Kinetic evaluation of low-grade gliomas in adults before and after treatment with CCNU alone

*Gentian Kaloshi, MD,1 Ermir Rocici, MD,1 Arben Rroji, MD,1 Francois Ducray, MD,2 and Mentor Petrela, MD, PhD1

1Department of Neurosurgery, University Hospital Center “Mother Theresa,” Tirana, Albania; and 2Department of Neuro-oncology, Hospices Civils de Lyon, Hôpital Neurologique, Lyon, France

OBJECT The aim of this study was to evaluate the impact of CCNU chemotherapy alone on low-grade glioma (LGG) growth dynamics.

METHODS The authors measured the evolution of the mean tumor diameter (MTD) in adult patients with LGG before (n = 28 patients) and after (n = 38 patients) CCNU administration.

RESULTS Natural (spontaneous) growth of LGG in the present study was 4.3 mm/year (range 2.1–6.6 mm/year). The median MTD decrease after CCNU was 5.1 mm/year (range 1–8.9 mm/year). MTD decrease was noted in 30 patients (late decrease in 4 patients, and ongoing decrease in 24 patients with oligodendroglial tumors and 2 with astrocytic tumors). The median duration it took for the MTD to decrease after initiation of CCNU treatment was 619 days (1038 days for oligodendroglial tumors vs 377 days for astrocytic tumors; p = 0.003).

CONCLUSIONS These results show that CCNU as a single agent has a significant impact on LGG tumor growth. The impact of CCNU seems to be comparable to the previously reported impact of temozolomide therapy and of combined procarbazine, CCNU, and vincristine chemotherapy.


KEY WORDS kinetic analysis; low-grade glioma; CCNU; mean tumor diameter; oncology
of oral administration of CCNU on Day 1 at a starting dose of 130 mg/m², repeated every 6 weeks.

Patients were required to have at least 2 consecutive MRI scans to be eligible for kinetic analysis before and after treatment with CCNU. As only printed MRI scans were available, tumor diameters were manually measured by the principal investigator (G.K.), as previously described. Of note, the principal investigator was blinded to the timing of treatment.

The evaluation of the growth rate of the mean tumor diameter (MTD) over time for each patient under each condition (i.e., before, during, and after CCNU administration) was performed using linear regressions of the MTD of each patient versus time. The median duration of MTD decrease and overall survival were calculated according to the Kaplan-Meier technique. To compare the median MTD slopes during and after CCNU treatment, we performed a nonparametric Wilcoxon test.

### Results

A total of 38 patients met the eligibility criteria. Their clinical characteristics are listed in Table 1. Of these, 28 had at least 2 successive MRI scans before the initiation of CCNU, allowing the evaluation of spontaneous growth of these tumors (Fig. 1).

The median growth rate before CCNU was 4.3 mm/year (range 2.1–6.6 mm/year). During and after CCNU therapy, at least 3 consecutive MRI scans (median 5, maximum 8) were available from all patients. During CCNU therapy, among the patients whose tumors did not progress (34 of 38), the MTD decreased by approximately 5.1 mm/year (range 1–8.9 mm/year). No statistically significant association was noted between MTD decrease and other prognostic factors such as histology (astrocytic vs oligodendroglial tumors), pretreatment tumor size, or contrast enhancement. Interestingly, at the individual level, more rapid tumor growth before CCNU therapy correlated with faster MTD decrease, and slower tumor growth before CCNU therapy correlated with slower MTD decrease (p < 0.001).

After CCNU discontinuation, a late response was observed in 4 patients, and an ongoing MTD decrease was seen in 26 patients (24 with oligodendroglial tumors and 2 with astrocytic tumors). The median duration it took for the MTD to decrease was 619 days; the duration of response was longer in oligodendroglial tumors than in astrocytic tumors (median 1038 vs 377 days, respectively; p = 0.003).

### Discussion

We have previously shown that first-line CCNU alone resulted in a similar objective radiological response rate and survival profile as first-line temozolomide or PCV chemotherapy. The aim of the present study was to assess the impact of CCNU alone on growth dynamics.

During CCNU therapy, we observed that the median decrease of MTD was 5.1 mm/year. Oligodendroglial tumors had a longer duration of response than astrocytomas, consistent with the known greater chemosensitivity of these tumors. Thus, our results are very similar to those achieved using temozolomide and PCV chemotherapy.

At an individual level, we found a close correlation between the growth rate before and after CCNU, with more rapid tumor shrinkage during chemotherapy being observed in gliomas that grew more rapidly before treatment, and slower tumor shrinkage in tumors that grew more slowly before treatment. This is consistent with the fact that rapidly growing tumors usually respond faster to chemotherapy.

Among the 34 patients whose tumors did not progress while receiving CCNU therapy, an ongoing response was observed after CCNU discontinuation in 30 patients. These results are also in agreement with those observed in patients treated with PCV chemotherapy.

It has been suggested that temozolomide chemotherapy in LGG might induce mutations that could drive progression to a higher-grade glioma. Whether the same phenomenon is observed in patients treated with CCNU remains to be determined.

### Conclusions

The present study shows that CCNU as a single agent has an impact on LGG tumor growth kinetics that is very similar to the impact previously reported with PCV and temozolomide chemotherapies. It suggests that CCNU alone...
might be an interesting treatment option in patients with LGG who cannot receive temozolomide chemotherapy.

Acknowledgment

We thank Prof. Khe Hoang-Xuan, Fédération Mazarin, Groupe Hospitalier Pitié-Salpêtrière, Paris, France.

References


Author Contributions

Conception and design: Kaloshi, Rocic, Petrela. Acquisition of data: Kaloshi, Rocic, Rroji, Petrela. Analysis and interpretation of data: Kaloshi, Rocic, Ducray, Petrela. Drafting the article: Kaloshi, Rocic. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Kaloshi. Statistical analysis: Kaloshi, Rocic. Administrative/technical/material support: Kaloshi, Rocic, Petrela. Study supervision: Kaloshi, Rocic, Petrela.

Correspondence

Gentian Kaloshi, Department of Neurosurgery, University Hospital Center “Mother Theresa,” Tirana, Albania. email: g_kaloshi@yahoo.com.