Lung toxicity of lomustine in the treatment of progressive gliomas

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Abstract
Background. Pulmonary fibrosis is a rare, but dangerous side effect of CCNU (lomustine). CCNU is a frequently used chemotherapeutic agent in the setting of recurrent or progressive glioblastoma. At present, CCNU is also administered in patients with newly diagnosed gliomas in combination with temozolomide. There is only little evidence if, and how, lung function should be monitored on treatment with CCNU.

Methods. We retrospectively collected data on patient characteristics, lung function analyses, and relevant toxicities among 166 brain tumor patients treated with CCNU at a German University Hospital and National Cancer Center.

Results. The patient collective mainly included patients with recurrent glioblastoma who received a mean number of 2.64 ± 1.57 cycles. There was overall no statistically significant change in parameters of pulmonary restriction among patients treated with CCNU. On an individual patient basis, a >10% decrease in the absolute vital capacity was primarily seen in patients with prior lung diseases and smokers. Other severe toxicities mainly included thrombocytopenia, leukopenia, nausea, and vomiting.

Conclusions. Our findings support to limit lung function analyses on CCNU to patients with gliomas and pulmonary risk factors. However, all patients should be closely followed for clinical symptoms of pulmonary restriction.

Key Points
- We analyzed serial lung function analyses in glioma patients treated with CCNU.
- The risk of pulmonary function decrease is generally dispensable in these patients.
- Regular lung function analysis should be restricted to pulmonary at-risk patients.

Diffuse gliomas are the most common primary brain tumors in adults.¹ They can be subdivided into different CNS (Central Nervous System) WHO (World Health Organization) grades and according to the presence versus absence of an IDH (isocitrate dehydrogenase) mutation.² IDH-mutated oligodendrogliomas (CNS WHO grades 2 and 3) and astrocytomas (CNS WHO grades 2–4) share a better prognosis as compared to IDH-wildtype gliomas including glioblastoma (CNS WHO grade 4), H3.3 G34-mutant diffuse hemispheric gliomas (CNS WHO grade 4), and H3 K27M-altered diffuse midline gliomas (CNS WHO grade 4).²

The standard of care for gliomas includes maximal safe surgical resection or biopsy followed by radio- and/or chemotherapy.³⁴ There are only few chemotherapeutic agents in the treatment of gliomas, as many substances are not sufficiently able to cross the blood–brain barrier. Whereas temozolomide is mostly used in the primary setting of glioblastoma,⁵ CCNU (chloroethyl-cyclohexyl-nitrosourea or equally called lomustine) is frequently used in the primary therapy of lower grade oligodendrogliomas and astrocytomas,⁶⁻⁸ and in recurrent glioblastomas.⁹ Furthermore, the addition of CCNU to radiochemotherapy with temozolomide may prolong survival.
Importance of the Study

CCNU is one of the standard therapies available for patients with recurrent glioblastoma and used with increasing frequency also for patients with newly diagnosed glioblastoma and hypermethylated MGMT promoter. While CCNU is widely used, there is uncertainty amongst therapists about the meaningfulness of repetitive lung function analyses for early detection of lung fibrosis—a rare but serious side effect of CCNU. As the first to analyze data on sequential lung function analyses in this patient collective, we aim to provide a guide in the pulmonary surveillance of patients treated with CCNU. Ultimately, we present evidence that there is a rationale for repeated pulmonary function testing only for patients at risk with prior lung diseases or other concurrent diseases. We do not see the necessity for repetitive pulmonary testing in patients that do not fulfill these criteria.

Lung Function Analyses

Lung function was measured by spirometry at the Department of ENT (Ear-Nose-Throat) at the University Hospital Heidelberg. Vital capacity (VC), forced vital capacity (FVC), and forced expiratory volume (FEV1) was measured in liters and additionally given in %-of normal before the start of CCNU treatment and before cycles 3 and 5, where available.

Assessment of Toxicities

Data on severe toxicities (grade 4) according to the Common Terminology Criteria for Adverse Events (CTCAE) were derived from database review.

Statistical Analyses

GraphPad Prism version 9.3.1 was used for all statistical analyses. Since the same cohort of patients were tested repetitively, we assumed dependent data and consequently applied paired calculations. Here, all the values that were only tested at 1 time point, but not at the other, are eliminated, that is, the sample size is reduced accordingly. Statistical significance was assessed by the 2-sided Student’s t-test for normally distributed data. Otherwise a Wilcoxon matched-pairs signed rank test was used for nonnormal distributions which was the case for the majority of data. All available data were depicted as column bar graphs with mean + SD. The level of significance was set at P < .05.

Results

Our cohort consisted of 166 patients treated with CCNU at the University Hospital Heidelberg. Most patients in our cohort were treated for glioblastoma (70.48%) and received CCNU in combination with etoposide (96.34%). Mean age of patients at the time of their lung function analysis was 54.56 ± 12.90 years. A KPS above 70% was present in 69.28% of patients and 64.46% of patients were men. Most patients (90.96%) were non-smoker and 63.86% of patients took steroids.

Materials and Methods

Patient Cohort

The patient cohort consisted of brain tumor patients treated with CCNU at the University Hospital and National Cancer Center Heidelberg, Germany. Patients were included if they were treated with CCNU in the time between 01.03.2014 and 01.08.2020 and if they had at least 1 lung function analysis. Data on sex, age, tumor histology, IDH-mutational status, MGMT promoter methylation status, number of recurrences, CCNU regimen, dexamethasone treatment, Karnofsky Performance Status (KPS), concurrent diseases, and smoking status were retrieved from database review. The appropriate institutional review board approved the project. Informed consent was not necessary as all data were anonymized and retrospectively collected from routine patient data.
The number of recurrences was as follows: 36.75% (first recurrence), 27.10% (second recurrence), 22.29% (third recurrence), 9.64% (fourth recurrence), and 4.22% (fifth recurrence). The MGMT promoter was hypermethylated in 43.37% of patients, not hypermethylated in 31.33% and unknown in 25.30%. IDH showed a wildtype status in 54.22% of patients, 33.73% of patients were IDH-mutant and 12.05% had an unknown IDH-mutational status (Table 1). The mean number of CCNU cycles was 2.64 ± 1.57.

Seventy-two patients received more than 1 pulmonary function test. There was no significant change of the mean VC in liters or %-of normal at baseline, after 2 cycles and after 4 cycles of CCNU. Correspondingly, the mean FVC in liters or %-of normal remained stable at the 3 respective time points. Whereas mean FEV1 in liters was not materially changed from baseline after 2 cycles and after 4 cycles of CCNU, mean FEV1 in %-of normal decreased slightly with 89.44 ± 23.08 at baseline, 84.85 ± 22.50 after 2 cycles and 81.00 ± 22.88 after 4 cycles. Mean FEV1/VC

Table 1. Patient characteristics

| Variable                      | Characteristic                                                                 | Frequency (N = 166) | Percentage |
|-------------------------------|-------------------------------------------------------------------------------|---------------------|------------|
| Sex                           | Male                                                                          | 107                 | 64.46      |
|                               | Female                                                                        | 59                  | 35.54      |
| Age group                     | ≤55                                                                           | 88                  | 53.01      |
|                               | >55                                                                           | 78                  | 46.99      |
| Histology                     | Glioblastoma                                                                  | 117                 | 70.48      |
|                               | Oligodendroglioma, IDH-mutant and 1p19q codeleted, CNS WHO grade 2            | 5                   | 3.01       |
|                               | Oligodendroglioma, IDH-mutant and 1p19q codeleted, CNS WHO grade 3            | 2                   | 1.20       |
|                               | Astrocytoma, IDH-mutant, CNS WHO grade 2                                      | 6                   | 3.61       |
|                               | Astrocytoma, IDH-mutant, CNS WHO grade 3                                      | 15                  | 9.04       |
|                               | Others                                                                        | 21                  | 12.65      |
| IDH mutation                  | IDH-mutant                                                                    | 56                  | 33.73      |
|                               | IDH-wildtype                                                                  | 90                  | 54.22      |
|                               | Not determinable                                                              | 20                  | 12.05      |
| MGMT promoter methylation     | Methylated                                                                    | 72                  | 43.37      |
|                               | Nonmethylated                                                                 | 52                  | 31.33      |
|                               | Unknown                                                                       | 42                  | 25.30      |
| Number of recurrences         | 1                                                                             | 61                  | 36.75      |
|                               | 2                                                                             | 45                  | 27.10      |
|                               | 3                                                                             | 37                  | 22.29      |
|                               | 4                                                                             | 16                  | 9.64       |
|                               | 5                                                                             | 7                   | 4.22       |
| CCNU regimen                  | CCNU monotherapy                                                             | 1                   | 0.60       |
|                               | CCNU + etoposide                                                             | 160                 | 96.34      |
|                               | CCNU + vincristine                                                           | 1                   | 0.60       |
|                               | Unknown                                                                       | 4                   | 2.41       |
| Dexamethasone treatment       | Yes                                                                           | 106                 | 63.86      |
|                               | No                                                                            | 59                  | 35.54      |
|                               | N/A                                                                           | 1                   | 0.60       |
| KPS                           | ≤70                                                                           | 52                  | 31.33      |
|                               | >70                                                                           | 112                 | 69.28      |
|                               | Unknown                                                                       | 2                   | 1.20       |
| Concurrent disease            | None                                                                          | 49                  | 29.52      |
|                               | Epilepsy                                                                      | 72                  | 43.37      |
|                               | Atrial fibrillation                                                          | 6                   | 3.61       |
|                               | Arterial hyertension                                                         | 39                  | 23.49      |
|                               | DVT/pulmonary embolism                                                       | 8                   | 4.82       |
|                               | Asthma                                                                        | 7                   | 4.22       |
|                               | Others                                                                       | 27                  | 16.27      |
| Smoking status                | Smoker                                                                        | 15                  | 9.04       |
|                               | Nonsmoker                                                                     | 151                 | 90.96      |

KPS, Karnofsky Performance Status.

*One patient suffered both from DVT (deep vein thrombosis) and pulmonary embolism.

*Including 1 patient with pulmonary fibrosis.
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(%) was comparable at the 3 time points. The only analysis that reached statistical significance was the comparison between FEV1% at baseline and after 2 cycles of CCNU (Figure 1 and Table 2).

We further looked at lung function analysis of glioma patients on an individual basis and studied 9 patients with a >10% decrease between the baseline and sequential absolute VC. About one-third (33.33%) of those patients were smokers and 55.56% of those patients had prior or concurrent lung diseases (pulmonary embolism, lung fibrosis, pneumonia). About one-third of patients (33.33%) with a >10% decrease in lung function had no lung diseases, but other concurrent diseases including arterial hypertension, breast cancer, and seizures. There was 1 patient (11.11%) with a significant decrease in lung function, but without other concurrent diseases, except for nicotine abuse.

Among the full cohort of 166 patients, 86.75% of patients had no toxicity greater than CTCAE grade 3. Grade 4 thrombocytopenia was present in 0.6% of patients, 2.41% of patients had grade 4 leukopenia, 0.6% had severe nausea and vomiting, or other severe toxicities, respectively (Table 3).

Discussion
In this cohort of 166 patients with recurrent and progressive glioma receiving CCNU, there was overall no increase in parameters of pulmonary restriction. Patients with a >10% decrease in baseline VC had either concurrent lung diseases including nicotine abuse or other concurrent diseases, which may reduce the general physical fitness and resilience against toxic side effects rather than exerting direct effects on lung function. Other severe toxicities mainly included thrombocytopenia, leukopenia, and nausea and vomiting.

The first reports on severe pulmonary toxicity in patients treated with nitrosoureas date back to the 1970s. Most of those studies reported on interstitial pulmonary fibrosis in patients with repeated administrations of carmustine (BCNU = 1,3-bis-(2chlooroethyl)-1-nitrosourea) at high-cumulative doses (1,200–1,500 mg/m² body surface), but there were also reports on patients that developed irreversible lung fibrosis after a single administration of BCNU. BCNU treatment led to diffuse alveolar damage and organizing interstitial pneumonia and fibrosis as seen for other agents like bleomycin. Lung toxicity (pulmonary infiltrates and/or fibrosis) has been reported to occur in up to 30% of patients in the official drug information of BCNU. Despite those observations, BCNU has been used in the routine treatment of glioma and pulmonary fibrosis was seen as rarely as in 0.6% of chemotherapy-naive patients in a retrospective cohort study. In studies based on patients with extracranial tumors, use of nitrosoureas significantly increased the risk of pulmonary fibrosis and risk estimates were especially high, when patients also received chest irradiation. If affected, lung fibrosis is a life-threatening condition, and may occur up to 17 years after BCNU administration.

Whereas the majority of studies on lung toxicity are based on BCNU, several studies also reported on lung fibrosis after administration of nimustine (ACNU), fotemustin, CCNU, and novel nitrosoureas such as SarCNU.
The frequency of lung toxicity after use of CCNU ranges between 1/1,000 and 1/10,000 patients. In clinical trial populations using CCNU as standard of care in recurrent glioblastoma, lung fibrosis has not been a toxicity of concern. Grade 3 and 4 respiratory toxicities according to the CTCAE in patients treated with CCNU were not reported in the BELOB trial. In the REGAL trial and INTELLANCE-2 trial, grade 3 and 4 lung toxicity in patients taking CCNU were limited to pulmonary embolism. In the primary therapy of glioblastoma, 3% of patients treated with the combination of CCNU and temozolomide developed grade 3 and 4 lung infections in the CeTeG trial, whereas 2% of patients in the temozolomide arm developed grade 3 and 4 lung infections. There were no reports on pulmonary fibrosis in the CCNU and temozolomide arm. Several studies explored PCV in the primary therapy of lower grade glioma. In the study conducted by Cairncross et al., PCV therapy led to grade 3 and 4 lung toxicity in 4% of patients during chemotherapy and 1% of patients after chemotherapy as compared to 0% of patients treated with radiotherapy only. Lung toxicity was not specified for lung fibrosis. In the study led by Van Den Bent et al. and Buckner et al., no grade 3 and 4 lung toxicity was reported.

Reports on toxicity of PCV or CCNU in the routine clinical setting are sparse, but important, as patients treated within clinical trials may be fitter and therefore may experience less side effects. Interestingly, although some groups evaluated PCV toxicity in routine clinical settings, lung toxicity was not even reported. Our data showed that there was overall no decrease in parameters of pulmonary restriction such as the absolute or relative VC or FVC. Decreases in the VC were seen in patients with prior lung diseases, nicotine abuse and other concurrent diseases. The small, but statistically significant decrease in FEV1 is a marker of pulmonary obstruction, but not restriction and therefore not associated with pulmonary fibrosis. Regular assessment of lung function by spirometry increases the duration and expenses of practice visits, and alternatives to CCNU in the recurrent setting of glioblastoma are rare. Therefore, regular monitoring of lung function by spirometry may not be justified in patients with recurrent glioblastoma. However, clinicians should be aware of patients at increased risk of pulmonary restriction and routinely ask and clinically examine for pulmonary symptoms in patients treated with CCNU.

Other severe toxicities (CTCAE grade 4) reported in our cohort are in line with published studies mainly including thrombocytopenia, leucopenia, and emesis.

Our study has several limitations. Data were collected retrospectively and numbers of patients with several lung function analyses were limited. Most patients in the analysis were diagnosed with recurrent glioblastoma with limited patient prognosis, therefore long-term pulmonary toxicities may have been lost and results cannot be

### Table 2. Mean results of lung function analyses

| Parameter       | Mean value ± SD at baseline | Mean value ± SD before cycle 3 | Mean value ± SD before cycle 5 |
|-----------------|----------------------------|--------------------------------|--------------------------------|
| VC (l)          | 3.96 ± 1.19                | 3.88 ± 1.22                    | 3.84 ± 1.15                    |
| VC (%)          | 94.98 ± 27                 | 90.68 ± 20.75                  | 88.18 ± 21.85                  |
| FVC (l)         | 3.68 ± 1.06                | 3.63 ± 1.11                    | 3.66 ± 1.14                    |
| FVC (%)         | 92.15 ± 24.19              | 88.64 ± 20.2                   | 85.82 ± 21.66                  |
| FEV1 (l)        | 2.96 ± 0.85                | 2.92 ± 0.96                    | 2.90 ± 0.96                    |
| FEV1 (%)        | 89.44 ± 23.08              | 84.85 ± 22.5                   | 81.00 ± 22.88                  |
| FEV1/VC (%)     | 94.20 ± 12.38              | 92.64 ± 14.26                  | 91.82 ± 16.54                  |

FEV1, forced expiratory volume; FVC, forced vital capacity; VC, vital capacity.
translated to younger people with lower grade tumors. Most patients were treated with CCNU and etoposide and results may not be translated to patients treated with PCV. The combination of nitrosoureas and etoposide/teniposide may be used in the treatment of recurrent glioblastomas (adapted from the German Neuro-Oncology Working Group 01 trial12), but standard of care at tumor recurrence may be used in the treatment of recurrent glioblastomas of tumors of the central nervous system: a summary. Neuro Oncol. 2021;23(8):1231–1251. 3. Weller M, van den Bent M, Preusser M, et al. EANO guidelines on the diagnosis and treatment of diffuse gliomas of adulthood. Nat Rev Clin Oncol. 2021;18(3):170–186. 4. Weller M, Le Rhun E, Preusser M, Tonn JC, Roth P. How we treat glioblastoma. ESMO Open. 2019;4(suppl 2):e000520. 5. Stupp R, Mason WP, van den Bent MJ, et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. N Engl J Med. 2005;352(10):987–996. 6. Cairncross G, Wang M, Shaw E, et al. Phase III trial of chemoradiotherapy for anaplastic oligodendroglioma: long-term results of RTOG 9402. J Clin Oncol. 2013;31(3):337–343. 7. van den Bent MJ, Brandes AA, Taphoorn MJ, et al. Adjuvant procarbazine, lomustine, and vincristine chemotherapy in newly diagnosed anaplastic oligodendroglioma: long-term follow-up of EORTC brain tumor group study 26951. J Clin Oncol. 2013;31(3):344–350. 8. Buckner JC, Shaw EG, Pugh SL, et al. Radiation plus procarbazine, CCNU, and vincristine in low-grade glioma. N Engl J Med. 2016;374(14):1344–1355. 9. Weller M, Le Rhun E. How did lomustine become standard of care in recurrent glioblastoma? Cancer Treat Rev. 2020;87:102029. 10. Herrlinger U, Tzaris T, Mack F, et al. Lomustine-temozolomide combination therapy versus standard temozolomide therapy in patients with newly diagnosed glioblastoma with methylated MGMT promoter (CoTeG/NOA-09): a randomised, open-label, phase 3 trial. Lancet. 2019;393(10172):678–688. 11. Buckner JC, Gesme D J Jr, O’Fallon JR, et al. Phase II trial of procarbazine, lomustine, and vincristine as initial therapy for patients with low-grade oligodendroglioma or oligoastrocytoma: efficacy and associations with chromosomal abnormalities. J Clin Oncol. 2003;21(2):251–255. 12. Weller M, Muller B, Koch R, Bamberg M, Krauseneck P. Neuro-Oncology Working Group of the German Cancer Society: CCNU, and vincristine in low-grade glioma. N Engl J Med. 2016;374(14):1344–1355. 13. Drug Information for Lomustine: http://www.bccancer.bc.ca/drug-database-site/DrugIndex/Lomustine_monograph.pdf. Accessed December 20, 2021. 14. CTCAE-criteria: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf. Accessed December 20, 2021. 15. Weiss RB, Shah S, Shane SR. Pulmonary toxicity from carmustine (BCNU): a case report. Med Radiat Oncol. 1979;6(3):255–259. 16. Holloye PY, Jenkins DE, Greenberg SD. Pulmonary toxicity in long-term administration of BCNU. Cancer Treat Rep. 1976;60(11):1691–1694. 17. Crittenden D, Tranum BL, Haut A. Pulmonary fibrosis after prolonged therapy with 1,3-bis(2-chloroethyl)-1-nitrosourea. Chest. 1977;72(3):372–373. 18. Bailey CC, Marsden HB, Jones PH. Fatal pulmonary fibrosis following 1,3-bis(2-chloroethyl)-1-nitrosourea (BCNU) therapy. Cancer. 1978;42(1):74–76. 19. Lieberman A, Ruoff M, Estray E, et al. Irreversible pulmonary toxicity after single course of BCNU. Am J Med Sci. 1980;279(1):53–56. 20. Sostman HD, Marrahy RA, Putman CE. Cytotoxic drug-induced lung disease. Am J Med. 1977;62(4):608–615. 21. Product Information for Carmustine: https://www.ema.europa.eu/en/documents/product-information/carmustine-obvius-epar-product-information_en.pdf. Accessed December 20, 2021. 22. Jungk C, Chatziaslanidou D, Ahmadi R, et al. Chemotherapy with BCNU in recurrent glioma: analysis of clinical outcome and side effects in chemotherapy-naive patients. BMC Cancer. 2016;16(1):81.
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