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Procarbazine, lomustine and vincristine toxicity in low-grade gliomas

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ABSTRACT

Background Procarbazine, lomustine, and vincristine (PCV) significantly improve survival outcomes in LGG (low-grade gliomas). Administration of PCV to LGG patients increased tremendously over the past years as it went from 2 patients per year between 2005 and 2012 to 23 patients in 2015 only in our centre. However, serious hematological and non-hematological adverse events may occur. The purpose of this study was to evaluate the toxicity of PCV and its clinical relevance in our practice.

Methods We retrospectively reviewed the charts of 57 patients with LGG who received PCV at the Centre hospitalier de l'Université de Montréal between 1 January 2005 and 27 July 2016.

Results Procarbazine, lomustine, and vincristine were associated with severe hematological toxicity as clinically significant grade 3 anemia, neutropenia, and thrombocytopenia occurred in 7%, 10%, and 28% of patients, respectively. Other frequent adverse events such as the increase of liver enzymes, cutaneous rash, neurotoxicity, and vomiting occurred in 65%, 26%, 60%, and 40% of patients, respectively. Patients with prophylactic trimethoprim/sulfamethoxazole had more grade 3 hematological toxicity with PCV, especially anemia ($p = 0.040$) and thrombocytopenia ($p = 0.003$) but we found no increase in PCV toxicity in patients on concurrent anticonvulsants. Patients with grade 3 neutropenia had a significantly lower survival (median survival 44.0 months vs. 114.0 months, $p = 0.001$). Patients who were given PCV at diagnosis had more grade 3 anemia than those who received it at subsequent lines of treatment ($p = 0.042$).

Conclusion Procarbazine, lomustine, and vincristine increase survival in LGG but were also associated with major hematologic, hepatic, neurologic, and cutaneous toxicity. Anti-*Pneumocystis jiroveci* pneumonia (PJP) prophylaxis, but not anticonvulsants, enhances hematologic toxicity.

Key Words Chemotherapy, toxicity, gliomas

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INTRODUCTION

Low-grade gliomas (LGG) are relatively uncommon tumours, accounting for approximately 15% of all primary brain tumours, and are usually diagnosed in younger patients[1]. Prognostic factors and clinical variables such as male gender, age over 40, and presence of neurological symptoms at diagnosis have been correlated with worst outcomes[2]. Midline shift, large tumour diameter, and astrocytic component to the tumour have also been reported as bad prognostic factors[3-5]. Histologically, the presence of the 2 mutations, 1p19q and *IDH1*, have been identified as factors with a favourable prognosis[6,7]. The documentation of the impact of these mutations on the clinical course of glioma patients has led to a change in the World Health Organisation (WHO) classification in 2007[8].

Appropriate management of patients with LGG has been a source of controversy[9]. Long-term follow-up of prospective randomized trials has recently led to a change in the management of LGG. Buckner *et al.* published the

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finding that chemotherapy with procarbazine, lomustine, and vincristine (PCV), when added to radiotherapy, improves overall survival of selected LGG patients[10]. Following publication of various articles on the subject, PCV use has therefore increased in our centre.

However, PCV chemotherapy is associated with major adverse events that need to be taken into consideration. Procarbazine, lomustine, and vincristine-induced hematological toxicity is not negligible as the scientific literature reported grade 3 lymphopenia and thrombocytopenia in as many as 75% and 64% of patients, respectively[10]. A study also stated that procarbazine can produce major hepatotoxicity as it is metabolized by hepatic enzymes[11]. Vincristine, as well as anticonvulsants, can add to hepatic toxicity[12]. Nausea and emesis are seen in as many as 70 to 80% of patients receiving PCV without antinausea drugs[10,13]. Neurotoxicity, mostly attributable to vincristine, was also reported[14]. Finally, rash was portrayed in several articles as a side effect of PCV[10,13,15].

The high toxicity associated with PCV has an important impact on the course of treatment. A study published in the *Journal of Clinical Oncology* stated that 28.5% of patients had to stop the chemotherapy because of the severe side effects[9]. Another study reported a delay in treatment in 31.3% of its patients to permit toxicity to resolve[12].

No study has been published with the sole purpose of describing in detail the adverse events of PCV. The prospective studies referenced above report toxicity in a selected study population. The use of PCV chemotherapy has since increased and has been extended to a wider patient population.

On the other hand, patients under chemotherapy often take a considerable amount of medication. One of them is trimethoprim/sulfamethoxazole (TMP/SMX), which is given as an anti-*Pneumocystis jiroveci* pneumonia (PJP) prophylaxis when patients develop cluster of differentiation 4 (CD_4) < 200. Trimethoprim/sulfamethoxazole has been related to major non-negligible side effects. Gastrointestinal and cutaneous symptoms are observed in 3% to 10% of the patients under TMP/SMX and various hematological disorders such as anemia and thrombocytopenia are also known to be induced by this antibiotic[16].

The primary objective of our study was therefore to focus on selected toxicity of the PCV in an unselected population treated in a Canadian academic centre. The secondary objectives were to determine the impact of toxicity on patient survival and to determine whether concomitant medication increases the toxicity experienced by patients.

METHODS

Population

This study included all patients (n = 57) with LGG who received PCV chemotherapy at the Centre hospitalier de l'Université de Montréal (CHUM) between 1 January 2005 and 27 July 2016. To be included in our review, patients had to be diagnosed either with oligodendroglioma, oligoastrocytoma, or astrocytoma. Grade 2 and 3 gliomas were considered. Patients needed to have received PCV at some point in the course of their illness. Some received it at diagnosis while others were given the PCV only at progression. Each patient's paper and electronic records were retrospectively reviewed. This study was approved by our local ethics review committee.

Medication

All anti-PJP prophylaxis (TMP/SMX and atovaquone) and anticonvulsants (levetiracetam, phenytoin, and carbamazepine) were documented, including the duration of use.

PCV Cycles

The standard interval between each cycle of PCV (procarbazine 100 mg/m^2 orally from day 8 to 22, lomustine 110 mg/m^2 on day 1, and vincristine 1.4 mg/m^2 [maximum of 2 mg] on days 8 and 29) was determined to be 8 weeks to quantify treatment delays. It was also possible to document the number of cycles received without 1 or more medication of the tritherapy (if either procarbazine, vincristine, and/or lomustine were omitted). Finally, we were able to quantify the number of cycles in which the dosage had to be reduced.

Toxicity

Hematological, hepatic, renal, neurologic, and cutaneous toxicities were reviewed. The events had to have happened during the PCV toxicity period, which we defined as extending from the first day of the chemotherapy to 8 weeks from day 1 of the last cycle. For laboratory toxicity, the presence or absence of an abnormal value was first determined, and the toxicity was then graded based on the Common Terminology Criteria for Adverse Events version 4.0[17]. All patients had complete blood count (CBC) and biochemistry (including alanine aminotransferase [ALT], aspartate aminotransferase [AST], phosphatase alkaline, bilirubin, and creatinine) draws before days 1, 8, and 29 of each cycle in order to authorize the administration of each agent.

The presence or absence of bronchospasm, rash, neurotoxicity, nausea, vomiting, and/or constipation was also collected using the clinical note of the doctors, nurses, and pharmacists in the patient's electronic file (OACIS, Telus Health, Montréal, Canada). The clinical evaluation of the nurse was made with a standardized print questionnaire before administration of vincristine on days 8 and 29.

Statistical Analysis

To determine whether the toxicity occurring during the PCV had an impact on the survival of patients, Kaplan-Meier survival curves were used. Comparisons between the various toxicities and the line of treatment were made using the Chi-squared test with a significant threshold of p value at 0.05. The same analysis was used to compare adverse events patients experienced according to their anti-PJP prophylaxis and anticonvulsant use. All the analyses were conducted using SPSS 24 (IBM, Armonk, NY, U.S.A.).

RESULTS

Socio-Demographic Characteristics

The patients included in this study had a mean age of 42 years (range 18 to 68) and 40.4% (n = 23) of them were female. Neurological symptoms at diagnosis were found in 87.7% (n = 50). In 63.2% (n = 36) of our patients, epilepsy was documented as a symptom present at diagnosis. The

majority of the patients had an *Eastern Cooperative Oncology Group* (ECOG) status of 0 or 1 (Table I).

Tumour characteristics are also presented in Table I. Oligodendroglioma accounted for 40.4% ($n = 23$) of diagnoses while oligoastrocytoma was diagnosed in 12.3% ($n = 7$) of the patients. Lastly, astrocytoma was identified in 47.4% ($n = 27$) of the individuals included in this study. The 1p19q mutation was present in 45.6% ($n = 26$) of the patients but not available for 35.1% ($n = 20$). Isocitrate dehydrogenase 1 was identified in 52.6% ($n = 30$) of patients. Specific pathological testing in our centre started in 2015, which explains why the information remains unknown for 36.9% ($n = 21$) of the patients. Nearly half of patients received PCV as the first line of treatment right at diagnosis (50,9%) and the other half received the chemotherapy at the subsequent lines.

TABLE I Patient and tumour characteristics of LGG who received PCV between 1 January 2005 and 27 July 2016

Patient and tumour characteristics	Patients (n=57)
Gender	
Female (%)	23 (40.4)
Male (%)	34 (59.6)
Age at diagnosis	
Mean±SD	42±13.3
Median	40
Presence of neurological symptoms at diagnosis	
Yes (%)	50 (87.7)
No (%)	1 (1.8)
Unknown (%)	6 (10.5)
Epilepsy at diagnosis	
Yes (%)	36 (63.2)
No (%)	12 (21.1)
Unknown (%)	9 (15.7)
ECOG, mean±SD	
0 (%)	26 (45.6)
1 (%)	13 (22.8)
2, 3 or 4 (%)	1 (1.8)
Unknown (%)	17 (29.8)
Oligodendroglioma	
Grade 2 (%)	12 (21.1)
Grade 3 (%)	11 (19.3)
Oligoastrocytoma	
Grade 2 (%)	4 (7.0)
Grade 3 (%)	3 (5.3)
Astrocytoma	
Grade 2 (%)	18 (31.6)
Grade 3 (%)	9 (15.7)
1p19q	
Positive (%)	26 (45.6)
Negative (%)	11 (19.3)
Unknown (%)	20 (35.1)
IDH1	
Positive (%)	30 (52.6)
Negative (%)	6 (10.5)
Unknown (%)	21 (36.9)

LGG = low-grade gliomas; PCV = procarbazine, lomustine, and vincristine; SD = standard deviation; ECOG = Eastern Cooperative Oncology Group.

Toxicity

The main objective of this study is to describe PCV toxicity (Table II). During the toxicity period, 80.7% experienced hematological toxicity. Clinically significant grade 3 anemia occurred in 7.0% ($n = 4$). Grade 3 neutropenia and thrombocytopenia occurred in 10.5% ($n = 6$) and 28.1% ($n = 16$) of patients, respectively. Of all LGG, 31.6% ($n = 18$) had low CD4 counts (< 200) while under chemotherapy.

Liver toxicity reflected as an increase of aminotransferases occurred in 64.9% ($n = 37$) of patients. Also, 17.5% ($n = 10$) had a grade 3 rise in ALT significant enough to be clinically considered.

Regarding reported clinical adverse events, 26.3% ($n = 15$) of the patients reacted to the chemotherapy by presenting a rash at some point during the PCV administration (Table II). Of all the patients, 59.6% ($n = 34$) experienced neurotoxicity. Concerning gastrointestinal toxicity, 70.2%

TABLE II Toxicity experienced by LGG who received PCV

Toxicity	Patients % (n=57)	
	All grade	Grade 3–4
Hematological		
Anemia (%)	46 (80.7)	4 (7.0)
Lymphopenia (%)	46 (80.7)	21 (36.8)
Low CD4 (%)	36 (63.2)	18 (31.6)
Neutropenia (%)	15 (26.3)	6 (10.5)
Thrombocytopenia (%)	46 (80.7)	16 (28.1)
Hepatic		
High AST (%)	23 (40.4)	2 (3.5)
High ALT (%)	37 (64.9)	10 (17.5)
High alkaline phosphatase (%)	12 (21.1)	0 (0.0)
High bilirubin (%)	7 (12.3)	0 (0.0)
Renal		
High creatinine (%)	6 (10.5)	0 (0.0)
Clinical		
Allergic reaction (cutaneous rash) (%)	15 (26.3)	
Bronchospasm (%)	0 (0.0)	
Neurotoxicity (%)	34 (59.6)	
Constipation (%)	28 (49.1)	
Nausea (%)	40 (70.2)	
Vomit (%)	23 (40.3)	

LGG = low-grade gliomas; PCV = procarbazine, lomustine, and vincristine; CD4 = cluster of differentiation 4; AST = aspartate aminotransferase; ALT = alanine aminotransferase.

($n = 40$) had nausea and 40.3% ($n = 23$) vomited despite an in-house mandatory anti-nauseous protocol during the PCV administration.

Impact of Hematological Toxicity on Survival

In our study, severe neutropenia was strongly related to mortality (Table III). Indeed, patients who experienced grade 3 neutropenia while under PCV had a significantly lower survival than those who did not (median overall survival [OS]: 44.0 months vs. 114.0 months, $p = 0.001$), independently related to febrile neutropenia as only 1 patient experienced it. The mean number of cycles received by patients did not differ between the 2 groups (mean number of cycles: 3.51 vs. 3.67, $p = 0.815$) and the number of cycles delayed ($\chi^2 = 0.052$, df = 1, $p = 0.820$) or reduced ($\chi^2 = 1.788$, df = 1, $p = 0.181$) was not statistically significant when comparing patients who experienced grade 3 neutropenia with those who did not (Figure 1).

Impact of Line of Treatment on Toxicity

When comparing our PCV population who received the chemotherapy as first line with the relapsing LGG receiving PCV in other treatments lines, patients who were given PCV at diagnosis had significantly more clinically relevant grade 3 anemia ($\chi^2 = 4.154$, df = 3, $p < 0{,}05$) than those who received it at subsequent lines of treatment (Table IV). The same correlations were not found regarding neutropenia or thrombocytopenia.

Impact of Medication on Toxicity

In our study population, 31.6% of patients ($n = 18$) developed grade 3 low CD_4 counts during PCV chemotherapy. Despite an institutional practice to prescribe anti-PJP prophylaxis when CD_4 counts decrease under 200 cells/mm^3, only 55.6% ($n = 10$) of those who had $CD_4 < 200$ received either TMP/SMX ($n = 8$) or atovaquone ($n = 2$).

When comparisons were made between the patients who received prophylaxis and those who didn't, we observed that those with the anti-PJP prophylaxis had significantly more grade 3 anemia ($p < 0.05$) and thrombocytopenia ($p < 0.001$) (Table V). However, the same correlation was not found for the anticonvulsants.

Impact of Toxicity on Course of Therapy

Treatment delays that occurred in 45.6% ($n = 26$) of patients most certainly can be attributed to PCV toxicity (Table VI). Indeed, the hematological toxicity influenced the course of treatment as patients who manifested abnormal platelet levels had significantly more delayed cycles ($\chi^2 = 7.329$, $\chi^2 = 4.154$, df = 1, $p = 0.007$) than those who did not. The same correlation was found when comparing patients who experienced neurotoxicity with those free of neurological symptoms ($\chi^2 = = 8.860$, df = 1, $p = 0.003$). Furthermore, 21.1% ($n = 12$) of patients needed a dose reduction to pursue chemotherapy without accentuating toxicity. Patients who

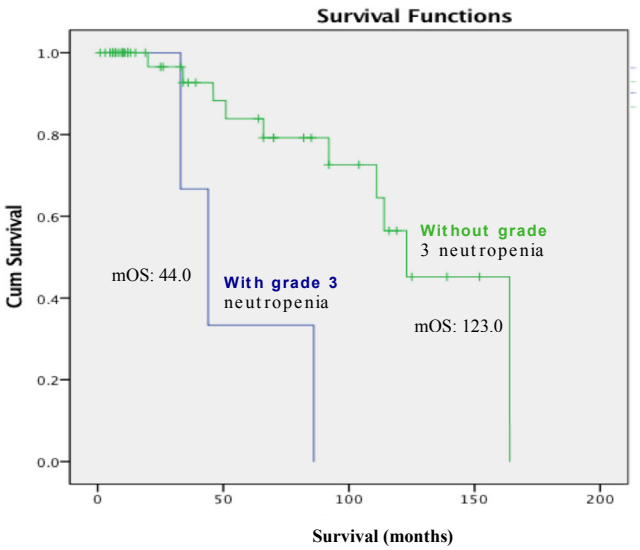

FIGURE 1 Overall median survival of patients comparing those who experienced grade 3 neutropenia (neutro<1.0×10^9) with those who did not. mOS = median overall survival.

TABLE III Median overall survival and overall survival at 5 years according to the presence or absence of hematological toxicity during the PCV toxicity period

Survival classified by hematological toxicity	Toxicity experienced	No toxicity	*P* value
≥ grade 3 anemia[a]	*N*=4	*N*=53	
mOS (mo)	NR	114.0	
5y OS, (%)	100	78.3	
≥ grade 3 neutropenia[b]	*N*=6	*N*=51	
mOS (mo)	44.0	123.0	0.001
5y OS, (%)	33.3	83.9	
≥ grade 3 thrombocytopenia[c]	*N*=16	*N*=41	
mOS (mo)	114.0	164.0	0.390
5y OS, (%)	64.3	84.8	

[a] Grade 3 anemia: Hb<80 g/L.
[b] Grade 3 neutropenia: Neutro<1.0×10^9.
[c] Grade 3 thrombocytopenia: Plt<50×10^9.
mOS = Median overall survival; 5y OS = overall survival at 5 years; PCV = procarbazine, lomustine, and vincristine; NR = not reported.

experienced neurotoxicity had significantly more reduced dosage than those who did not ($\chi^2 = 6.474$, df = 1, $p = 0.011$). Finally, 38.6% ($n = 22$) of patients had at least 1 incomplete cycle as 1 or more medication was stopped during treatment due to toxicity. Those who had an elevation in their aminotransferases had significantly more cycles without procarbazine than those without hepatic toxicity ($\chi^2 = 7.447$, df = 1, $p = 0.006$).

DISCUSSION

The main objective of this study was to assess the toxicity of PCV in an unselected population of patients diagnosed with LGG who received this chemotherapy between 1 January 2005 and 27 July 2016.

Our results are congruent with the literature regarding the hematological toxicity of PCV. More than a third of our patients developed grade 3 hematological toxicity. Kim *et al.* reported that this specific adverse event occurred in 28.1% of their patients[13]. Moreover, in our study, 28.1% of patients developed grade 3 thrombocytopenia that required transfusions while receiving PCV. This event occurred more frequently in a study conducted by Buckner *et al.* as 64% of their patients experienced it[9]. Grade 3 neutropenia also occurred in a significant proportion of patients. This specific adverse event can lead to febrile neutropenia, and one study even described that 1 of their patients died following a neutropenic sepsis[18]. No toxic death occurred in our centre, but the incidence of hematological toxicity is not to be underestimated as it can have major impacts on the health of patients.

TABLE IV Hematological toxicity according to the line of treatment at which PCV was received

Hematological toxicity	First line (*n*=29)	Other lines (*n*=28)	*P* value
≥ grade 3 anemia[a] (%)	4 (7.0)	0 (0.0)	0.042
≥ grade 3 neutropenia[b] (%)	3 (10.3)	3 (10.7)	0.964
≥ grade 3 thrombocytopenia[c] (%)	7 (24.1)	9 (32.1)	0.501

[a] Grade 3 anemia: Hb<80 g/L.
[b] Grade 3 neutropenia: Neutro<1.0×10^9.
[c] Grade 3 thrombocytopenia: Plt<50×10^9.
PCV = procarbazine, lomustine, and vincristine.

Hepatic toxicity was also present in our study as it is currently stated in the scientific literature. King *et al.* declared that procarbazine is associated with hepatotoxicity as it is converted to azo-procarbazine by hepatic enzymes[11]. They stated that lomustine was also associated with elevation of aminotransferases and it was described that vincristine may produce hepatotoxicity in combination with radiation. The authors suggested a "modification of [procarbazine] dosage in the face of hepatic dysfunction"[11]. Following this proposition, a significant proportion of our patients had to be watched carefully to evaluate the need to modify the dosage or even omit procarbazine, as 64.9% experienced grade 1 ALT toxicity and 17.5% of the patients had grade 3 ALT toxicity. Indeed, when comparing those with elevation of aminotransferases while under PCV with the others, the first group received an increased number of cycles in which procarbazine was omitted.

Moreover, to our knowledge, no study has reported the exact impact of PCV on renal function. However, in our patients, 10% had an increase of creatinine significant enough to consider reduction of lomustine and/or procarbazine. The impact of chemotherapy on the biochemical labs is noteworthy, and patients under PCV should be carefully monitored to minimize accumulation of chemotherapy.

Regarding clinically important adverse events, several studies reported the different inconveniences produced by PCV. Two different studies reported urticaria and maculopapular rash secondary to the administration of procarbazine in patients with Hodgkin's disease and non-Hodgkin's lymphoma[19,20]. Another study reported that 32% of their patients developed a rash following the administration of chemotherapy, which is congruent with our findings as 26.3% of our population had a cutaneous rash while receiving procarbazine. These patients had to stop procarbazine and were referred to allergy, where the majority of them underwent desensitization. Cutaneous reactions must be taken into consideration, as they may necessitate rapid discontinuation of the chemotherapy and definitely have an impact on patients' quality of life.

Neurotoxicity is also a known side effect of vincristine[21]. Polyneuropathy was reported in 2% of the patients in a study conducted by Van den Bent *et al.*[22]. However, neurotoxicity was reported in as many as 59.6% of our patients. This difference in proportion can probably be attributed to the fact that in the present article, the diagnosis

TABLE V Hematological toxicity in LGG during the PCV toxicity period according to the anti-PJP prophylaxis usage

Hematological toxicity	Anti-PJP Prophylaxis				Anticonvulsants		
	Septra (*n*=8)	Mepron (*n*=2)	No prophylaxis (*n*=47)	*P* value	No ATB/No AC *n*=6	AC only *n*=41	*P* value
≥ grade 3 anemia[a] (%)	1 (12.5)	1 (50.0)	2 (4.2)	0.040	1 (16.7)	1 (2.4)	0.107
≥ grade 3 neutropenia[b] (%)	2 (25.0)	1 (50.0)	3 (6.4)	0.056	0 (0.0)	3 (7.3)	0.493
≥ grade 3 thrombocytopenia[c] (%)	5 (62.5)	2 (100.0)	9 (19.1)	0.003	1 (26.7)	8 (19.5)	0.869

[a] Grade 3 anemia: Hb<80 g/L.
[b] Grade 3 neutropenia: Neutro<1.0×10^9.
[c] Grade 3 thrombocytopenia: Plt <50×10^9.
LGG = low-grade gliomas; PCV = procarbazine, lomustine, and vincristine; PJP = Pneumocystis jiroveci pneumonia; ATB = antitubercular; AC = anticonvulsant.

TABLE VI Impact of the toxicity of PCV on the course of the therapy for LGG

Impact on treatment	Patients (*n*=57)
Delay of at least 1 cycle (%)	26 (45.6)
Dose reduction (%)	12 (21.1)
Discontinuation of chemotherapy	
CCNU (%)	0 (0.0)
Vincristine (%)	9 (15.8)
Procarbazine (%)	14 (24.6)
Complete discontinuation (%)	3 (5.3)

PCV = procarbazine, lomustine, and vincristine; LGG = low-grade gliomas.

of neurotoxicity did not require an *electromyography* (EMG) confirmation and was only clinically reported. Nonetheless, this clinical adverse event certainly had an impact on the course of therapy. Indeed, those who experienced neurotoxicity had more delayed cycles and more reduced dosage than those who did not.

This neurotoxicity may also have repercussions on the digestive tract and induce constipation. Other concomitant drugs could also contribute to constipation. Almost 1 out of 2 patients experienced this adverse event. Other digestive side effects included nausea and emesis, as 40% of the patients in our study vomited despite an anti-nausea protocol. This is somewhat congruent to what is found in the literature and shows a possible need to modify the antiemetic protocol.

With this assessment of all clinical adverse events showing important impact of the chemotherapy on the well-being of patients, it is essential to acknowledge their importance as clinical toxicity may cause patients to delay or discontinue their PCV even if they do not constitute a threat to their lives.

The evaluation of the impact of the hematological toxicity on survival of the patients was also examined. Indeed, it was found that patients who suffered from severe grade 3 neutropenia had significantly lower survival than those who did not, not counting febrile neutropenia that only occurred in 1 patient. Various variables can contribute to this finding. However, the mean number of cycles received by patients and the course of therapy (delayed cycles and dosage reduction) did not differ between the 2 groups of patients. Hence, this difference in survival cannot be explained by the makeup of the drug delivery. Therefore, this discovery definitely generates a hypothesis for future prospective studies.

On another note, over the last decade, administration of PCV has tremendously increased. In our study alone, only 2 patients were treated in 2005 compared with more than 20 in 2015. This impressive increase is in part due to recent studies demonstrating the efficacy of PCV when added to radiotherapy to improve outcomes in LGG[10]. The impact of the line of treatment on the incidence of toxicity was therefore examined to determine whether more toxicity was experienced by a particular group of patients classified according to the line at which PCV was received. The statistical analysis revealed that the patients receiving PCV as a first line of treatment had significantly more hematological toxicity, and specifically more grade 3 anemia, than those who had it only at progression. One hypothesis for this finding is that there might be a selection bias as patients who experienced any cytopenia at their first chemotherapy, most likely Temodal, were not given PCV at subsequent lines of treatment. Therefore, the patients who received PCV during later lines of treatment might represent a subgroup less susceptible to cytopenias, all patients who presented a sensitivity to alkylating agents being previously excluded. This finding is nonetheless noteworthy, and physicians need to be particularly careful with the administration of PCV at diagnosis since patients are naïve to chemotherapy and might be more vulnerable to its hematological toxicity.

As mentioned above, patients in our study often took a large amount of concomitant medication. One of them was TMP/SMX, given in keeping with our institutional guideline to prescribe anti-PJP prophylaxis to patients whose CD_4 counts fall under 200 cells/mm^3. However, 44% (n = 8) of patients with CD_4 under 200 in our centre did not receive the medication. On the other hand, TMP/SMX has been known to induce major non-negligible side effects[16]. Various hematological disorders, such as anemia and thrombocytopenia, are known to be induced by this antibiotic[16]. We questioned whether patients under PCV who also received concomitant TMP/SMX or atovaquone experienced more toxicity than with chemotherapy alone. Analysis revealed that patients taking TMP/SMX in addition to chemotherapy had more grade 3 anemia and thrombocytopenia. Some may argue that this appearance of increase in toxicity simply comes from the fact that low CD_4 is an indication for TMP/SMX and that a decrease in a hematological line necessarily means that the patient is more susceptible to a decrease in other lines. However, when patients with CD_4 under 200 (independently of the usage of prophylaxis) were compared with those who maintained their CD_4 elevated, the toxicity experienced did not differ. It then becomes clear that the increase in toxicity may not be attributed to an increased medullary sensitivity, but more to the combination of PCV and anti-PJP prophylaxis. This finding is quite interesting as physicians need to be aware of the potential interaction between 2 medications frequently administered together and maybe consider pentamidine as anti-PJP prophylaxis.

As most LGG patients also initially presented epilepsy at diagnosis, an anticonvulsant was frequently added to their medication. When analyses were conducted to determine whether this type of drug increases toxicity like TMP/SMX does, the same correlation was not found.

The tremendous toxicity described above leads to various concerns with the administration of PCV. Congruent with the literature stating that almost 30% of patients had to discontinue chemotherapy due to severe toxicity[9], almost a quarter of our patients discontinued 1 or more medications of the tritherapy at some point. In the present study, 45.6% of patients had at least 1 cycle delayed because of toxicity and 21.1% needed their dosage reduced. Again, this is of serious importance as the chemotherapy that increases survival also produces toxicity severe enough to cause disturbances in its administration and potentially reduce efficacy.

The underlying advantage of our study was its relatively large sample size. Indeed, even if 57 patients may seem like a small number, it is, to our knowledge, the largest study population published in the literature. The use of a meticulously compiled database is also a strong element of our research. On the other hand, there are certainly some limitations to our study. The retrospective and subjective nature of certain elements of our research limits the validity of our findings and the potential conclusions that could be drawn from them. Since other studies have not found similar results regarding increased toxicity of PCV when given as a first line of treatment and decreased survival for patients with neutropenia induced by the chemotherapy, these surprising retrospective findings should be validated prospectively. A longitudinal study observing the toxicity of PCV over several years with predetermined structured follow-up, such as periodic blood samples and detailed objective assessment of the clinical side effects, would definitely be useful in the evaluation of the toxicity of PCV. Quality-of-life data would also be interesting to add as it could objectify the real impact of PCV toxicity on the well-being of patients.

CONCLUSION

This study characterized the various toxicity that can be experienced with PCV. It demonstrated in a population of LGG patients treated with PCV at a university hospital that severe hematological, hepatic, renal, and clinical side effects are induced by this chemotherapy. It was also established that TMP/SMX, an anti-PJP prophylaxis, adds to the toxicity produced by PCV. Anticonvulsants, on the other hand, do not increase toxicity. Such findings emphasize the fact that PCV is a chemotherapy causing severe adverse events that can be disturbing and unpleasant for patients. Physicians should be aware of its important toxicity and of the potential increase in side effects produced by combining drugs such as PCV and TMP/SMX. Careful administration of this chemotherapy is essential.

Finally, interesting findings regarding the shorter survival in patients who developed grade 3 neutropenia while under PCV and increased hematological toxicity in LGG who received PCV as their first chemotherapy are intriguing hypotheses that need further consideration.

CONFLICT OF INTEREST DISCLOSURES

We have read and understood Current Oncology's policy on disclosing conflicts of interest, and we declare that we have none.

AUTHOR AFFILIATIONS

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