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

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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.

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KEY WORDS kinetic analysis; low-grade glioma; CCNU; mean tumor diameter; oncology

THE management of low-grade glioma (LGG) remains a great challenge. Maximal safe resection is currently considered the first therapeutic option whenever possible. Chemotherapy or radiotherapy is usually provided for patients with residual and/or recurrent disease after surgery.

The dynamic history of LGG has shown that these tumors grow continuously for many years before anaplastic transformation.⁴ Several studies have attempted to report a detailed kinetic analysis of the natural history of LGG and to analyze the impact of oncological treatments on their growth dynamics.^{3,4}

We have shown that the response rate of LGG to first-

line CCNU alone was similar to the response rates reported with first-line temozolomide or procarbazine, CCNU, and vincristine (PCV) chemotherapy.² The aim of the present study was to evaluate the impact of CCNU alone on LGG growth kinetics.

Methods

This study included adult patients with pathologically proven, supratentorial, Grade II astrocytoma, oligodendroglioma, or oligoastrocytoma who were treated with CCNU alone and who had not undergone previous specific oncological treatment except surgery. The treatment consisted

ABBREVIATIONS LGG = low-grade glioma; MTD = mean tumor diameter; PCV = procarbazine, CCNU, and vincristine.

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TABLE 1. Patient characteristics

Clinical Variable	Data Value
Total no. of patients	38
Age, yrs	
Median	41.8
Range	18.2–63
Sex, no. of patients	
Male	23
Female	15
Histology, no. of patients	
Astrocytoma	12
Oligodendroglioma	18
Oligoastrocytoma	8
MTD at CCNU initiation, mm	
Median	48.8
Range	18–96
Timing of CCNU administration, no. of patients	
Immediately after operation	4
At clinical/radiological progression	34
Interval btwn MRI scans, days	
Median	89
Range	34–416
Follow-up before CCNU, mos	
Median	13.5
95% CI	6.8–19.4
Follow-up after CCNU, mos	
Median	39.8
95% CI	19.8–56.3

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.^{3,4} 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.² 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 temozolomide³ and PCV³ 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.³

It has been suggested that temozolomide chemotherapy in LGG might induce mutations that could drive progression to a higher-grade glioma.¹ 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

FIG. 1. Graph showing evolution of MTD over time. The graph provides tumor size data from immediately after surgery (white dashed lines), before surgery (black long-dashed lines), during surgery (black continuous lines), and after discontinuation of CCNU treatment (white continuous lines). Almost all patients had an initial decrease of MTD. No regrowth of the tumor was observed during the treatment period. In several patients, there was an ongoing response after CCNU discontinuation. At progression, second-line surgery and/or chemotherapy was offered (black short-dashed lines).

might be an interesting treatment option in patients with LGG who cannot receive temozolomide chemotherapy.

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Conception and design: Kaloshi, Roci, Petrela. Acquisition of data: Kaloshi, Roci, Rroji, Petrela. Analysis and interpretation of data: Kaloshi, Roci, Ducray, Petrela. Drafting the article: Kaloshi, Roci. 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, Roci. Administrative/technical/material support: Kaloshi, Roci, Petrela. Study supervision: Kaloshi, Roci, Petrela.

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