl J Med *352*: 997-1003, 2005.

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