Relationships Between Dose Intensity, Toxicity, and Outcome in Patients with Oligodendroglial Tumors Treated with the PCV Regimen

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Abstract. *Background/Aim: The drug combination of procarbazine, lomustine (CCNU) and vincristine (PCV) has been associated with efficacy in oligodendroglial gliomas (OG) when added to radiotherapy as the first line of treatment, despite the important toxicity of this treatment schedule. The aim of the present study was to analyze the tolerance, feasibility and impact of the dose intensity of the PCV regimen on outcome for patients with OG. Patients and Methods: We retrospectively reviewed all patients with OG receiving PCV (CCNU=110 mg/m²) who were referred to our two Institutions. The total dose and dose adaptation, cycle delay, dose intensity, toxicity and discontinuation of CCNU were analyzed. Impacts on the outcome were evaluated. Results: Between 2007 and 2011, 89 patients received PCV. PCV was administered at relapse in 73% of patients. Only 37% completed six cycles, 13.4% discontinued PCV because of toxicity, the other patients discontinued due to tumor progression. Cycle delay and dose reduction were observed for 62% and 70% patients, respectively. Grade 3 and 4 toxicities were observed in 38% and 8% patients, respectively. Among patients whose disease did not progress under the PCV regimen, discontinuation due to toxicity was significantly correlated to poor progression-free survival (PFS: p=0.023, hazard ratio=2.354) and poor overall survival (OS: p=0.021, hazard ratio=5.093). A factor that negatively impacted PFS was the absence of CCNU dose adaptation (p=0.001), while OS was negatively impacted by the absence of cycle delay (p=0.049) and grade 3/4 toxicities (p=0.045). Conclusion: Despite the efficacy of the PCV regimen, significant toxicity is associated with this schedule, which appears to impact its feasibility and efficacy. The optimal PCV schedule with the appropriate CCNU dose-intensity adaptation should be redefined taking into account this finding.*

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Oligodendroglial anaplastic gliomas (OAG) are rare neoplasms that account for 10% of all brain gliomas. They are associated with a pronounced chemosensitivity that has been documented in the first- and second-line settings with various treatment regimens (1, 2). Among these regimens, the activity of the combination of procarbazine, lomustine (CCNU), and vincristine (PCV) is the most widely documented used to treat OAG. The first report of PCV activity in OAG by Cairncross and colleagues describes a response rate of 75% for patients with newly-diagnosed or recurrent disease (1). This was subsequently confirmed by others, although, with variable magnitude. Based on these results, two phase III trials led by the European Organisation for Research and Treatment of Cancer (EORTC) and Radiation Therapy Oncology Group (RTOG) were conducted to evaluate the efficacy of adding PCV chemotherapy to radiotherapy in patients with OAG (3, 4). A recent update of long-term follow-up of these trials (5, 6) showed a significant advantage both for progression-free (PFS) and overall (OS) survival for patients receiving PCV in addition to radiotherapy (RT) for the sub-group of patients with tumors harboring the 1p/19q co-deletion. These studies led clinicians to consider the combination of RT and the PCV regimen to be the new standard-of-care in this patient population. In addition, a prospective study (RTOG 9802) evaluated the benefit of this regimen for patients with newly-diagnosed low-grade glioma (7) and reported an improvement of PFS and OS impact, suggesting a possible extension of indications for PCV (8).

Table I. *Patient characteristics of the entire study population, global population experiencing toxicity, and details of the patients in the population experiencing toxicity according to discontinuation due to toxicity.*

	Entire population		Toxicity-study population	
Characteristic	Data	%	Data	%
Median (range) age, years	46.5 (20-79.7)		44.5 (20-76)	
Gender				
Male	52	58.4	26	56.5
Female	37	41.6	20	43.5
Grade				
II	38	43.7	20	44.4
III	49	56.3	25	55.6
Histology				
Oligodendroglioma	64	71.9	36	78.3
Mixed	25	28.1	10	21.7
Loss of 1p19q	19/63	30,2	14/37	37.8
Previous chemotherapy	65	73	26	56.5
Toxicity				
Grade III/IV	29/6	37.7/7.9	20/5	46.5/11.9
Hematological III/IV	29/4	37.2-5.3	20/3	46.5/7.1
Thrombopenia grade I/II	36	50.7	23	60.5
Hepatological III/IV	5/2	6.6/2.6	4/2	9.5/4.8
Neuropathy I & II	23	30.2	16	38.1
Survival analyses				
Death	42	47	14	30.4
Progression	74	83.1	33	71.7
Median OS (95% CI), months	26.3 (7.5-45.1)		Not reached	
Median PFS (95% CI), months	9.7 (7.1-12.3)		21.0 (7.5-34.5)	
Median follow-up (range), months	27.5 (5.9-91)		39.5 (9-91)	

OS: Overall Survival, PFS: progression-Free survival, 95% CI: 95% Confidence Interval

However, grade 3 or 4 toxicities are observed in more than one-third of patients, while PCV discontinuation related to toxicity is reported in 20% to 40% of patients (3, 4). Despite this discontinuation rate, limited data are available on dose adaptations, delays of cycle, and treatment discontinuation. These data remain crucial in order to manage patient treatment and to optimize for tolerability and efficacy of PCV. Importantly, in other chemosensitive tumor types, such as breast cancer and lymphoma (9), the toxicity profile of alkylating agent-based chemotherapy regimens impacts the dose intensity and this dose intensity has been correlated with survival. In patients with oligodendroglial tumors, the potential impact of the dose intensity of CCNU-PCV on patient survival has not been previously explored. Considering the toxicity of the PCV regimen, this type of analysis is warranted and could lead to an adjustment in the PCV schedule that will improve the completion rate and potentially the efficacy of this treatment.

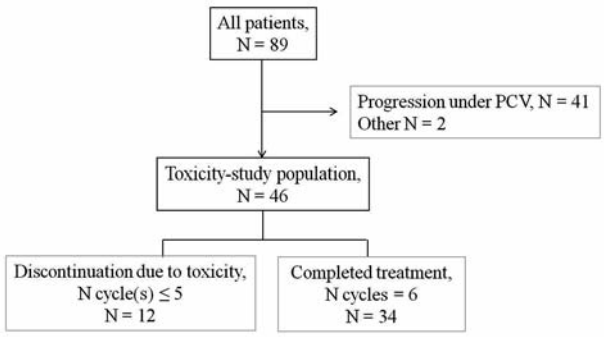

Figure 1. *Flow chart of patients receiving procarbazine-lomustine-vincristine.*

The main objective of this retrospective study was to analyze the tolerance, feasibility, and impact of the dose intensity of the PCV regimen on the outcome for patients with grade II or III oligodendroglioma.

Patients and Methods

We performed a multicenter retrospective study that included patients treated at Assistance Publique-Hôpitaux de Marseille (Timone hospital) and Assistance Publique-Hôpitaux de Paris (Pitié-Salpétrière Hospital) between January 2007 and August 2011. Patients aged 18 years and older with histologically proven diagnosis of grade II or III oligodendroglioma or mixed glioma who received at least one cycle of PCV at our Institutions (based on pharmacy registries) were included in the study. There was no restriction on the number of previous lines administered before PCV. All patients provided written consent for clinical data collection according to the institutional policies and Institutional Review Boards.

Treatment consisted of lomustine (110 mg/m^2 on day 1 of each cycle), procarbazine (60 mg/m^2 orally per day on days 8 through 21 of each cycle) and vincristine (1.4 mg/m^2 on day 8 and 29 of each cycle, capped at 2 mg). The planned cycle length was six weeks and the planned number of cycles was six, unless progression or unacceptable toxicity occurred. Clinical examination and brain Magnetic Resonance Imaging were performed every six weeks, while blood counts and blood chemistry tests were performed three times per cycle.

Adverse events were graded based on the Common Terminology Criteria for Adverse Events v3.0 (10). Analysis of factors related to tolerance and feasibility included: total number of cycles, cycle delay (interval between two cycles ≥7 weeks), PCV discontinuation, total dose of lomustine delivered during the whole treatment (<median *versus* >median total dose) and dose reduction of chemotherapies (all drugs and CCNU only) corresponding to a decrease of the dosage inferior to 80% of the planned dose. Dose intensity was defined by the amount of drug (mg/m^2) delivered to a patient per week of treatment (11).

Data were described as frequencies (percentages) and medians (range). The impact of toxicity (discontinuation due to toxicity, delayed cycle, dose adaptations and severe toxicity) on PFS and OS was restricted to patients whose disease did not progress during treatment time. The time-to-event end-points was estimated using the Kaplan–Meier method and was compared using a log-rank test.

Table II. *Dose of lomustine and number of patients in the entire population receiving procarbazine-lomustine-vincristine therapy for each cycle.*

No. of cycles	Cumulative no. of patients under PCV	No. of patients per dose				Total no. of patients receiving cycles
		% Of theoretical dose of lomustine				
		90-100%	70-80%	50-60%	<50%	
1	89 (100%)	62 (69.7%)	22 (24.7%)	4 (4.5%)	1 (1.1%)	14 (15.7%)
2	75 (84.3%)	44 (58.7%)	24 (32%)	6 (8%)	1 (1.3%)	9 (10.1%)
3	66 (74.2%)	32 (48.5%)	24 (36.4%)	8 (12.1%)	2 (3%)	10 (11.2%)
4	56 (62.9%)	19 (33.9%)	25 (44.6%)	9 (16.1%)	3 (5.4%)	10 (11.2%)
5	46 (51.7%)	12 (26.1%)	15 (32.6%)	14 (30.4%)	5 (10.9%)	13 (14.6%)
6	33 (37.1%)	5 (15.1%)	11 (33.3%)	12 (36.4%)	5 (15.1%)	33 (37.1%)

Table III. *Details of the patients in the population experiencing toxicity according to discon.*

	Discontinuation due to toxicity		No discontinuation due to toxicity		
	Data	%	Data	%	*p*-Value
Median (range), age, years	50 (27-68.8)		43 (20-76)		0.305
Gender					
Male	2	16	24	71	0.001
Female	10	84	10	29	
Grade					
II	3	25	17	52	0.113
III	9	75	16/33	48	
Histology					
Oligodendroglioma	8	66	28	82	0.501
Mixed	4	34	6/34	18	
Loss of 1p19q	3/9	33	11/28	39	1.000
Previous chemotherapy	7/12	58	19/34	56	0.883

Overall survival was defined from day 1 of the first cycle of PCV to death or last contact. Progression-free survival was defined by the time from the first cycle of PCV to progression or death. Multivariate Cox analysis included all relevant variables defined by a *p*-value ≤0.05 by univariate analysis.

Qualitative values were analyzed by Fisher exact test and Chi-square test; quantitative values were analyzed by the Mann-Whitney *U*-test and a Receiver Operating Characteristic (ROC) analysis. Two-sided *p*-values of less than 0.05 were considered statistically significant. Statistical analyses were performed with SPSS version17® (IBM®, New York, State of New York, USA).

Results

Patients. Eighty-nine patients received at least one cycle of PCV therapy at our Institutions (Table I, Figure 1). Patient characteristics were as follows: the median age was 46.5 years (range=20-79.7 years), histological diagnoses were oligodendrogliomas (n=64), and mixed glioma (n=25). Sixty-five patients (73%) had received a previous chemotherapy lines. Nineteen out of 63 patients for whom 1p/19q status was available presented with loss of 1p/19q (30.2%).

PCV tolerance and feasibility. In the entire cohort, 63% of patients completed at least for cycles of treatment and only 37% completed six cycles (Table II). Discontinuation occurred in 61.8% of patients, for reasons that included progressive disease (44.9%), toxicity (13.5%) or other complications (3.4%). For patients whose disease did not progress under PCV, discontinuation due to toxicity occurred for 26% of them. Discontinuation for toxicity did not correlate with previous chemotherapy line administration (p=0.883) (Table I). Delay of at least one cycle because of toxicity was observed in 49/89 (62%) patients. The total doses of cytotoxic agents were reduced for 70% of patients, while lomustine dose was reduced for 52% of the whole population (Table II). The median CCNU dose intensity was 13.2 mg/m²/week (range=4.2-19.0 mg/m²/week) and was significantly lower (p=0.001) for patients who completed six cycles. In this retrospective analysis, we observed grade 3 or 4 toxicities in 38% and 8% of the patients, respectively (Table I).

Clinical impact of toxicity and treatment administration (Figure 2). In the population whose disease did not progress under PCV treatment, the dose of lomustine was reduced for 85% of patients and a delay of at least one cycle due to toxicity was observed in 39/46 (82.4%) patients. Moreover, 12 patients discontinued PCV due to toxicity. There was no significant difference regarding prognostic factors between patients who completed all PCV cycles and those who ly discontinued treatment (Table III). Factors that negatively affected PFS, by univariate analysis, were discontinuation due to toxicity (p=0.013) and the absence of lomustine dose adaptation (lomustine dose >80% theoretical dose, p=0.032). High CCNU dose intensity (p=0.053) tended to correlate with a shorter PFS. Factors that negatively impacted OS by univariate analyses

Table IV. *Clinical impact of Procarbazine-Lomustine-Vincristine toxicity on the patients in the population experiencing toxictiy.*

Factor	Progression-free survival				Overall survival			
	Duration (months)	*p*-Value		HR	Duration (months)	*p*-Value		HR
		Univariate	Multivariate[a]			Univariate	Multivariate[b]	
Discontinuation due to toxicity								
Yes	13.9 (10.5-17.3)	0.013	0.023	2.354 (1.126-4.920)	18.3 (15.1-21.5)	<0.001	0.021	5.093 (1.284-20.208)
No	27.6 (16.0-39.2)				NR			
CCNU dose-intensity								
>Median	7.6 (5.0-10.2)	0.053			21.0 (17.2-24.8)	0.112		
<Median	16.4 (6.4-26.4)				NR			
Total dose of CCNU								
<Median	14.1 (12.4-14.7)	0.089			47.0 (15.7-78.3)	0.029	0.441	
>Median	27.6 (16.4-38.8)				NR			
Cycle delay								
Yes	27.6 (8.5-46.7)	0.129			NR	0.009	0.049	0.253 (0.064-0.993)
No	16.0 (11.4-20.6)				31.0 (0-68.2)			
Dose adaptation						0.485		
Yes	21.0 (8.6-33.4)	0.962			NR			
No	13.0 (9.6-16.4)				NR			
CCNU dose adaptation								
Yes	27.6 (7.6-47.6)	0.032	0.001	0.251 (0.109-0.582)	NR	0.020	0.124	
No	13.0 (10.6-15.4)				19.0 (15.3-22.7)			
Grade III or IV toxicity								
Yes	18.5 (12.3-24.7)	0.085			47.0 (–)	0.013	0.045	5.875 (1.040-33.186)
No	45.0 (15.0-74.9)				NR			
Hematological toxicity								
Yes	16.7 (11.1-22.3)	0.061			47.0 (0.4-93.6)	0.004	0.022	7.269 (1.329-39.764)
No	45.0 (12.4-77.6)				NR			

[a]Adjusted by previous chemotherapy line treatment. [b]Adjusted by previous chemotherapy line treatment and 1p19q codeletion. NR, Not reached; HR: hazard ratio; CCNU: lomustine.

included discontinuation due to toxicity ($p<0.001$), low cumulative total dose of CCNU ($p=0.029$), absence of delayed PCV cycles ($p=0.009$), absence of lomustine dose adaptation ($p=0.020$), grade 3 or 4 toxicity ($p=0.013$), and grade 3 to 4 hematological toxicity ($p=0.004$). High CCNU dose intensity ($p=0.112$) tended to negatively impact OS.

When the analyses were restricted to patients with discontinuation due to toxicity (after at least two cycles) without previous CCNU dose reduction (*i.e.* with high dose density) compared to patients who completed six cycles with CCNU dose reduction (*i.e.* with low dose density), discontinuation remained significantly pejorative both for PFS and OS ($p<0.001$) (Figure 3). By multivariate analyses (Table IV), adjusted for previous chemotherapy administration for PFS and OS and by the 1p/19q co-deletion status for OS (Table V), discontinuation due to toxicity (Figure 2) remained significant both for PFS [hazard ratio (HR)=2.354, $p=0.023$] and OS (HR=5.093, $p=0.021$). For patients treated with PCV as a first line of chemotherapy, discontinuation due to toxicity remained significant both for PFS ($p=0.025$) and OS ($p=0.004$). Finally, in this population, discontinuation due to toxicity tended to correlate with CCNU dose intensity ($p=0.064$, Area Under the Curve=0.687).

Discussion

Despite the well-documented activity and efficacy of the PCV regimen, significant toxicity is associated with this schedule that impacts its feasibility and could negatively affect the benefit of this therapy. In this retrospective study, grade 3-4 toxicity occurred in 41% of patients, leading to discontinuation for 14% of them. Both toxicity and

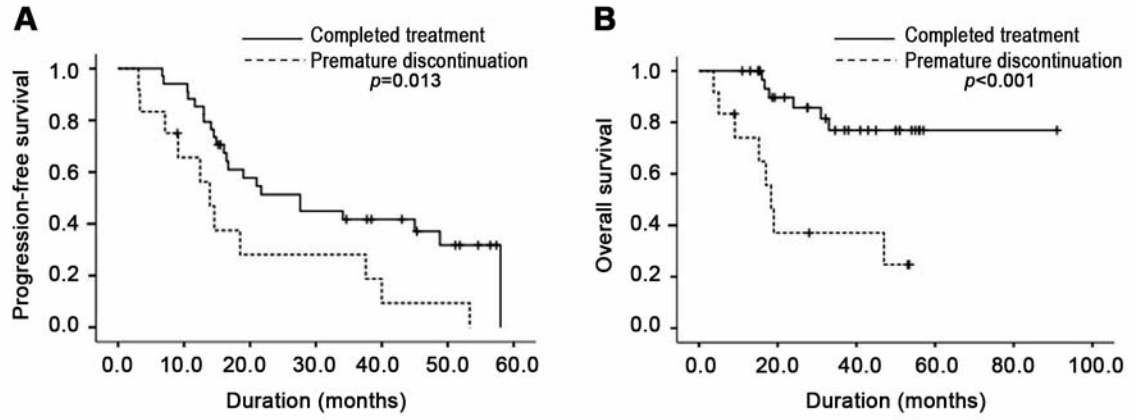

Figure 2. *Progression-free (A) and overall (B) survival according to therapy discontinuation due to toxicity.*

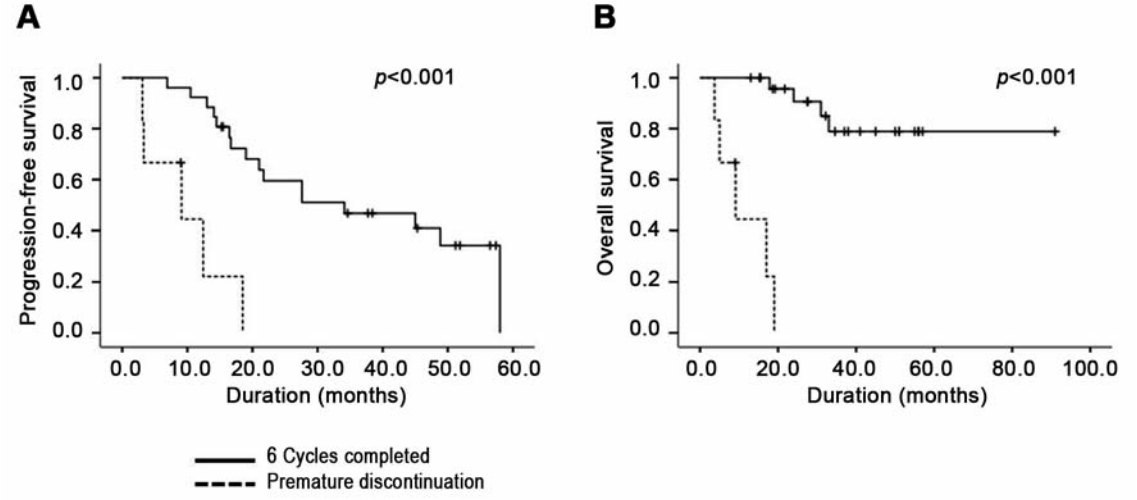

Figure 3. *Restrictive analyses between patients who discontinued procarbazine-lomustine-vincristine after at least two cycles without dose reduction (high dose intensity) and patients who completed the six cycles with dose reduction (low dose intensity). Progression-free (A) and overall (B) survival according to discontinuation due to toxicity.*

discontinuation of therapy appeared to negatively impact PFS and OS. Such analyses have not been previously reported, although the PCV regimen is now considered to be the standard-of-care for patients with 1p/19q co-deleted OAG (and low-grade glioma) based on the long-term results of the EORTC and RTOG phase III trials (5, 6) that evaluated the addition of PCV to RT in anaplastic gliomas.

The toxicity of PCV, related to each drug of this regimen, is well-documented. We observed grade 3-4 toxicities in 41% of cases, similar to the rate observed in the EORTC trial (46%) (4). The majority of our patients were receiving PCV at relapse, these results suggest a similar toxicity profile for PCV in first-line treatment and at recurrence. Moreover, in the RTOG trial (3), which applied an intensive PCV regimen with lomustine administered at 130 mg/m^2, grade 3-4 toxicities were observed in 65% of patients, even though the number of cycles was limited to four, while the number of planned cycles was six in the EORTC trial (Table VI). The rate of grade 4 toxicities alone was smaller in our study (8%) than it was for others (14-32%). In the recent RTOG trial that explored the benefit of PCV treatment for low-grade glioma, severe hematological toxicity was again reported (51% grade 3 and 15% grade 4), despite an 8-week delay between each cycle (7). The major implication of this toxicity was the impairment of the health-related quality of life during and after treatment (12).

In the EORTC and RTOG trials 38% and 20% of patients, respectively, discontinued chemotherapy due to toxicity (Table VI). In the retrospective trial by Brandes *et al*., discontinuation

Table V. *Prognostic factors in the entire study population.*

Factor	Progression-free survival	Overall survival	
	Univariate *p*-Value	Univariate *p*-Value	Multivariate *p*-Value
Age	0.730	0.305	
Gender	0.230	0.928	
Grade	0.252	0.821	
Histology	0.311	0.099	0.966
Loss of 1p19q	0.266	0.086	0.112
Previous chemotherapy	<0.001	0.015	0.149

because of toxicity occurred in 37% of patients (13), while in the NOA-04 trial that tested an adapted schedule of PCV (four 8-week cycles), discontinuation was reported for only 9% of patients (14). In our retrospective cohort study, discontinuation due to toxicity was observed in 13.5% of patients. This variability in the rate of PCV discontinuation due to toxicity between studies could be related to patient characteristics such as age or the number of previous therapy lines. However, a lower rate of grade 4 toxicities and of treatment discontinuation in our study was observed, despite the older age of our cohort and the fact that 73% of our patients had received a previous line of chemotherapy (mostly temozolomide), while patients treated in the EORTC, RTOG or NOA trials were chemonaive. An alternative explanation could be related to the way physicians apply the PCV schedule. Although this schedule was defined 30 years ago, the dose and schedule adaptation rules in cases of toxicity are not clearly defined; therefore, we may anticipate that this adaptation can be highly variable between physicians/investigators. It should be noted that potentially supporting data, such as the dose of chemotherapy delivered or the number of delayed cycles, were generally not reported in previous trials. These data could be crucial because of their potential implication on the feasibility and the expected benefit of this schedule, as well as its applicability in clinical practice. Moreover, in two recent prospective trials, severe toxicity of CCNU was again reported, leading to the revision of the trials' design. Indeed, in the BELOB trials, the CCNU dose was reduced from 110 mg/m^2 to 90 mg/m^2, while in the phase III trial of cediranib for recurrent glioblastoma, the CCNU dose was reduced from 130 mg/m^2 to 110 mg/m^2. Nevertheless, the toxicity related to CCNU remained important. These necessary and questionable adaptations of trial methodology underline the potentially negative impact of drug toxicity, which can lead to failure of therapeutic development because of an inadequate treatment schedule and not drug inactivity.

To date, no clinical impact of toxicity, dose adaptation or discontinuation of PCV on outcome has been reported. To test this impact, we defined the toxicity study population as that excluding patients who discontinued treatment because of progression to analyze a 'pure' signal without the confounding factor of progression. Moreover, the two patient groups (discontinuation *versus* no-discontinuation) differed only by the discontinuation of treatment due to toxicity (and gender), suggesting a balance of prognostic factors between the two groups. In this toxicity sub-population, PCV discontinuation due to toxicity was associated with a poor prognosis, both for PFS and OS, while the number of PCV cycles and dose adaptation did not negatively affect the outcome. Moreover, this result was reinforced by other measures that were consistent with this observation: hematological grade 3-4 toxicities negatively impacted OS with a trend for impact on PFS with a high CCNU dose intensity, represented by the CCNU dose per week. Both were influenced by CCNU dose and cycle duration and tended to negatively affect outcome. The negative impact of discontinuation due to toxicity may be explained, firstly, by the relationship between the completion of PCV cycles and a high total dose of CCNU delivered (high cumulative dose). Although this factor did not reach significance in our multivariate analyses, prolonged duration of alkylating agent administration was reported to be of prognostic value for patients with other neoplasic diseases or glioma (15). Secondly, prolonged response after PCV chemotherapy was reported for patients with low-grade glioma. Completion of six cycles of PCV in association with its extended effect might explain the better outcome of patients who completed the schedule (16). With the exception of a high CCNU dose intensity, no clear individual factor, including age, histology, 1p/19q status or number of previous therapy lines, was found to predict discontinuation due to toxicity.

Optimization of the PCV schedule should be considered and adaptation of the interval between cycles should be investigated. In our study, delay for at least one cycle was applied for 62% of patients and this cycle delay was recorded in 85% of the patients that completed all six cycles. An 8-week interval was applied in the NOA-04 trial and the RTOG trial in low-grade glioma. In the RTOG trial, 95% of patients benefited from six cycles of PCV. However, the interval, grade and incidence of toxicities appeared to be similar to those observed with the standard PCV regimen. Adaptation of CCNU dose was applied, but not clearly reported. In the NOA-04 trial, the 8-week interval together with a decrease from six planned cycles to four was associated with low rates of discontinuation (9%), cycle delay (18%) dose adaptation (16%) and toxicities. Adaptation of the CCNU dose should also be considered. In a study performed in Singapore examining PCV administration to Asian patients with OAG,

Table VI. *Literature comparison of tolerance and toxicity reported for the Procarbazine-Lomustine-Vincristine regimen.*

	Completed cycles		Cause of discontinuation			Delay of cycle for toxicity	Dose adaptation	CCNU dose adaptation ≤60 %		Toxicity	
Study	At least 4	At least 6	Toxicity	Progression	Other		All drugs	At cycle 4	At cycle 6	Grade 3	Grade 4
Our	62.9%	37.1%	13.5%	44.9%	3.4%	62%	70.4%	21.5%	51.5%	37.7%	7.9%
Van Den Bent (4)	49%	30%	38%	24%	9%					32%	14%
Cairncross (3)	48%	-	20%	14%	14%					33%	32%
Shaw (7)	95%	95%								51%*	15%*
Wick (14)			9%			18%	16%			20%*	

*Hematological only.

the authors developed a 'decreased-dose-intensity' regimen in order to limit cumulative myelosuppression with a lomustine dose of 90 mg/m² (17). With this dose, treatment was discontinued for only one patient, whereas dose adaptation remained necessary for all other patients. In our study, the lomustine dose was adapted for 85% of our patients who did not discontinue PCV. The dose was reduced to 60% or less of the theoretical dose in 20% and 40% of the patients at cycles 4 and 5, respectively, suggesting that a dose of about 80 mg/m2 might be more applicable in clinical practice. The fact that lomustine dose adaptation did not negatively impact PFS or OS favors this adaptation.

There were some limitations to our work. Data were retrospectively collected of two different centers (APHM, APHP) with potential differences in dose adaptation schedules; however, the numbers of discontinuations due to toxicity were similar. Co-deletion 1p/19q status was available for only 71% of patients. Exclusion of patients with progressive disease leads to a potential selection bias, but no significant differences were found between the two populations in terms of major clinical characteristics. Another potential limitation of our study was the major use of the PCV schedule in a recurrent setting (73%) that differs from the actual first-line indication for patients with anaplastic glioma; although this factor does not appear to impact the discontinuation rate due to toxicity.

Conclusion

Despite the efficacy of the PCV regimen in patients with OAG, significant toxicity remains associated with this schedule and appears to impact the feasibility and efficacy of this protocol. In addition to the immediate effect of the toxicities, discontinuation of the PCV regimen due to toxicity might be detrimental to patients' outcomes. The optimal PCV schedule with an appropriate CCNU dose-intensity adaptation should be redefined taking into account this finding. Studies are needed to identify the biological drivers of this heterogeneous toxicity.

Conflicts of Interest

None.

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