Safety and Efficacy of Procarbazine and Lomustine Chemotherapy as a Salvage Treatment for Recurrent Adult Glioma

Stephen Ahn

The Catholic University of Korea

Young Il Kim

The Catholic University of Korea

Ja Young Shin

The Catholic University of Korea

Jae-Sung Park

The Catholic University of Korea

Changyoung Yoo

The Catholic University of Korea

Youn Soo Lee

The Catholic University of Korea

Yong-Kil Hong

The Catholic University of Korea

Sin-Soo Jeun

The Catholic University of Korea

Seung-Ho Yang (✉ 72ysh@catholic.ac.kr)

St. Vincent's Hospital, The Catholic University of Korea <https://orcid.org/0000-0002-3490-1064>

Research Article

Keywords: Recurrent glioma, PCV chemotherapy, procarbazine, lomustine, toxicity

Posted Date: September 9th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-878192/v1>

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Abstract

Purpose

While procarbazine, lomustine, and vincristine (PCV) chemotherapy is considered a salvage option for adult glioma, whether vincristine included in this regimen is beneficial is uncertain due to its potential toxicity and uncertain efficacy. In this study, we evaluated the safety and efficacy of PC chemotherapy in contrast with those of PCV chemotherapy.

Methods

Using electronic medical records, all patient 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 our eligibility criteria. Among them, 15 patients received PC chemotherapy (PC group) and 44 patients received PCV chemotherapy (PCV group).

Results

The PC group presented a significantly lower hematology toxicity (anemia: 6.7% vs. 45.5%; $p = 0.02$ and thrombocytopenia: 20.0% vs. 70.4%; $p < 0.001$). Also, 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 (26.7% vs. 68.2%; $p = 0.012$). The overall survival of PC group was 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 two groups (284.5 vs. 131 days; $p = 0.077$).

Conclusion

This is the first comparative study to suggest that PC chemotherapy leads to less toxicity than PCV chemotherapy without loss of clinical efficacy in patients with recurrent adult glioma. Further prospective and larger studies are needed 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]. Bevacizumab has shown significant clinical responses in some patients; however, identifying good

responders and predicting the clinical outcome in the overall population remain difficult[11, 12]. Procarbazine, lomustine, and vincristine (PCV) chemotherapy has long been trialed as one of the salvageable options for recurrent adult gliomas[13–16]. However, the toxicity of vincristine, including peripheral neurotoxicity frequently seen in neuro-oncology clinics, has been documented, resulting in its reduction or discontinuation in many outpatients[17–19]. 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[20]. In this context, a few studies recently have trialed modified procarbazine and lomustine (PC) therapy protocols for recurrent gliomas[21–24]. However, to the best of our knowledge, no study has yet compared the safety and efficacy of PC chemotherapy and PCV chemotherapy in a single study cohort.

In this study, we evaluated whether PC chemotherapy is less toxic than PCV chemotherapy and whether the survival outcomes of PC chemotherapy are noninferior to those of PCV chemotherapy in patients with recurrent adult glioma, whose data were collected retrospectively from two hospitals.

Methods

Study population

This multicenter retrospective study was approved by the Institutional Review Board of Seoul St. Mary's Hospital and St. Vincent's Hospital. The electronic medical records of adult glioma patients treated at these two hospitals between 2010 and 2020 were examined. The study inclusion criteria were (1) glioma pathologically confirmed by craniotomy or biopsy, (2) glioma recurrence confirmed radiologically and/or pathologically, (3) receipt of PC or PCV chemotherapy following recurrence diagnosis, and (4) accessible baseline clinical variables and survival data. The study exclusion criteria were (1) received PC or PCV chemotherapy as adjuvant therapy after initial diagnosis and (2) a medical history of hematologic or rheumatologic disease. A flow of the study design is presented in Fig. 1.

Treatment Protocol

After maximal safe resection at initial surgery, we performed adjuvant therapy following the best treatment protocol(s) at each institution. 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 often 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 was considered.

At St. Vincent's Hospital, patients with recurrent adult glioma received PC chemotherapy instead of PCV chemotherapy. PC chemotherapy was composed of lomustine (75mg/m², day 1) and procarbazine (60mg/m², days 11–24) administered orally every four weeks. This modified protocol was discussed in a previous study of one of our authors[21]. At Seoul St. Mary's Hospital, 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 direct sequencing. If necessary, IDH 2 mutation was evaluated by direct 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. 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 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 1.

Table 1

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

	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 (range 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 (%)			0.107
Yes	3 (20.0)	7 (15.9)	
No	10 (66.7)	18 (40.9)	
Unknown	2 (13.3)	19 (43.2)	
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 (10.0)	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
ECOG, Eastern Cooperative Oncology Group; GBM, glioblastoma; MGMT, O ⁶ -methylguanine-DNA-methyltransferase; PC, procarbazine and lomustine; PCV, procarbazine, lomustine, and vincristine; TMZ, temozolomide			

	PC group (n = 15)	PCV group (n = 44)	<i>p</i> -value
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, O ⁶ -methylguanine-DNA-methyltransferase; PC, procarbazine and lomustine; PCV, procarbazine, lomustine, and vincristine; TMZ, temozolomide			

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 2.

Table 2
Toxicity in patients with recurrent adult glioma who received PC or PCV chemotherapy

	All grades*			Grades III and IV*		
	PC group (n = 15)	PCV group (n = 44)	<i>p</i> -value	PC group (n = 15)	PCV group (n = 44)	<i>p</i> -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
<i>*Toxicities were graded according to CTCAE version 5.0</i>						

We describe the adverse impacts of toxicity on chemotherapy schedule in Table 3. 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.

Table 3
Adverse impacts of the toxicity of PC or PCV on the course of chemotherapy for recurrent adult glioma

	PC group (n = 15)	PCV group (n = 44)	<i>p</i> -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

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. We also conducted a subgroup analysis according to initial diagnosis. In the nonglioblastoma subgroup, the OS of the PC group was significantly better than that of the PCV group (514 vs. 250 days; $p = 0.037$), while there was no significant difference in PFS between the two groups (442 vs. 174 days; $p = 0.163$). In the glioblastoma subgroup, there were no significant differences in OS and PFS between the two groups (OS: 154 vs. 190 days; $p = 0.671$ and PFS: 102 vs. 87 days; $p = 0.310$). The Kaplan–Meier survival curves of OS and PFS in the two subgroups are illustrated in Supplementary Figs. 1 and 2.

Discussion

In our retrospective and comparative study between two institutions, we tried to compare not only the safety, but also the efficacy of PC chemotherapy compared to those of PCV chemotherapy using electronic medical records from tertiary hospitals in Koreans. 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 than the PC group. Peripheral neurotoxicity, which is a major concern regarding vincristine, was more frequently observed in the PCV group than the PC group (0.0% vs. 11.4%), as expected, however, there was no statistical significance ($p = 0.408$). 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 can be explained by numerous studies showing that the occurrence of less toxicity after chemotherapy correlates with better prognosis[25, 26].

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, 11, 12, 27, 28]. As a salvage therapy after TMZ for recurrent glioma, numerous clinical trials have assessed the efficacy of PCV-based chemotherapy[13, 14, 16]. 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[17, 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[20].

In this context, a few studies have put forth the idea of adopting a modified PC-based chemotherapy regimen without vincristine for glioma patients[21–24]. 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[23]. 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[22].

To the best of our knowledge, this is the first study to compare the safety and efficacy of PC and PCV chemotherapy as salvage treatment in recurrent glioma patients. In accordance with two previous studies exploring the use of PC chemotherapy in primary oligodendroglial patients[22, 23], we have added some evidence that PC chemotherapy is as beneficial as PCV chemotherapy but with significantly less toxicity due to omitting vincristine. 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, contrary to previous studies designed to compare the efficacy and safety of PC chemotherapy with those of PCV chemotherapy, our study included heterogeneous recurrent gliomas, which can better reflect real-world situations but cause bias due to the heterogeneity of the study population. 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, while the hematological toxicity is not the major concern with vincristine, but rather the peripheral neurotoxicity, our findings shows that hematological toxicities were more frequently occurred in the PCV group than the PC group and that the rates of peripheral neurotoxicity was not different statistically (0.0% vs. 11.4%, $p = 0.408$). This may be due to a smaller dose of lomustine used in the PC group than that of the PCV group (75 mg/m² vs. 110 mg/m²), which is known to be a frequent cause of hematologic toxicity. Due to these several limitations of our study, 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, our comparative study involving patients from two institutions showed that toxicities after PC chemotherapy were significantly fewer than those after PCV chemotherapy in recurrent glioma

patients. The OS and PFS of PC chemotherapy were also noninferior to those of PCV chemotherapy. Further prospective and larger studies are needed to validate whether PC chemotherapy had a better toxicity profile than that of PCV chemotherapy without loss of clinical efficacy in glioma patients.

Declarations

Conflict of Interest

Nothing to declare.

Ethics approval

The Institutional Review Board of Seoul St. Mary's Hospital approved the study design (ethical code: XC21RIDI0089).

Consent to participate

Due to the retrospective manner of the study, the requirement for informed consent to participate was waived.

Consent for publication

Due to the retrospective manner of the study, the requirement for informed consent for publication was waived.

Availability of data and material

Data available on request due to privacy/ethical restrictions.

Funding

None

Author's contribution

Stephen Ahn: Writing original draft, data collection & curation

Young Il Kim: Writing original draft, data collection & curation

Ja Young Shin: Data collection & curation

Jae-Sung Park: Writing – review & editing

Changyoung Yoo: Supervision

Youn Soo Lee: Supervision

Yong-Kil Hong: Supervision

Sin-Soo Jeun: Writing – review & editing, supervision, conceptualization

Seung Ho Yang: Writing – review & editing, supervision, conceptualization

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Figures

Figure 1

Flow of the study design.

(a)

(b)

Figure 2

(a) OS and (b) PFS of the PC and PCV groups.

Supplementary Files

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