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Lomustine with or without procarbazine in recurrent glioblastoma—A propensity score matching analysis

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Abstract

Background. Despite recent advances, survival in patients with glioblastoma remains poor. Outside clinical trials, lomustine is commonly considered standard of care in recurrent disease. However, comparative data between lomustine and other chemotherapy regimens are limited.

Methods. We performed a retrospective multicenter cohort study including patients from seven certified neuro-oncology centers in Germany to compare lomustine monotherapy with combination therapy using lomustine and procarbazine in first recurrence of glioblastoma. Propensity score matching was applied to obtain comparable groups based on sex, age, extent of resection at primary diagnosis, Karnofsky performance status at the start of recurrence therapy, and MGMT promoter methylation status. Post-recurrence survival (PRS) and progression-free survival (PFS) were analyzed using Kaplan-Meier estimation and multivariable Cox regression analysis.

Results. Seventy-seven patients were matched in each treatment group. PRS was comparable, with a median of 11.6 months for lomustine monotherapy and 10.0 months for lomustine plus procarbazine (log-rank test, $P=.120$). Multivariable Cox regression showed no significant difference (HR 1.33, 95% CI, 0.93-1.90, $P=.123$). PFS was shorter in patients receiving combination therapy compared to monotherapy (3.7 vs. 5.1 months, log-rank test, $P=.042$). Multivariable Cox regression did not reveal significant differences (HR 1.31, 95% CI, 0.90-1.90, $P=.166$).

Conclusions. Our data indicates that potential additive toxicity by intensified combination chemotherapy should be avoided due to lack of efficacy compared to lomustine monotherapy.

Key Points

- Optimal treatment in first recurrence of glioblastoma remains unclear.
- Lomustine plus procarbazine does not improve survival compared to lomustine monotherapy.
- The results argue against use of intensified combination therapy in this situation.

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Importance of the Study

Lomustine is commonly used as chemotherapy in recurrent glioblastoma. However, comparative evidence against other classic chemotherapeutic regimens is scarce. In this multicenter propensity score-matched cohort study including patients from seven certified neuro-oncology centers, we show that combination therapy with lomustine plus procarbazine is not superior to lomustine monotherapy in terms of post-recurrence survival or progression-free survival. These findings provide real-world evidence against treatment intensification and support lomustine monotherapy as the preferred standard of care for recurrent glioblastoma if clinical trials are not suitable or available.

Glioblastoma, isocitrate-dehydrogenase (IDH) wildtype (CNS WHO Grade 4), is the most common primary malignant brain tumor in adults. It is marked by aggressive growth and poor prognosis.[1] The incidence is around 3.3 cases per 100,000 individuals.[1] Median overall survival (OS) with the current standard of care, consisting of resection followed by concomitant radiochemotherapy with temozolomide and adjuvant chemotherapy with temozolomide is 14.6 months.[2] Even in more recent studies with highly selected patient populations and despite progress in surgical resection techniques and the introduction of novel approaches such as tumor-treating fields and targeted therapies, the median OS for glioblastoma patients remains limited, at approximately 20.9 months.[3]

Apart from clinical trials, standard first-line therapy usually consists of maximum safe resection, radiotherapy with concomitant temozolomide and 6 cycles of adjuvant temozolomide.[2] National and international guidelines recommend adjustments dependent on age, general medical condition of patients, and O6-methylguanine-DNA methyltransferase (MGMT) promoter methylation.[4,5] The optimal systemic treatment option in recurrent glioblastoma (rGB) remains unclear. Options include temozolomide rechallenge,[6,7] alternative alkylating chemotherapy, bevacizumab, or inclusion in a clinical trial.[4,5] However, an interventional trial is not always available. Bevacizumab is not approved for use in many countries and showed no improvement of OS.[8]

Lomustine is an alkylating agent that leads to crosslinking of DNA and RNA, induces apoptosis/necrosis and is able to cross the blood-brain barrier.[9,10] It has been used in rGB for many years,[11] is accepted as standard of care in rGB in many centers, and has been used as standard arm in many clinical trials.[12] Usually, the progression-free survival (PFS) of lomustine in the recurrent setting was around 2 months, the rate of PFS at 6 months was around 20% and the post recurrence survival (PRS) was approximately 6-9 months after randomization.[12] In lower-grade gliomas and oligodendrogliomas, lomustine was commonly combined with procarbazine and vincristine (PCV)[13-15] and invented the treatment standard in this combination. However, in recurrent high-grade glioma, PCV showed a similar effect on outcome as temozolomide.[16] Due to its high risk of polyneuropathy and its inability to cross the blood-brain barrier, vincristine is often omitted from therapy plans (PC regimen).[17,18] In a phase II study from 2000, temozolomide showed better OS and PFS compared to procarbazine in rGB.[19] However, temozolomide vs. PC or lomustine vs. PC were never directly compared in a prospective randomized setting in glioblastoma.

In summary, there is no clear standard of care treatment in most rGB[4] and treatment plans differ across neuro-oncology centers. So far, no clinical trial has been conducted to compare lomustine monotherapy with PC. We therefore performed a multicenter cohort study in patients with recurrent glioblastoma that were treated either with lomustine or with PC and implemented a propensity score matching analysis to account for possible imbalances.

Methods

Study Cohort

We designed this study as a retrospective multicenter cohort study with propensity score matching. Data were collected from 7 German certified neuro-oncology centers as part of a study investigating targeted therapy recommendations issued by molecular tumor boards (MTB). The participating centers were asked to include all patients with a diagnosis of recurrent glioblastoma, IDH wildtype (CNS WHO grade 4)[20] who were discussed in MTB. In addition, centers were asked to report patients with rGB treated with conventional alkylating chemotherapy (eg, temozolomide rechallenge, lomustine, or PC), irrespective of MTB discussion, to establish a control cohort for comparison with patients receiving targeted therapies as part of the overarching MTB study. From the whole patient cohort provided by these centers, we identified individuals who received either lomustine monotherapy (d 1/42) or a combination therapy of PC (lomustine day 1/42, procarbazine d 8-21/42).

At the Regensburg Neuro-Oncology Center, combination alkylating chemotherapy has historically been used based on its established role in the treatment of lower-grade gliomas.[13-15] However, the PC regimen is preferred over PCV because vincristine has limited penetration through the blood-brain barrier[17] and is associated with a well-recognized risk of peripheral neuropathy.[18]

The participating centers were the University Hospitals of Regensburg, Essen, Bonn, Mannheim and Frankfurt am Main, Technical University of Munich and Charité-Universitätsmedizin Berlin.

Before we started data collection, approval was obtained from the local ethics committee of the University of Regensburg (Ethics vote: 23-3342-101). We obtained informed consent for data use from all patients that were still alive. After

data collection, the data were subjected to a pseudonymization process and securely stored locally in compliance with European Union and local data protection regulations.

Data Acquisition

We collected baseline data for all known prognostic factors and outcome data, including age at diagnosis, sex, extent of resection, Karnofsky Performance Status (KPS), MGMT promoter methylation status, dates of recurrence, and date of death or last follow-up.

Information on sequencing of brain tumor tissue and corresponding MTB recommendations, when available, was also obtained. For each recurrence, we recorded systemic therapy and KPS at the start of recurrence treatment. Although the best response was prespecified as an outcome, reporting across centers was heterogeneous, precluding a standardized analysis.

Endpoints

The clinical endpoints of interest were OS, PRS, and PFS. OS was defined as the time from diagnosis to death. PRS was defined as the time from the date of recurrence to death. PFS was defined as the time from that same recurrence date to the next documented recurrence or death, whichever occurred first. PFS1 was defined as the time from diagnosis to first recurrence. Progression was assessed according to the Response Assessment in Neuro-Oncology (RANO) criteria[21] and determined during interdisciplinary neuro-oncology tumor board conferences.

To ensure consistent follow-up, survival status and disease recurrence information were updated across all centers as of March 1, 2025. Patients who were alive on that date were censored at the time of their most recent follow-up.

Propensity Score Matching

We performed propensity score matching to reduce possible confounding. First, we identified all patients that received one of the two relevant treatment regimes, lomustine monotherapy or PC combination therapy at first recurrence of glioblastoma.

Next, propensity scores were estimated using logistic regression, with treatment group as the dependent variable. We included the following possible confounders as predictors: sex, age, extent of resection at primary diagnosis (biopsy, partial resection, complete resection), KPS at the start of recurrence therapy, MGMT promoter methylation status. Nearest-neighbor matching without replacement was applied using a caliper of 0.2 on the propensity score scale to ensure acceptable distances between matched pairs. Balance before and after matching was assessed using standardized mean differences (SMD). Different propensity score specifications and matching strategies were evaluated. The chosen nearest-neighbor matching approach provided the most favorable covariate balance (lowest SMDs) compared with alternative matching methods.

Statistical Analysis

The creation of database and calculation of individual survival times was performed with IBM SPSS Statistics (version 29). We conducted statistical analyses using RStudio (R 4.3.0). Propensity score matching and related procedures were performed using the MatchIt package. Patients with a KPS ≤60 (patients that require frequent assistance) were combined into a single analytical group.

Frequencies of categorical variables were calculated, and associations were assessed using the chi-square test. Survival outcomes were evaluated using Kaplan-Meier analyses with log-rank tests and univariable Cox regression analyses. We implemented robust standard errors in our Cox regression models to account for the matched design.

We also performed adjusted Cox regression analyses on the matched dataset, including variables with SMDs >0.1 into our model to adjust for potential residual confounding despite matching. We also used a model including all the potential confounders used for matching, MTB status, and PFS1. We used the same variables for an adjusted multivariable Cox regression analysis in the unmatched entire cohort.

The significance level was set to $P<.05$ (two-sided), and 95%-confidence intervals (CI) of Hazard ratios (HR) and survival times are reported.

Results

Baseline Characteristics

We identified a total of 300 patients that received the therapy of interest in recurrent disease. From these, 167 patients (55.7%) received lomustine monotherapy and 133 (44.3%) received combination therapy with PC.

Taking into account only the first recurrence, we identified 193 patients, from whom 108 patients were treated with lomustine and 85 patients received PC combination therapy (Supplement 1). Fifty-nine (30.6%) of these patients were female, and the majority of patients showed no MGMT promoter methylation before matching (139 patients, 73.5%) (Table 1). There were imbalances between the treatment groups with regard to age (SMD 0.379, $P=.011$). Differences of MGMT promoter methylation (SMD 0.190) and KPS (SMD 0.305) were not statistically significant (Table 1).

After propensity score matching, 39 patients were excluded. The imbalances between the treatment groups were improved by matching (Figure 1). SMDs improved to 0.027 for age, 0.060 for MGMT promotor methylation, and 0.221 for KPS (Table 2).

All of the 77 matched patients with PC combination therapy were recruited at the certified neurooncology unit in Regensburg. For the lomustine monotherapy group, patients were recruited at the following centers: 9 (11.7%) Regensburg, 4 (5.2%) Berlin, 25 (32.5%) Munich, 9 (11.7%) Bonn, 20 (26.0%) Essen, 10 (13.0%) Frankfurt. No patient from Mannheim was included in the final analysis (Supplement 2).

Table 1. Baseline characteristics before matching

		Treatment				*P*-value	SMD
		Lomustine monotherapy (*n*=108)		Lomustine+Procarbazine (*n*=85)			
		Mean	SD	Mean	SD		
Age (years)		54.9	11.3	58.8	8.9	.011	0.379
		n	%	n	%		
Sex	Male	76	70.4	58	68.2	.871	0.046
	Female	32	29.6	27	31.8		
Extent of	Complete	67	63.8	50	60.2	.926	0.099
resection	Partial	26	24.8	21	25.3		
	Biopsy	12	11.4	12	14.5		
	Unknown	3	2.8	2	2.4		
KPS*	100	13	12.0	4	4.7	.519	0.305
	90	30	27.8	26	30.6		
	80	26	24.1	22	25.9		
	70	24	22.2	17	20.0		
	<=60	7	6.5	9	10.6		
	No data	8	7.4	7	8.2		
MGMT	Yes	30	28.8	18	21.2	.483	0.178
Promotor	No	73	70.2	66	77.6		
Methylation	Unknown	1	1.0	1	1.2		

*KPS before start of recurrence treatment.
Abbreviations: KPS—Karnofsky Performance Status, MGMT—O6-methylguanine-DNA methyltransferase, SMD—Standardized Mean Differences.

Survival Analysis in Patients With First Recurrence

Within the observation period, 125 out of 154 patients of the matched cohort died (81.1%). The matched cohort showed a median OS of 19.4 months (95% CI, 17.6-23.0) after time of diagnosis.

Median PFS1 was 7.9 months (95% CI, 7.0-9.3) in patients with lomustine monotherapy and 7.4 months (95% CI, 7.0-8.5) in patients with PC combination therapy (log-rank test, *P*=.657) (Supplement 3).

Patients treated with lomustine monotherapy showed no significantly different PRS than patients that received PC (HR 1.33, 95% CI, 0.93-1.90, *P*=.123) with 11.6 months (95% CI, 9.5-16.1) compared to 10.0 months (95% CI, 8.5-12.2) (log-rank test, *P*=.120) (Figure 2). Survival rates after recurrence were 40.3% vs 29.9% after one year (*P*=.237) and 13.0% vs. 9.1% after 2 years (*P*=.608), respectively.

PFS in patients with PC was significantly worse than in patients treated with lomustine monotherapy (HR 1.45, 95% CI, 1.02-2.06, *P*=.038) with 3.7 months (95% CI, 3.4-4.7) compared to 5.1 months (95% CI, 3.9-6.4) (log-rank test, *P*=.042) (Figure 3). PFS rates at 6 months were 33.8% in the lomustine group and 16.9% in the PC group (*P*=.025). At 12 months, PFS rates were 13.0% vs. 5.7%, respectively (*P*=.159).

In order to exclude residual confounding despite matching, we also performed a multivariable Cox regression analysis with inclusion of KPS (SMD after matching >0.1). This did not substantially change the results for PRS (HR 1.26, 95% CI, 0.87-1.81, *P*=.223). For PFS, the negative effect of PC was not statistically significant anymore (HR 1.31, 95% CI, 0.90-1.90, *P*=.166).

We also used a model for multivariable Cox regression with inclusion of all matching variables, MTB status, and PFS1. The results for the therapy groups were similar to the unadjusted model (Table 3).

Any Recurrence

In another exploratory analysis, we used the entire cohort without matching. The cohort also included patients that received lomustine or PC at second, third, or fourth recurrence (Supplement 4). Overall, patients with lomustine monotherapy showed a better median PRS than patients with PC with 11.3 months (95% CI, 9.8-12.6) compared to 8.8 months (95% CI, 8.1-10.3) (log-rank test, *P*<.001) (Supplement 5). PC was associated with worse PRS in multivariable Cox regression (HR 1.58, 95% CI, 1.20-2.09, *P*=.001). Survival rates were higher in the lomustine group with 40.7% vs. 25.6% after 1 year (*P*=.007) and 14.4% vs. 6.8% after 2 years (*P*=.041).

Furthermore, there was also a better median PFS with 5.1 months (95% CI, 4.0-6.2) in patients with lomustine monotherapy compared to 3.7 months (95% CI, 3.5-4.6) in patients with PC (*P*=.004) (Supplement 6). Adjusted Cox regression also showed worse PFS after treatment with PC (HR 1.46, 95% CI. 1.11-1.92, *P*=.006). Six-month-PFS rates were higher in patients with lomustine monotherapy with 37.1% vs. 24.8% in patients who received PC (*P*=.025). This was also observed for 12 months PFS rates (15.6% vs. 6.8%, *P*=.019).

Finally, we evaluated if the difference in PRS was dependent on MGMT promoter methylation status. Indeed, better PRS in patients with lomustine monotherapy compared to

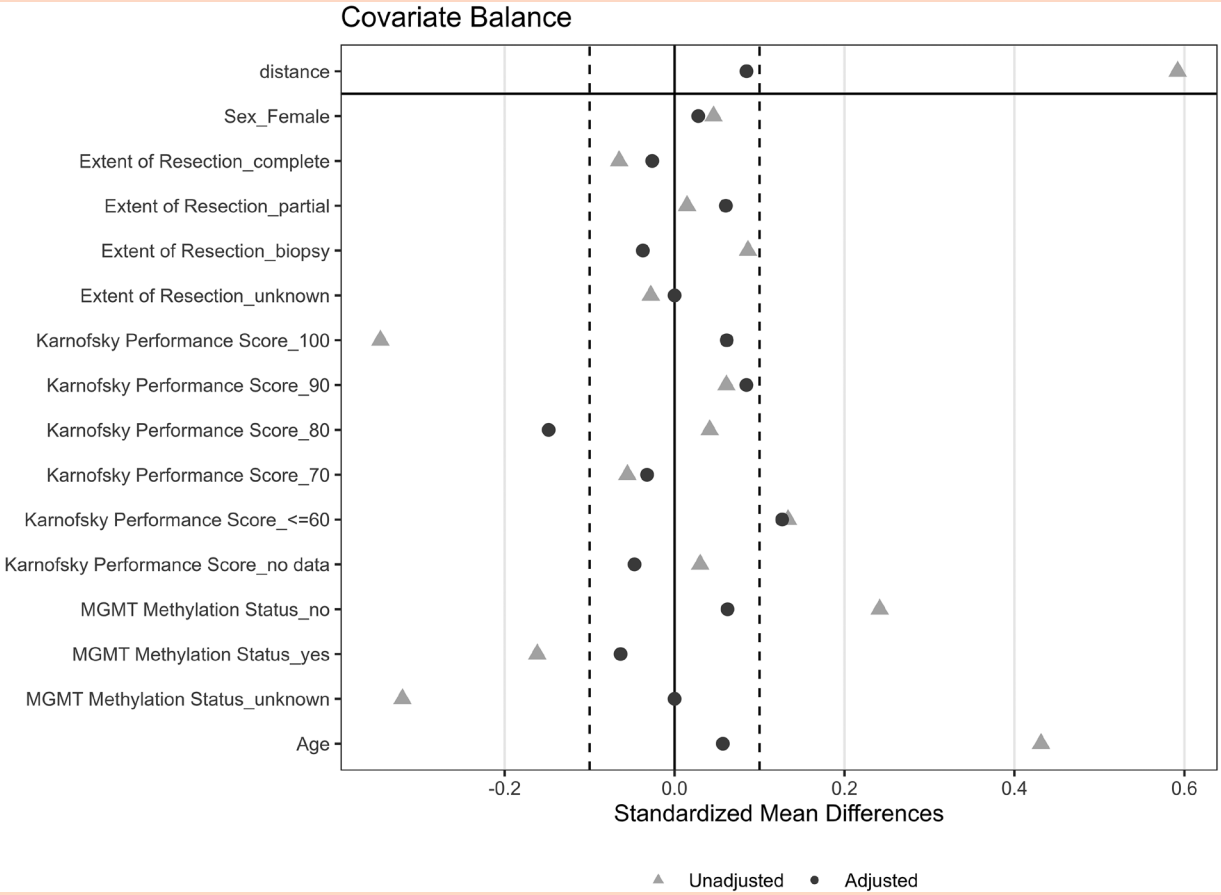

Figure 1. Standardized Mean Differences (SMD) of possible confounders before and after propensity score matching.

Table 2. Patient and tumor characteristics by therapy group after matching

		Treatment				*P*-value	SMD
		Lomustine monotherapy (*n*=77)		Lomustine+Procarbazine (*n*=77)			
		Mean	SD	Mean	SD		
Age (years)		57.3	10.2	58.1	8.9	.589	0.088
		n	%	n	%		
Sex	Male	51	66.2	50	64.9	1.00	0.027
	Female	26	33.8	27	35.1		
Extent of	Complete	47	61.0	46	59.7	.982	0.066
resection	Partial	18	23.4	20	26.0		
	Biopsy	10	13.0	9	11.7		
KPS*	100	3	3.9	4	5.2	.868	0.221
	90	23	29.9	26	33.8		
	80	23	29.9	26	33.8		
	70	17	22.1	16	20.8		
	<=60	4	5.2	7	9.1		
	No data	7	9.1	6	7.8		
MGMT	Yes	20	26.0	18	23.4	.932	0.060
promotor	No	56	72.7	58	75.3		
methylation	Unknown	1	1.3	1	1.3		

*KPS before start of recurrence treatment.
Abbreviations: KPS—Karnofsky Performance Status, MGMT—O6-methylguanine-DNA methyltransferase, SMD—Standardized Mean Differences.

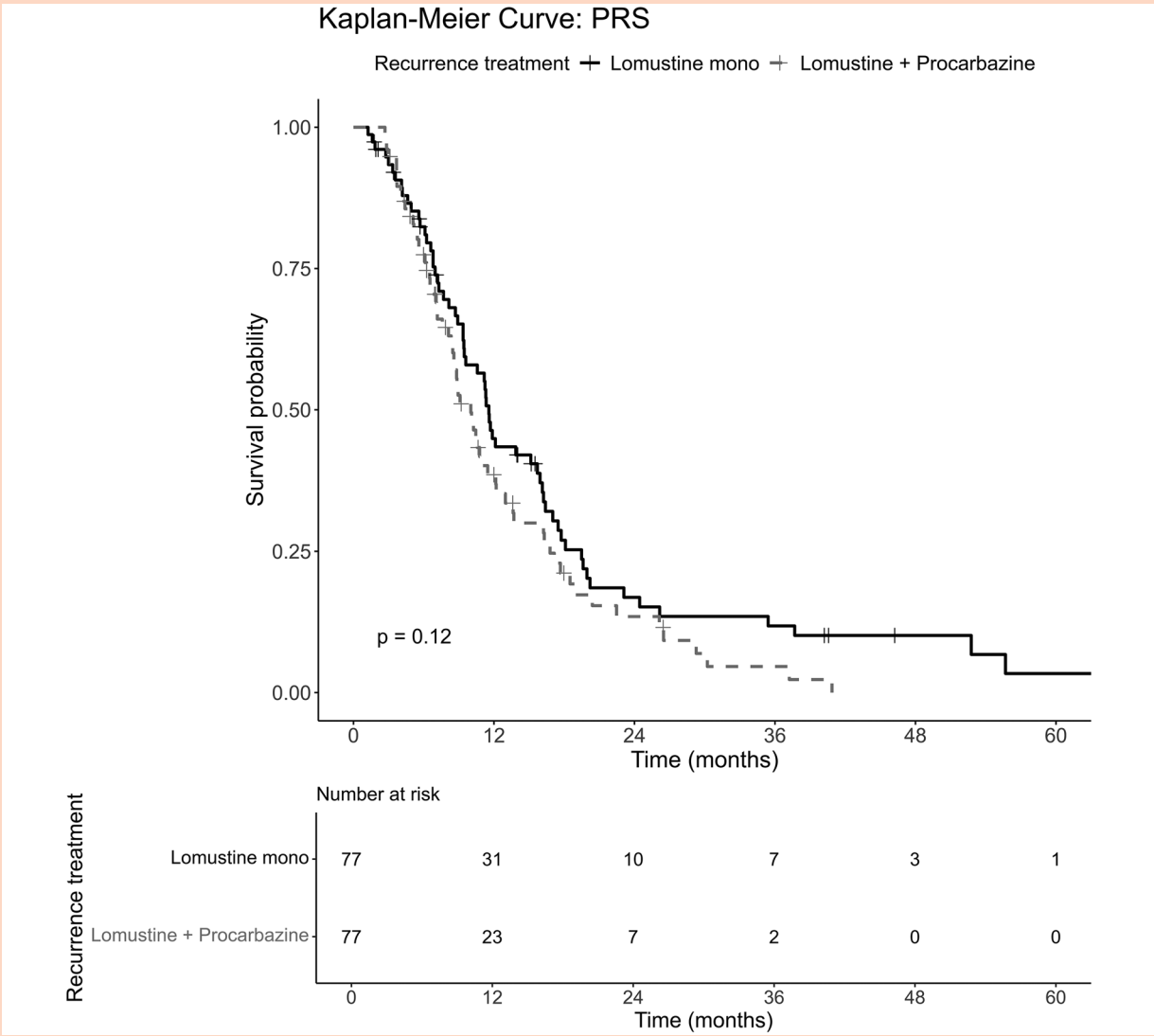

Figure 2. Kaplan Meier curves of post recurrence survival (PRS) after first recurrence of glioblastoma in patients who received Lomustine monotherapy compared to Lomustine plus procarbazine combination therapy. There was no significant difference between both treatment arms.

PC combination therapy was more prevalent in patients with methylated tumors (Supplement 7).

Discussion

In this propensity score-matched study, we compared outcome of patients with recurrent glioblastoma who received either lomustine monotherapy or combination therapy with PC. Overall, in first recurrence, patients with combination therapy showed not significantly different PRS in comparison to patients with lomustine monotherapy. Surprisingly, median PFS was worse in patients with combination therapy.

OS in our study was 19.4 months, which is comparable to reported outcomes of large treatment studies.[3] However, our analysis was performed in a highly selected cohort, which limits the generalizability of our findings. Patients had to survive long enough and maintain a sufficient KPS to receive treatment at recurrence, which introduces immortal time bias. This is assumably not distinctive since it occurs in both treatment arms. Furthermore, a substantial proportion of patients were recruited as part of an overarching study that focused on MTBs, likely enriching the cohort for fitter patients with characteristics similar to those of patients enrolled in clinical trials. Although these factors probably contributed to the survival outcomes observed, they were present in both treatment groups.

Lomustine in rGB usually shows poor median survival after randomization of around 6-9 months.[12] Median PFS is reported to be around 2 months, which usually reflects the interval between treatment initiation and first follow-up. Six-month PFS rates are approximately 20% in most studies.[12] One small single-arm trial with 8 patients investigated treatment with PC in rGB and similarly showed median PFS of 8 weeks and survival from the start of PC therapy of 9.7 months.[22]

In our matched cohort, patients treated with lomustine monotherapy or PC combination therapy showed a longer PRS with 11.6 months and 10.0 months, respectively. The median PFS of 5.1 months and 3.7 months, respectively, was also higher than commonly reported. However, 6-month

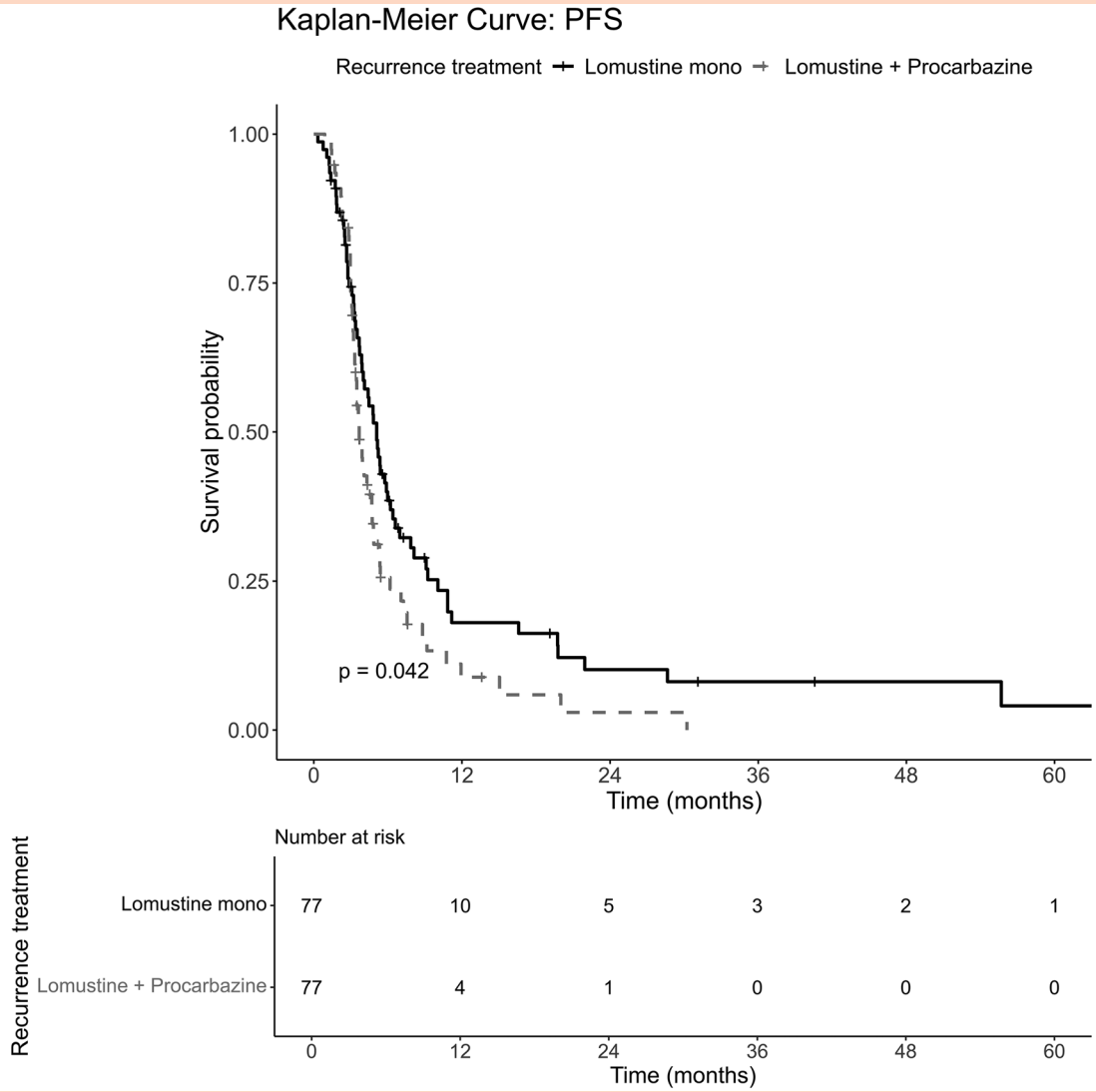

Figure 3. Kaplan Meier curves of progression free survival (PFS) after first recurrence of glioblastoma in patients who received Lomustine monotherapy compared to Lomustine plus procarbazine combination therapy. PFS was better in patients that received monotherapy.

PFS rates with 33.8% were only improved in patients treated with lomustine monotherapy, whereas rates of 16.9% in patients treated with combination therapy were comparable to published data.[12]

It remains unclear why we observed worse PFS for patients that were treated with combination therapy. This finding cannot be explained by differences in the disease course prior to treatment initiation in rGB, as PFS1 was comparable between both treatment groups and was not independently associated with either PRS or PFS. It is well known that combination therapies may be associated with a higher risk of chemotherapy-related toxicity.[8,23] Also in this study, increased toxicity may have led to more frequent dose reductions, treatment delays, or premature discontinuation of therapy. However, myelotoxicity was not associated with worse outcomes of first-line treatment.[24] A recent meta-analysis did not show significant differences with regard to PFS, response rates, or OS between different combination therapies and monotherapies, whereas some combination therapies showed higher rates of toxicity.[25]

A major limitation of the present study is the lack of detailed data on treatment exposure, including the number of administered chemotherapy cycles, toxicity, treatment interruptions, and reasons for treatment discontinuation. This missing data precludes conclusions regarding the mechanisms underlying our findings. For example, the observed difference may be explained by higher rates of treatment discontinuation due to increased toxicity, but this hypothesis could not be evaluated in the present analysis.

Our study also has some additional limitations. First, this is a retrospective study, which leads to potential confounding. We therefore performed propensity score matching to minimize imbalances between the two treatment groups. Recruitment in our study was also prone to selection bias, as many patients were identified as possible candidates for MTB. However, this applied for both treatment groups, and consequently, inclusion of MTB status in a multivariable model did not change the results. Another limitation is that all patients receiving combination therapy with PC were treated at a single neuro-oncology center, whereas all

Table 3. Results from multivariable Cox regression analyses on post recurrence survival (PRS) and progression free survival (PFS) by therapy and risk factors

	Hazard ratio (95% CI)	*P*-value
Cox regression—Post recurrence survival		
PC vs. Lomustine	1.40 (0.91-2.15)	.126
Sex—Female vs. Male	0.42 (0.26-0.67)	<.001
EOR—partial vs. complete	0.94 (0.55-1.60)	.808
EOR—biopsy vs. complete	0.93 (0.51-1.69)	.804
EOR—unknown vs. complete	1.60 (0.80-3.18)	.182
Age at diagnosis	1.03 (1.01-1.05)	.005
KPS 90 vs. 100	1.86 (0.98-3.55)	.059
KPS 80 vs. 100	2.59 (1.31-5.14)	.006
KPS 70 vs. 100	3.74 (2.05-6.80)	<.001
KPS <=60 vs. 100	22.49 (9.15-55.25)	<.001
KPS—no data vs. 100	1.51 (0.51-4.53)	.459
MGMT promotor methylation—yes vs. no	0.49 (0.29-0.85)	.011
MGMT promotor methylation—unknown vs. no	0.24 (0.14-0.40)	<.001
PFS1	1.02 (0.98-1.06)	.334
MTB discussion yes vs. no	0.79 (0.52-1.22)	.292
Cox regression—Progression free survival		
PC vs. Lomustine	1.34 (0.89-2.03)	.160
Sex—Female vs. Male	0.53 (0.35-0.79)	.002
EOR—partial vs. complete	0.92 (0.49-1.72)	.786
EOR—biopsy vs. complete	1.32 (0.74-2.36)	.351
EOR—unknown vs. complete	1.47 (0.68-3.17)	.321
Age at diagnosis	1.02 (0.99-1.05)	.164
KPS 90 vs. 100	1.25 (0.39-3.97)	.706
KPS 80 vs. 100	1.27 (0.38-4.21)	.693
KPS 70 vs. 100	2.05 (0.66-6.33)	.214
KPS <=60 vs. 100	6.40 (1.86-22.03)	.003
KPS—no data vs. 100	1.06 (0.26-4.35)	.930
MGMT promotor methylation—yes vs. no	0.72 (0.43-1.21)	.211
MGMT promotor methylation—unknown vs. no	0.26 (0.15-0.47)	<.001
PFS1	1.00 (0.97-1.04)	.810
MTB discussion yes vs. no	0.91 (0.59-1.41)	.667

Abbreviations: EOR—extent of resection, KPS—Karnofsky Performance Status, MGMT—O6-methylguanine-DNA methyltransferase, MTB—molecular tumor board, PC—lomustine plus procarbazine, PFS1- time from diagnosis to first recurrence.

centers provided data on patients with lomustine monotherapy. Consequently, we cannot exclude the presence of center-specific or structural differences that may not be fully captured by the recorded confounding variables. Nevertheless, the consistent results across multiple analyses argue against a relevant impact of such center-specific effects on the main findings. Interpretation of our findings is also limited by the lack of detailed information on first-line treatment, including prior exposure to bevacizumab or other nonstandard therapies, which may have influenced outcomes. As our primary analysis focused on first recurrence, we expect that the majority of patients received standard first-line therapy according to current practice. However, this assumption cannot be verified with the available data. Furthermore, the retrospective assessment of progression represents an additional source of bias. Although progression was determined according to the RANO criteria[21] in interdisciplinary neuro-oncology tumor board conferences and MRI follow-up was usually performed every 2-3 months,[4] the latter was not mandatory. Consequently, variability in follow-up intervals may have affected the estimation of PFS.

This study has several important strengths. It is a large, multicenter retrospective cohort study including 300 patients with glioblastoma. The main analysis was conducted in 77 patients per treatment arm. Although the retrospective design is a limitation, we applied propensity score matching using the most relevant prognostic factors, resulting in well-balanced baseline characteristics with a distribution that is comparable to that in a randomized clinical trial. Of note, Lomustine monotherapy is the standard treatment for rGB in many neuro-oncology centers. However, as PC bears higher hematological side effects and comes along with dietary restrictions and prolonged phases of antiemetic intake, which also increases side effects, a practice change in the minority of centers will also generate benefit. Our study provides real-world evidence that PC does not improve outcomes and may even be associated with inferior survival. We therefore believe that our data indicate that intensified combination

chemotherapy should be avoided due to lack of efficacy compared to lomustine monotherapy. Our findings therefore remain clinically relevant, as they discourage the use of combination alkylating chemotherapy in this setting and support the continued use of lomustine monotherapy.

In summary, to our knowledge, this is the first study to directly compare lomustine monotherapy with combination therapy consisting of PC in first recurrent glioblastoma. Our results demonstrate no benefit of combination therapy over monotherapy, with some subanalyses even suggesting inferior outcomes in patients receiving combination therapy. Therefore, apart from clinical trials, lomustine monotherapy should be preferred over combination therapy with PC.

Supplementary Material

Supplementary material is available online at *Neuro-Oncology Advances* (https://academic.oup.com/noa).

Keywords

chemotherapy | glioblastoma | lomustine | procarbazine | recurrence

Author Contributions

Study concept and design: Tareq Haedenkamp, Anna Fischl, and Peter Hau. Data collection: all authors. Statistics and data interpretation: Tareq Haedenkamp and Peter Hau. Literature search and writing of the manuscript: Tareq Haedenkamp and Peter Hau. Creation of figures and tables: Tareq Haedenkamp. All authors reviewed and approved the final version of the manuscript.

Conflict of Interest Statement

J. Steinbach has received honoraria for presentations, educational events and advisory board participation from GSK, Boehringer Ingelheim, Roche, Novocure, Seagen, Servier and Med-Update. Martin Glas reports honoraria from Roche, Novartis, UCB, AbbVie, Daiichi Sankyo, Novocure, CeTeG, CeGaT, Noxon, Bayer, Janssen-Cilag, Medac, Merck, and Kyowa Kirin; travel support from Novocure and Medac; and a research grant from Novocure. All other authors declare that they have no conflicts of interest.

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Ethics Approval Statement

Approval was obtained from the local ethics committee of the University of Regensburg (Ethics vote: 23-3342-101).

Data Availability

Anonymized data underlying the results of this study, as well as the SPSS and R code used for the analyses, can be obtained from the corresponding author upon reasonable request, in accordance with institutional approval and applicable data use agreements.

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