

Clinical feasibility of modified procarbazine and lomustine chemotherapy without vincristine as a salvage treatment for recurrent adult glioma

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Abstract. Procarbazine, lomustine and vincristine (PCV) chemotherapy is considered a salvage option for adult glioma; however, its significant toxicities frequently lead to dose reduction or discontinuation in patients with recurrent glioma. The current study evaluated the safety and efficacy of modified procarbazine and lomustine (PC) chemotherapy that omits vincristine and reduces the lomustine dose compared with those of conventional PCV chemotherapy. Using electronic medical records, all patients with adult recurrent glioma who received PC or PCV chemotherapy between 2009 and 2020 at Seoul St. Mary's Hospital or St. Vincent's Hospital were examined retrospectively. A total of 59 patients met the eligibility criteria. Among them, 15 patients received modified PC chemotherapy (PC group) and 44 patients received PCV chemotherapy (PCV group). The PC group presented a significantly lower hematology toxicity (anemia, 6.7 vs. 45.5%, $P=0.02$; thrombocytopenia 20.0 vs. 70.4%, $P<0.001$). Additionally, the clinical impacts of PC chemotherapy, including delay of a cycle, dose reduction, discontinuation of drug(s) or total cessation of chemotherapy, were significantly less frequent compared

with the PCV group (26.7 vs. 68.2%, $P=0.012$). The overall survival of the PC group was also significantly longer than that of PCV group (396 vs. 232 days, $P=0.042$), while there was no significant difference in progression-free survival between the two groups (284.5 vs. 131 days, $P=0.077$). The results suggested that modified PC chemotherapy may be an alternative chemotherapeutic regimen with tolerable toxicity and without loss of clinical efficacy in patients with recurrent adult glioma. Further prospective and larger studies are required to validate our findings.

Introduction

Glioma is the most common and most malignant brain tumor in adults, composing most of all brain malignancy diagnoses in this population (1,2). Typically, the clinical outcomes of this condition are devastating, although aggressive multimodal treatments, including surgery, radiotherapy, and chemotherapy-which mainly is composed of drugs in the temozolomide (TMZ) and nitrosourea classes-can have some effect (3,4). For cases of recurrent glioblastoma, which is the most common and most malignant type of glioma, almost all patients eventually experience a recurrence and die within six months after diagnosis of recurrence (5,6).

There is no consensus regarding salvageable options for recurrent and TMZ-resistant adult glioma (7-10). Among the current treatments, procarbazine, lomustine, and vincristine (PCV) chemotherapy is one of the representative salvageable options for recurrent adult glioma (11-14). However, the various and severe toxicities of this treatment, including hematologic toxicity from lomustine and peripheral neurotoxicity from vincristine, often result in its reduction or discontinuation in glioma patients (15-17). In addition to its toxicity, vincristine is composed of relatively heavy molecules (825 Daltons), and concerns exist about its successful crossing of the blood-brain barrier (18).

In this context, a few studies have suggested procarbazine and lomustine (PC) chemotherapy without vincristine as an alternative to PCV chemotherapy with lesser toxicity and no loss of efficacy (19-22). Vesper *et al* first suggested that

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PC chemotherapy protocols might be as effective as PCV chemotherapy while avoiding the toxicity of vincristine (20). In addition, Webre *et al* suggested that PC chemotherapy can achieve comparable clinical outcomes to PCV chemotherapy with lesser neurotoxicity in anaplastic oligodendroglioma (21). We have also tested the modified PC chemotherapy protocol of reduced dose of lomustine (75 mg/m², day 1) and procarbazine (60 mg/m², days 11-24) every four weeks in recurrent glioblastoma patients with expectation of lesser toxicity and non-inferior efficacy (19).

In this study, we retrospectively analyzed the efficacy and safety of modified PC chemotherapy in recurrent glioma patients compared with those of conventional PCV chemotherapy. This study tried to validate that the modified PC chemotherapy is less toxic than PCV chemotherapy, and that the survival outcomes of PC chemotherapy are noninferior to those of PCV chemotherapy in patients with recurrent adult glioma.

Materials and methods

Study population. This retrospective study was approved by the institutional review board of our institution. The electronic medical records of adult glioma patients treated at our institution between 2010 and 2020 were examined. The study inclusion criteria were i) glioma pathologically confirmed by craniotomy or biopsy, ii) glioma recurrence confirmed radiologically and/or pathologically, iii) receipt of PC or PCV chemotherapy following recurrence diagnosis, and iv) accessible baseline clinical variables and survival data. The study exclusion criteria were i) received PC or PCV chemotherapy as adjuvant therapy after initial diagnosis, ii) a medical history of hematologic or rheumatologic disease, iii) failure to complete the first cycle of PC or PCV chemotherapy. A flow of the study design is presented in Fig. 1.

Treatment protocols. After maximal safe resection at initial surgery, we performed adjuvant therapy following the best treatment protocol(s) by glioma subtype. If the diagnosis was glioblastoma, we performed concomitant chemoradiation (TMZ dose: 75 mg/m²) and six cycles of adjuvant TMZ chemotherapy (TMZ dose: 150-200 mg/m²). If the diagnosis was grade II or III glioma, we conducted adjuvant radiotherapy, in which the dosage was either 5,940 cGy for 33 fractions or 6,000 cGy for 30 fractions. In the case of grade III glioma, we added adjuvant chemotherapy of PCV or PC chemotherapy. When recurrence occurred, the first chemotherapy considered was TMZ; when the use of TMZ chemotherapy was not possible due to various reasons, such as prior history of TMZ administration within 6 months, and swallowing difficulty, then bevacizumab or nitrosourea-based chemotherapy including the modified PC chemotherapy or the conventional PC chemotherapy, was considered according to clinician preference.

PC chemotherapy was composed of lomustine (75 mg/m², day 1) and procarbazine (60 mg/m², days 11-24) administered orally every four weeks. This modified protocol was discussed in a previous study of one of our authors (19). PCV chemotherapy was administered to recurrent glioma patients, with lomustine (110 mg/m², day 1) and procarbazine (60 mg/m²,

days 8-21) administered orally but vincristine administered intravenously [1.4 mg/m² (maximum of 2 mg), days 8 and 29] every six weeks.

Clinical variables. The clinical variables of sex; age; pathological diagnosis, including molecular features; prior history of surgery, radiation, or chemotherapy; radiological findings; performance status; and survival status and/or death date were collected. Diagnosis of recurrent glioma was performed by two neuropathologists according to the 2016 World Health Organization classification of the central nervous system. IDH mutation was evaluated by immunohistochemistry or directing sequencing. If necessary, IDH 2 mutation was evaluated by directing sequencing. The presence of a 1p19q co-deletion was examined using fluorescence *in situ* hybridization. The O⁶-methylguanine-DNA-methyltransferase (MGMT) gene methylation status was evaluated by polymerase chain reaction. Performance status was estimated according to the scale of the Eastern Cooperative Oncology Group (ECOG). All kinds of toxicities were evaluated according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. Also, the related impact of the toxicity of PC or PCV chemotherapy on the course of the treatment schedule was classified into four categories: delay of a cycle, dose reduction, discontinuation of drug(s), or total cessation of chemotherapy. Radiographic responses on magnetic resonance imaging (MRI) were determined by specialized neuroradiologists according to the response assessment in neuro-oncology (RANO) criteria. The date of recurrence was defined as the date of MRI showing recurrence. Survival status and/or death date were collected from the Korea Central Cancer Registry database.

Statistical analysis. The overall survival (OS) after recurrence was defined as days from the starting date of PC or PCV chemotherapy to death, while progression-free survival (PFS) was defined as days from the starting date of PC or PCV chemotherapy to disease progression was confirmed by MRI. Patients who were confirmed to be alive on March 31, 2021, were censored. The mean duration of follow-up was 424.6 days (range: 55-2,491 days). All clinical variables were considered with descriptive statistics. The differences of clinical variables between the two treatment groups were compared using Fisher's exact test or the Chi-square test. The normality test was performed for continuous variables. Kaplan-Meier survival analysis and the log-rank test were used to calculate the median OS and PFS values of the groups. Univariate and multivariate analyses were conducted using a Cox proportional regression model. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated. Multivariate analysis was performed on the variables with P-values <0.2, and P-values <0.05 were considered to indicate statistical significance. All statistical analyses were conducted using the R version 4.0.5 software program (R Foundation for Statistical Computing, Vienna, Austria).

Results

Patient characteristics. Among a total of 59 patients enrolled in this study, 15 received PC chemotherapy (PC

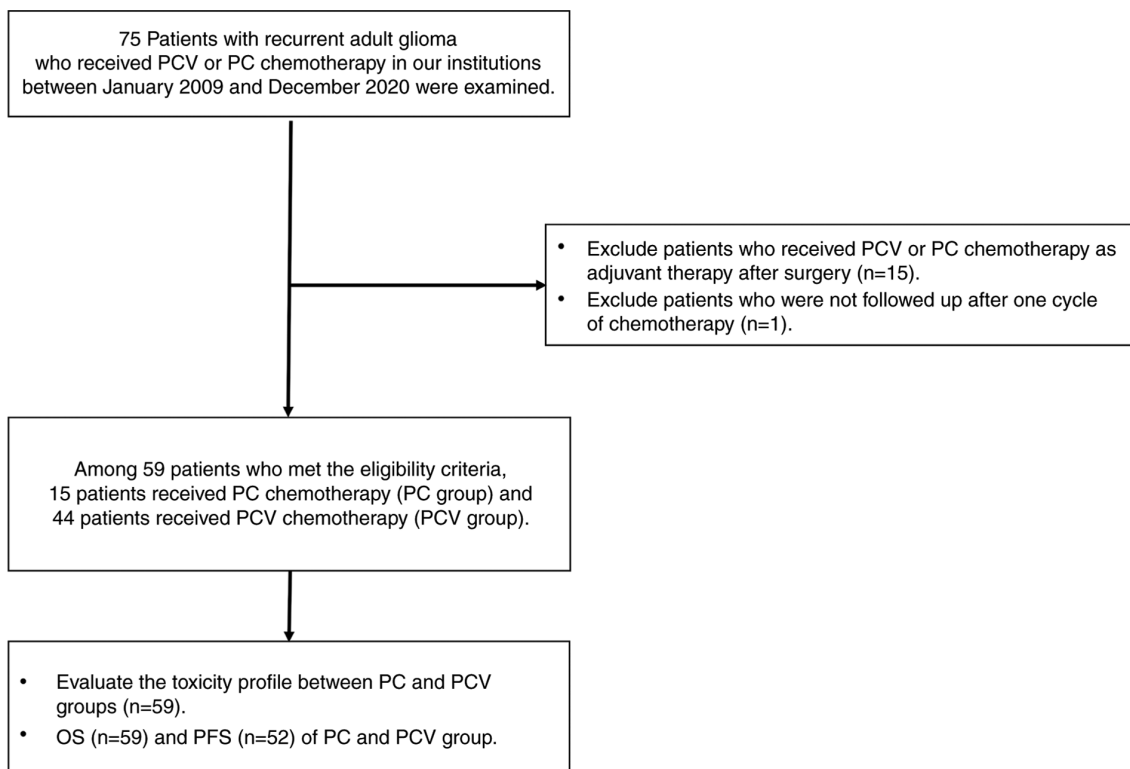


Figure 1. Flow of the study design. PC, procarbazine and lomustine; PCV, procarbazine, lomustine and vincristine; PFS, progression-free survival; OS, overall survival.

group) and 44 patients received PCV chemotherapy (PCV group) as salvage treatment for recurrent gliomas. Clinical characteristics, including sex, age, initial diagnosis, IDH mutation, 1p19q co-deletion, MGMT promoter methylation, and prior history of radiotherapy were not statistically different between the two groups. However, the median interval from radiation to chemotherapy in the PC group was shorter than that of the PCV group [4.0 (range: 0-42) months vs. 22.0 (range: 0-167) months, $P=0.004$]. Also, fewer patients in the PC group had prior history of any chemotherapy (33.3 vs. 84.7%; $P=0.003$), while there was no difference in the median interval from the last chemotherapy session to initiation of PC or PCV chemotherapy between the two groups. The summarized baseline characteristics of these patients are described in Table I.

Toxicity experiences and the impact of toxicity on chemotherapy schedule. The PC group presented a significantly lower hematology toxicity profile (anemia: 6.7 vs. 45.5%; $P=0.017$ and thrombocytopenia: 20.0 vs. 70.4%; $P<0.001$) and liver function (elevated liver enzymes: 0 vs. 25.0%; $P=0.078$). CTCAE grade III or IV toxicities were less frequently observed in the PC group, although there was no statistically significant difference. Rates of other toxicities, including neutropenia, kidney injury, allergic skin reactions, and peripheral neurotoxicity, were not significantly different between the two groups. Detailed information about toxicities is presented in Table II.

We describe the adverse impacts of toxicity on chemotherapy schedule in Table III. The PC group significantly less frequently experienced any of delay of cycle, dose reduction, discontinuation of one of the chemotherapeutic drugs, or

cessation of the entire chemotherapy regimen than did the PCV group (26.7 vs. 68.2%; $P=0.012$). Each type of toxicity was less frequently observed in the PC group, although this result failed to show statistical significance.

Comparison of clinical outcomes between the PC and PCV groups. The OS of the PC group was significantly longer than that of the PCV group (396 vs. 232 days; $P=0.042$), while there was no significant difference in PFS between the two groups (284.5 vs. 131 days; $P=0.077$). The Kaplan-Meier survival curves of OS and PFS in the two groups are illustrated in Fig. 2. Univariate and multivariate Cox analyses for OS were performed and are described in Table IV. In multivariate analysis for OS, the PCV group (HR 2.09 CI, 1.07-4.25, $P=0.023$) and older age (≥ 65) (HR 3.12 CI, 1.12-8.66, $P=0.029$) were associated with inferior OS, while presence of 1p19q co-deletion (HR 0.34 CI, 0.13-0.87, $P=0.024$) was associated with superior OS.

Discussion

In our retrospective and comparative study, we tried to compare the safety and the efficacy of our modified PC chemotherapy, compared to those of PCV chemotherapy. We also tried to evaluate how the toxicity of these chemotherapies affected the course of chemotherapy in patients with recurrent adult glioma. Our findings showed that anemia and thrombocytopenia were significantly more frequent in PCV groups than in the PC groups (anemia: 45.5 vs. 6.7%; $P=0.017$ and thrombocytopenia: 70.4 vs. 20.0%; $P<0.001$, respectively). Anemia of higher than CTCAE grade III was also more frequent in the PCV group

Table I. Baseline characteristics of patients with recurrent adult glioma who received PC or PCV chemotherapy.

Characteristic	PC group (n=15)	PCV group (n=44)	P-value
Male sex, n (%)	11 (73.3)	27 (61.4)	0.600
Age at chemotherapy (years), n (range)	52.2 (20-79)	49.6 (21-73)	0.528
Initial diagnosis, n (%)			>0.999
GBM	5 (33.3)	14 (31.8)	
Non-GBM	10 (66.7)	30 (68.2)	
IDH mutation, n (%)			0.103
Yes	3 (20.0)	13 (29.5)	
No	10 (66.7)	31 (70.5)	
Unknown	2 (13.3)	0 (0.0)	
1p19q co-deletion, n (%)			0.392
Yes	2 (13.3)	7 (15.9)	
No	11 (73.3)	24 (54.5)	
Unknown	2 (13.3)	13 (29.5)	
MGMT methylation, n (%)			0.311
Yes	8 (53.4)	16 (36.4)	
No	4 (26.7)	16 (36.4)	
Unknown	3 (20.0)	12 (27.3)	
Prior radiation therapy, n (%)			>0.999
Yes	15 (100.0)	43 (97.7)	
No	0 (0.0)	1 (2.3)	
Median interval from radiation to PC or PCV (months), n (range)	4.0 (0-42)	22.0 (0-167)	0.004
Prior chemotherapy, n (%)			<0.003
Never	10 (66.7)	7 (16.3)	
TMZ	5 (33.3)	30 (69.8)	
TMZ, bevacizumab	0 (0.0)	1 (2.3)	
TMZ, PCV	0 (0.0)	5 (11.6)	
Median interval from last chemotherapy to PC or PCV (months), n (range)	1.0 (0-13)	2.0 (0-61)	0.610
ECOG score, n (%)			0.311
0-1	7 (46.7)	29 (65.9)	
≥2	8 (53.3)	15 (34.1)	

ECOG, Eastern Cooperative Oncology Group; GBM, glioblastoma; MGMT, O⁶-methylguanine-DNA-methyltransferase; PC, procarbazine and lomustine; PCV, procarbazine, lomustine and vincristine; TMZ, temozolomide.

than the PC group. Peripheral neurotoxicity, which is a major concern with vincristine, was not observed in the PC group, while it was observed in 11.4% of patients in the PCV group. In addition, frequent and severe adverse events in the PCV group also resulted in greater disruption to the course of chemotherapy, such as delay of a cycle, dose reduction, discontinuation of vincristine, and cessation of salvage chemotherapy (68.2 vs. 26.7%; $P=0.012$). In contrast, regarding concerns about inferior efficacy when omitting vincristine, our findings suggest that survival outcomes were not different between the two groups. Interestingly, the OS of the PC group was significantly superior to that of the PCV group (396 vs. 232 days; $P=0.042$), while the PFS of the PC group was not different from that of the PCV group (284.5 vs. 131 days; $P=0.077$). This may be explained by numerous studies showing that the occurrence

of less toxicity after chemotherapy correlates with better prognosis (23,24). In summary, our modified PC chemotherapy, which omitted vincristine and reduced the dose of lomustine, showed lower toxicity and non-inferior efficacy for adult recurrent glioma patients compared to those of conventional PCV chemotherapy.

There were significant differences regarding prior history of chemotherapy and the interval from radiation to chemotherapy between the two groups, although several baseline characteristics, including initial diagnosis, molecular features, and prior history of radiotherapy, were not significantly different between the two groups. In detail, significantly fewer patients in the PC group had a prior history of any chemotherapy and in the PC group, 5 patients were diagnosed with primary glioblastoma at initial diagnosis, and these patients received concomitant

Table II. Toxicity in patients with recurrent adult glioma who received PC or PCV chemotherapy.

Toxic indicator	All grades ^a			Grades III and IV ^a		
	PC group (n=15)	PCV group (n=44)	P-value	PC group (n=15)	PCV group (n=44)	P-value
Anemia, n (%)	1 (6.7)	20 (45.5)	0.017	1 (6.7)	6 (13.6)	0.796
Neutropenia, n (%)	3 (20.0)	17 (38.6)	0.317	3 (20.0)	8 (18.2)	>0.999
Thrombocytopenia, n (%)	3 (20.0)	31 (70.4)	<0.001	3 (20.0)	14 (31.8)	0.587
Elevated liver enzymes, n (%)	0 (0.0)	11 (25.0)	0.078	0 (0.0)	6 (13.6)	0.310
Elevated creatinine, n (%)	0 (0.0)	2 (4.6)	0.989	0 (0.0)	1 (2.3)	>0.999
Allergic reaction, n (%)	0 (0.0)	1 (2.3)	>0.999	0 (0.0)	0 (0.0)	>0.999
Peripheral neurotoxicity, n (%)	0 (0.0)	5 (11.4)	0.408	0 (0.0)	0 (0.0)	>0.999

^aToxicities were graded according to CTCAE version 5.0. PC, procarbazine and lomustine; PCV, procarbazine, lomustine and vincristine.

chemoradiation therapy followed by TMZ. Regarding to the difference of the median interval from radiation to chemotherapy, we thought that the PCV group had a longer period of stable state after radiation compared that of the PC group. Another explanation is that the PC group received earlier chemotherapy as salvage treatment than did the PCV group.

When considering chemotherapeutic drugs for recurrent glioma, there have been options identified to date, including TMZ rechallenged or continuously administered with low-dose, bevacizumab, and PCV-based chemotherapy (4,25-28). As a salvage therapy after TMZ for recurrent glioma, numerous clinical trials have assessed the efficacy of PCV-based chemotherapy (11,12,14). However, in clinics, toxicities including hematologic, neurologic, liver, kidney, and skin problems were diagnosed frequently and sometimes very severe, which is a major hindrance when choosing PCV chemotherapy as salvage therapy for recurrent glioma patients, especially in those who are elderly or with a lower performance status (15,29). In addition, there have been concerns about the efficacy of vincristine because its molecular weight (825 Daltons) might be too high to penetrate the blood-brain barrier (18). In this context, a few studies have put forth the idea of adopting a modified PC-based chemotherapy regimen without vincristine for glioma patients (19-22). Vesper *et al* retrospectively analyzed clinical outcomes and toxicities of 315 patients with oligodendroglial brain tumors who received PCV or PC chemotherapy as adjuvant treatment after surgical resection and radiation. Their study showed that the PFS of patients who received PC chemotherapy was not different from that of patients who received PCV chemotherapy, with significantly fewer hematologic and neurological toxicities (20). Webre *et al* also evaluated 97 patients with primary anaplastic oligodendroglioma who received PCV or PC chemotherapy as adjuvant treatment, reporting that the clinical outcomes of PC chemotherapy for primary anaplastic oligodendroglial tumors were not different from those of patients who received PCV chemotherapy, with lower hematologic toxicities (21).

In accordance with two previous studies exploring the use of PC chemotherapy in primary oligodendroglial

Table III. Adverse impacts of the toxicity of PC or PCV on the course of chemotherapy for recurrent adult glioma.

Adverse impact	PC group (n=15)	PCV group (n=44)	P-value
Total, n (%)	4 (26.7)	30 (68.2)	0.012
Delay of a cycle, n (%)	3 (20.0)	14 (31.8)	0.587
Dose reduction, n (%)	1 (6.7)	6 (13.6)	0.796
Drug discontinuation, n (%)	0 (0.0)	8 (18.2)	0.180
Chemotherapy cessation, n (%)	0 (0.0)	2 (4.5)	0.989

PC, procarbazine and lomustine; PCV, procarbazine, lomustine and vincristine.

patients (20,21), we added evidence that our modified PC chemotherapy is as beneficial as PCV chemotherapy but with significantly less toxicity due to omission of vincristine and reduction of the dose of lomustine. Taken together, we suggest that PC chemotherapy can be an alternative option to PCV chemotherapy, especially for use in patients expected to be intolerable to PCV chemotherapy, including elderly patients or those with lower performance.

Our study should be considered within the scope of several limitations. First, our study included heterogeneous recurrent gliomas, and the unknown molecular status of 1p19q co-deletion in about 30% of these patients could cause severe bias. Second, although several baseline characteristics, including initial diagnosis, molecular features, and prior history of radiotherapy, were not significantly different between the two groups, there were significant differences regarding prior history of chemotherapy and the interval from radiation to chemotherapy between the two groups, which can cause several biases in both toxicity profile and clinical outcomes. Third, this is not a randomized study, and selection bias about treatment group have affected the results. Although our institution tried to minimize clinician biases through

Table IV. Univariate and multivariate Cox regression analysis for overall survival.

Variables	Univariate analysis		Multivariate analysis ^a	
	Hazard ratio (95% CI)	P-value	Hazard ratio (95% CI)	P-value
Male vs. female	1.04 (0.58, 1.86)	0.903	-	-
Age ≥65 vs. <65 (years)	3.45 (1.49, 8.00)	0.004	3.12 (1.12, 8.66)	0.029
Non-glioblastoma vs. glioblastoma	0.60 (0.33, 1.07)	0.081	0.66 (0.32, 1.35)	0.251
IDH mutated vs. non-mutated	0.45 (0.22, 0.93)	0.032	0.73 (0.58, 3.26)	0.472
1p19q co-deleted vs. not-deleted	0.35 (0.13, 0.90)	0.030	0.34 (0.13, 0.87)	0.024
MGMT methylated vs. non-methylated	0.45 (0.21, 0.98)	0.045	0.26 (0.08, 0.86)	0.028
Prior history of chemotherapy vs. no history of chemotherapy	1.61 (0.84, 3.11)	0.152	0.78 (0.35, 1.76)	0.557
Prior history of radiotherapy vs. no history of radiotherapy	2.67 (0.36, 19.58)	0.330	-	-
PCV group vs. PC group	2.06 (1.01, 4.18)	0.046	2.09 (1.07, 4.25)	0.023

^aMultivariable analysis was performed on the variables with P-values threshold <0.2. CI, confidence interval; IDH, isocitrate dehydrogenase 1; PC, procarbazine and lomustine; PCV, procarbazine, lomustine, and vincristine.

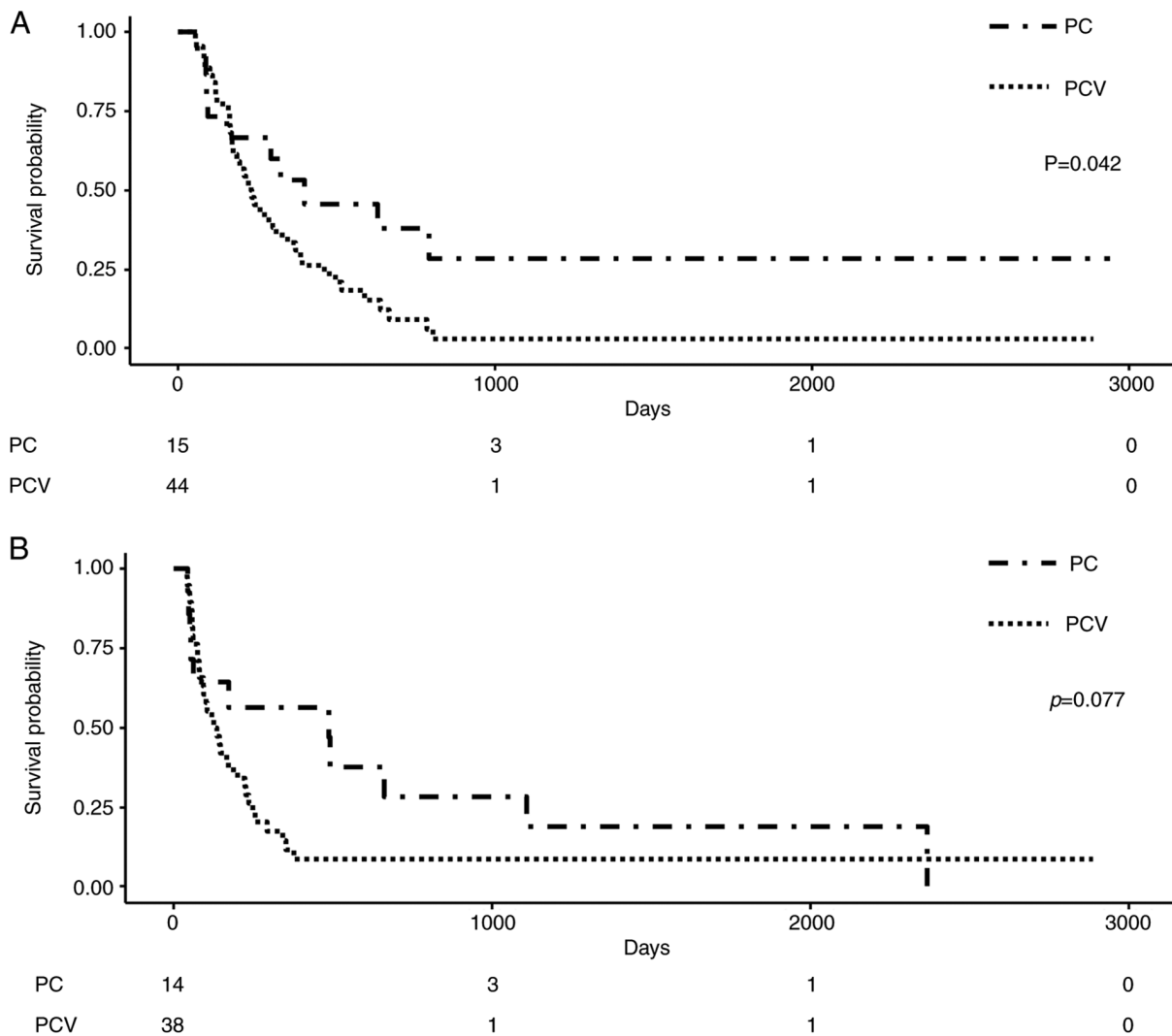


Figure 2. Kaplan-Meier survival curves. (A) Overall survival and (B) progression-free survival of the PC and PCV groups. PC, procarbazine and lomustine; PCV, procarbazine, lomustine and vincristine.

multi-disciplinary discussion, treatment characteristics could not be identical between the two groups. Fourth, due to the retrospective nature of this study, not all adverse reactions were considered. Fifth, the number of patients is insufficient to draw a strong conclusion. Therefore, further prospective and larger studies are needed to validate whether PC chemotherapy could be an alternative to PCV chemotherapy as a secondary salvage option for recurrent glioma patients.

In conclusion, this study showed significantly fewer toxicities after our modified PC chemotherapy than after PCV chemotherapy in recurrent glioma patients. The OS and PFS of the modified PC chemotherapy were noninferior to those of PCV chemotherapy. Further prospective and larger studies are needed to validate the modified PC chemotherapy without vincristine as an alternative option for the conventional PCV chemotherapy for recurrent glioma patients.

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Availability of data and materials

The datasets used and/or analyzed are available from the corresponding author on reasonable request.

Authors' contributions

SA and YIK wrote the manuscript. SA, YIK, JSP, JYS, CY, and YSL collected and analyzed the data. JSP, CY, YSL, YKH, SSJ and SHY supervised the current study. JSP, CY, YSL, YKH, SSJ and SHY wrote, reviewed and edited the manuscript. YKH, SSJ and SHY conceptualized the present study. SA, YIK, and JSP confirm the authenticity of all the raw data. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The Institutional Review Board of Seoul St. Mary's Hospital approved the current study (approval no. XC21RID10089). Due to the retrospective manner of the study, the requirement for informed consent to participate was waived.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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