



# Lomustine and temozolomide for newly diagnosed glioblastoma with methylated *MGMT* promoter: Lessons from the CeTeG/NOA-09 trial

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The Neuro-Oncology Working Group of the German Cancer Society (*Neuroonkologische Arbeitsgemeinschaft*, NOA), studied the effect of lomustine (CCNU, 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea) and temozolomide together to treat patients with newly diagnosed glioblastoma with a methylated O<sup>6</sup>-methylguanine DNA methyltransferase (*MGMT*) promoter (1). This strategy needed testing after the encouraging results of a phase II trial (2), and the synergistic or additive effect between temozolomide and lomustine since nitrosoureas have additional non-alkylating effects on DNA and cell replication (3).

To adequately present the context and relevance of this research, it is necessary to summarize its methods. CeTeG/NOA-09 (Ce: CeeCNU, an initial brand name for lomustine; Te: for temozolomide, G: glioblastoma; NOA-09 indicates the cooperative group and the inception year), was a multicenter, open-label, phase III study with random allocation. Masking was not possible because of the treatment sequences between the investigational and the control groups. The participants were patients aged 18–70 years with newly diagnosed, untreated glioblastoma with methylated *MGMT* promoter who had biopsy or tumor resection and a Karnofsky performance score (KPS) of 70% or higher. The inclusion and exclusion criteria were well outlined, and the ethics committees of all participating centers approved the trial. Patients were allocated randomly 1:1 by a software-generated randomization

list at a designated center to a control group (concurrent temozolomide at 75 mg/m<sup>2</sup> daily and conformal radiation therapy × 6 weeks for a total dose of 59–60 Gy, followed by adjuvant temozolomide at 150–200 mg/m<sup>2</sup> × 5 d every 28 d × 6 cycles), or to the investigational group, which began the first cycle of lomustine 100 mg/m<sup>2</sup> on day 1 and temozolomide 100 mg/m<sup>2</sup> on days 2–6 of radiation therapy × 6 weeks for a total dose of 59–60 Gy and repeated this schedule every 6 weeks × 6 cycles. Dose adjustments were based on toxicity, evaluations were clearly specified and radiographic responses were assessed with slightly modified Response Assessment in Neuro-Oncology (RANO) criteria.

With a modified intention to treat, the primary endpoint was overall survival (OS) from the day of allocation. The study had several secondary endpoints but for our commentary we will limit discussion on progression-free survival (PFS) and hematological toxicity. The statistical methods were solid and rational, addressing sample size with assumptions derived from 2-year survival rates of previous NOA studies and other assumptions necessary to establish sample size with 80% power to achieve a statistical significance at P=0.05. The trial sponsorship was governmental, not industry-based.

One hundred forty-one participants were randomized; 63 patients were in the control group and 66 in the investigational group, most of them with good KPS and subtotal or grossly complete resections. The group treated

**Table 1** Relevant outcomes in critically appraised topic

Outcome	Time of outcome	CER	EER	RRR (95% CI)	ARR (95% CI)	NNT or NNH
OS	5 years	0.86	0.64	25% (9% to 41%)	0.22% (0.08% to 0.36%)	5
PFS	5 years	0.88	0.65	25% (9% to 41%)	0.22% (0.08% to 0.35%)	5
Grade 3–4 hematological toxicity	NA	0.50	0.62	26% (–7% to 59%)	0.13% (–0.04% to 0.30%)	8

OS, overall survival; PFS, progression-free survival; CER, control event rate; EER, experimental event rate; RRR, relative risk reduction; ARR, absolute risk reduction; NNT, number needed to treat; NNH, number needed to harm; 95% CI, 95% confidence interval.

with temozolomide and lomustine survived a median of 48 months, about 15 months more than the control patients ( $P=0.049$ ), for a hazard ratio of 0.60, 95% CI: 0.35–1.03; log rank  $P=0.06$ ). There was no difference in PFS between both groups. Nearly 60% of patients treated with temozolomide and lomustine and 50% in the control group had grade 3 or higher toxicity. The authors concluded that “overall survival was significantly improved in the lomustine-temozolomide group compared with that of the temozolomide group”, with well tolerated toxicity.

The essential question in CeTeG/NOA-09 is whether the difference in OS is solid enough to persuade us into changing or modifying the standard of care. There are several reasons why the answer should be a “no”. First, the difference on OS barely made the level of significance. Mathematically we could call it a success, but a reduction in relative risk widely scattered from 0.35 to 1.03 is tantalizing. This observation is reinforced by the discrepancy between the PFS and the OS, which the authors discussed appropriately as a weakness along with a smaller-than-planned sample size. This problem with size arose when some of the prognostic factors (sex, center, and RPA class) were not well-balanced as expected for a study with random allocation. In the unstratified analysis, there was simply no difference in OS. These flaws were pointed out by van den Bent at the 13<sup>th</sup> congress of the European Association of Neuro-Oncology before final publication of the trial and by Stupp in a commentary (4,5).

As an exercise, we assessed the CeTeG/NOA-09 using a critically appraised topic (CAT) model (6). The analysis yielded two observations of practical importance; one, that relative risk reductions can be misleading; two, that the absolute risk reduction is probably closer to the truth when estimating a treatment effect size (see *Table 1*).

The second reason important to us as clinicians against a change of treatment paradigm is toxicity. In the study, lomustine and temozolomide had a 7% higher rate of grade

3–4 hematologic toxicity than the standard of care; yet 60% of patients receiving the standard of care completed all 6 cycles of temozolomide treatment, whereas 39% could complete therapy in the lomustine-temozolomide group. The probability of delay by cycle 5 was 40% among patients taking lomustine-temozolomide and only 17% in the standard of care. These data suggest that the lomustine-temozolomide combination was more toxic and less tolerated than the authors concluded. In this aspect, the CAT was not useful to us because information on delays and dose reductions was not included.

In summary, CeTeG/NOA-09 is an example of a well-designed and executed study based on sound preclinical and clinical premises, with results that from a best evidence standpoint suggest that the combination of lomustine-temozolomide failed to meet expectations. We think of it as a negative trial with no additive therapeutic effect from combining two alkylating agents plus the additional toxicity due to partially redundant mechanisms of action.

Using the 5-year OS and PFS data to estimate the event rates for both groups and derive the ARR and RRR, the interpretation of results could vary by metric; if we wanted to persuade the audience that the study was a success, we could state that the intervention reduced the risk of death by 25%. If we chose to be skeptical, the reduction in absolute risk (0.22%) was unimpressive. What interpretation is correct? The 2- and 3-year event control rates (not shown) gave slightly different results in the same direction. Thus, this case illustrates the quagmire of interpreting results of studies well-conceived, planned and executed with the shortcomings of real life. It seems clear that the RRR is misleading, and that the ARR was more informative and in tune with reality.

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