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LETTER TO THE EDITOR

# Upfront chemotherapy with CCNU alone for adults' low-grade gliomas: a clinical analysis

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To the Editor,

The role of chemotherapy for low-grade gliomas (LGG), classified as grade II astrocytoma, oligodendroglioma and oligoastrocytoma according to their cell of origin, remains to be defined. In the last decade, several studies have explored first-line (that is, prior radiotherapy) chemotherapy using either PCV or temozolomide [1–3]. Because of its lower rate of side effects, Temozolomide, an oral chemotherapeutic drug, represents a safe and efficacious alternative to PCV.

In a previous report, the omission of Vincristine from PCV chemotherapy avoided the disadvantages of Vincristine but did not weaken the efficacy [4]. The present study was designed to determine the efficacy and toxicity of upfront CCNU alone, an oral component of PCV regimen in patients with recurrent LGGs.

Thirty-eight patients, 18 years old and older, with histological diagnosis of grade II astrocytoma, oligodendroglioma or oligoastrocytoma treated with surgery alone and Karnofsky Performance Status (KPS) of at least 60 were included in this study.

At baseline, median age was 41.8 years (range 18.2–63 years), 23 were men, 18 had pure oligodendroglioma, 8 had mixed oligoastrocytoma and 12 had astrocytoma. Median baseline KPS was 90 (range 70–100). Median time-interval from surgery to CCNU onset was 13.5 months (range 1.2–99.1). The main indications for chemotherapy included: radiological progression in 26 patients, refractory epilepsy in 11 patients and neurological deficit in one patient.

The median number of CCNU cycles was 6 (range 1–6 cycles). A total of 173 cycles of CCNU were administered. Twenty-three patients completed all 6 cycles of treatment. Only one patient developed grade III neutropenia. Four patients stopped the CCNU treatment for economic issues after 4 cycles.

Tumor response to CCNU was evaluated using modified MacDonald's criteria for LGGs, as previously described [1, 4]. The median time to the radiographic response was 6 months. The maximum response was reached after a median of 12 months (ranging from 6 to 21 months) as follows: 17 patients (45 %) achieved a partial response, 9 patients (23 %) achieved a minor response, 8 patients (21 %) were stable, and 4 patients (11 %) had progressive disease. Thus, the maximal objective response rate was 68 %. An example of response is shown in Fig. 1. Independently to radiological response, a clear improvement in seizure control (50 % or more reduction in seizures frequency), was observed in 23 out of the 31 patients (72 %).

The median follow-up was 39.8 months (95 % CI 19.8–56.3 months). The median PFS was 27.8 months (95 % CI 21.2–59.6 months) and 1-year PFS rate was 81 %. Oligodendroglial tumors demonstrated a better prognosis than those with astrocytic features in term of PFS (46.3 vs 18.8 months; $P = 0.045$). We found no correlation between the PFS and other potential prognostic factors such as contrast enhancement, age (under 40 or older) or Karnofsky scale.

From enrollment, the median OS was not reached (95 % CI 29.1 to inf). Survival at 2- and 5-years from the diagnosis as well as from onset of chemotherapy were 92 and 75 %, 79 and 71 %, respectively. Pure oligodendrogliomas also tended to have a better OS than the other histological

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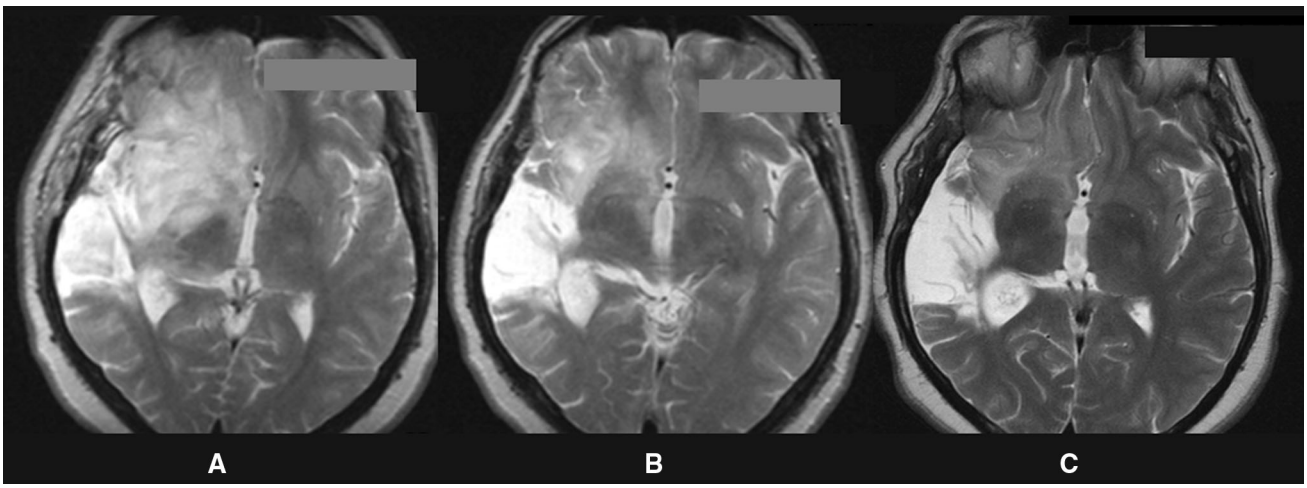


**Fig. 1** Case illustration: axial T2-weighted MRI **a** before CCNU onset, **b** after 6 cycles of CCNU, and **c** after 22 months from chemotherapy onset

subtypes though this did not reach significance ($P = 0.11$). It is possible, however, that the small sample size may have contributed to the failure to detect a difference between these groups of patients.

## Discussion

The objective radiological response rate of 55 % and the median PFS of 27.8 months are similar to those reported in progressive LGGs treated with up-front temozolomide or PCV chemotherapy [1, 2]. The idea that a prolonged duration of treatment might be important to achieve a prolonged response has also been advocated as a reason to treat LGGs with temozolomide rather than PCV chemotherapy, which has cumulative toxicity. However, a main limitation for the use of temozolomide in many countries, including ours, is its cost which is 10 times higher than the cost of CCNU. In addition, a recent study demonstrated that patients treated with up-front PCV chemotherapy commonly achieve a prolonged response despite the duration of PCV chemotherapy being shorter than the duration of temozolomide chemotherapy [5]. Accordingly, in the present study, the median duration of CCNU treatment was 9 months and the median duration of response after CCNU disruption was 19.6 months. This prolonged response was especially obvious in pure oligodendrogliomas (30.7 months).

Our results support the hypothesis that CCNU, much better tolerated and easier to administrate than PCV, may be as effective as PCV in the treatment of patients with LGG.

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**Conflict of interest** The authors report no conflict of interest.

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