



Adjuvant chemotherapy in patients with newly diagnosed non-co-deleted anaplastic gliomas—a new standard

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Comment on: van den Bent MJ, Baumert B, Erridge SC, *et al.* Interim results from the CATNON trial (EORTC study 26053-22054) of treatment with concurrent and adjuvant temozolomide for 1p/19q non-co-deleted anaplastic glioma: a phase 3, randomised, open-label intergroup study. *Lancet* 2017;390:1645-53.

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Many clinical trials in neuro-oncology have sought to define treatment paradigms for glioblastomas [World Health Organization (WHO) grade IV gliomas], the most common adult primary CNS malignancy. Substantially fewer have been performed in patients with newly diagnosed anaplastic (WHO grade III) gliomas, most likely reflecting the lower incidence of grade III gliomas. Fewer still have been large randomized clinical trials that have established standards of care.

Anaplastic gliomas (AG) are comprised of anaplastic astrocytomas (AA) and anaplastic oligodendrogliomas (AO). While these tumors have been defined histologically, the 2016 WHO classification of CNS tumors has for the first time distinguished certain CNS malignancies on the basis of an integrated diagnosis based on histologic and molecular features (1). Thus, histological AGs are subdivided first by IDH mutational status—IDH wild-type (IDH wt) or mutant—and subsequently on the basis of deletions of the short arm of chromosome 1 (1p) and the long arm of chromosome 19 (19q). The defining feature of AO is the loss of both the 1p and the 19q arms. This co-deletion of 1p/19q serves as a prognostic biomarker of improved survival compared to that of non-co-deleted AGs. Under the 2016 WHO classification, 1p/19q co-deleted grade III gliomas are by definition AO. All other grade III gliomas are not co-deleted (i.e., either 1p or 19q or both not deleted), and have a worse survival and are less responsive

to chemotherapy than co-deleted tumors (2).

In two large randomized trials in patients with AO, patients with 1p/19q co-deleted tumors had a clear survival benefit with radiation plus chemotherapy compared to radiation alone (3,4). AOs in those trials were defined histologically and thus did include patients who on post hoc molecular analysis had non-co-deleted tumors. Those patients with non-co-deleted tumors had little or no benefit from the addition of chemotherapy. Thus the role of chemotherapy in patients with non-co-deleted AGs is unclear.

The report “Interim results from the CATNON trial (EORTC study 26053-22054) of treatment with concurrent and adjuvant temozolomide for 1p/19q non-co-deleted AG: a phase 3, randomised, open-label intergroup study” by Martin van den Bent and colleagues seeks to define the role of temozolomide in the management of patients with 1p/19q non-co-deleted AGs (5). Specifically this trial will assess the role of concurrent (with radiation therapy) and adjuvant temozolomide in these patients. Although these tumors have a better prognosis than that of glioblastomas, they are incurable and have a worse prognosis than those with a 1p/19q co-deletion due to their lower sensitivity to chemotherapy. The CATNON trial seeks to define a treatment regimen for these tumors that would help to improve the overall survival of these patients. Based on the results of the definitive study in grade IV gliomas most

neuro-oncologists use a similar if not identical regimen for the treatment of patients with grade III gliomas (6). This regimen consists of radiation therapy with concurrent temozolomide followed one month later by 6 cycles of adjuvant temozolomide (6).

The CATNON trial has 2×2 factorial design, with four treatment arms, that enables a simultaneous test of two hypotheses (7). This trial addresses two critical questions in the treatment of patients with non-co-deleted astrocytomas. The first question under investigation is whether the addition of temozolomide concurrent with radiation improves overall survival compared to radiation alone. The second question is whether adjuvant temozolomide improves overall survival compared to no adjuvant therapy. This interim report addresses the second question. While accrual to the trial has been completed, the data are not mature enough to discern a benefit of temozolomide given during radiation therapy.

The CATNON trial used standard dosing and duration of therapy—radiation therapy, 59.4 Gy in 33 fractions; concurrent temozolomide 75 mg/m² for 42 days; and adjuvant temozolomide 150–200 mg/m² days 1–5 every 28 days for 12 cycles.

This study demonstrated a clear overall survival benefit for patients who received adjuvant temozolomide. These patients had a 5-year overall survival of 56% compared to 44% without adjuvant temozolomide with a hazard ratio of 0.65 (P<0.002). Similarly, this cohort had a substantial improvement in median (43 *vs.* 19 months) and 5-year progression-free survival.

The CATNON trial was efficiently designed and adequately powered to answer the important questions posed. It examined patients from many different countries, which makes the study population more diverse and perhaps more generalizable. The trial accrued a large number—745—of a specific, molecularly defined patient population in just under 8 years. In addition to providing confidence in the role of adjuvant temozolomide, these interim results also offer at least a suggestion that adjuvant temozolomide plays an essential role in the management of glioblastoma, the most common adult primary CNS malignancy. The CATNON trial is likely to be the closest we come to understanding the proper timing of adjuvant chemotherapy—concurrent, adjuvant, or both—to the use of temozolomide in patients with other gliomas for whom a decision is made to include temozolomide. In fact, given the results of trials in glioblastoma as well as low-grade (WHO grade II) gliomas, one could argue that all patients with newly diagnosed grade

II–IV gliomas for whom radiation therapy is planned should receive adjuvant temozolomide (3,4,8).

The traditional definition of adjuvant therapy has been therapy given after the definitive potentially curative initial therapy for a cancer with the goal of reducing the risk of recurrence. Survival benefits have been shown for a number of therapies for which complete resection has been achieved (9–11). In these malignancies, unlike gliomas, complete resection generally means resection of tumor and a margin of normal tissue and/or regional lymph nodes. Thus the amount of tumor remaining is microscopic at most.

In contrast, fewer than 1/3 of CATNON patients had a ‘total tumor removal’. The remaining 2/3 of patients had macroscopic tumor at the beginning of radiation therapy. Adjuvant therapy defined in the management of gliomas refers to treatment administered after the completion of radiation therapy. While radiation with or without chemotherapy reduces the tumor volume, it is unlikely that all patients are left with only microscopic tumor volumes at the beginning of adjuvant temozolomide. In this context of treating higher tumor volume than would be managed by adjuvant chemotherapy in non-CNS malignancies, the survival benefit conferred by adjuvant temozolomide against the relatively chemotherapy-resistant tumor is striking. In addition, adjuvant temozolomide in this trial was well tolerated with 8–12% of patients experiencing grade 3–4 toxicity.

The adjuvant regimen chosen in this trial was appropriate as temozolomide is by far the most commonly used adjuvant chemotherapy used in the management of gliomas. PCV [procarbazine, CCNU (lomustine), and vincristine] chemotherapy was the most commonly used adjuvant regimen before the advent of temozolomide. That combination was used in two large randomized trials of adjuvant chemotherapy in AO and is a reasonable alternative but at the cost of greater toxicity (3,4). The ongoing CODEL trial (NCT00887146) is comparing PVC to temozolomide as adjuvant therapy after radiation therapy for patients with 1p/19q co-deleted AGs.

Although the tumors in this trial were evaluated for 1p/19q co-deletion and MGMT promoter methylation, at the time of the trial initiation in 2009, IDH mutation status was not assessed. Subsequently, the importance of IDH mutation status in gliomas became apparent, and in 2011 the investigators amended the protocol to collect these data prospectively. More recently, it has been discovered that WHO grade II and III tumors that are IDH wt behave more like glioblastomas (12). While the patient population in this study included a mix of patients with and without

IDH mutations, the overall results are unlikely to be affected significantly. It remains to be seen, however, whether IDH evaluation in the cohort will add prognostic and/or predictive value for patients with non-co-deleted astrocytomas. Based on our current knowledge, IDH mutation status is a foundational biomarker that may guide management for patients with gliomas, and as the authors suggest, guide clinical trial design for these patients.

Several questions remain regarding treatment of grade III glioma. As the CATNON data mature, the role of temozolomide during radiation therapy should become clear. In CATNON, adjuvant temozolomide was administered in this study for 12 cycles, although the trial for grade IV gliomas included 6 cycles of therapy (6). The optimal duration of adjuvant chemotherapy in gliomas remains controversial, and it is unlikely that a trial comparing 6 *vs.* 12 cycles of adjuvant temozolomide will ever be conducted. Based on the results of CATNON, however, the standard of care for non-co-deleted AGs should include 12 cycles of adjuvant temozolomide.

Overall, this report answers a critical question regarding the role of temozolomide in the management of patients with non-co-deleted AGs. The authors are to be congratulated on the excellent design and conduct of this trial, which has refined the standard of care for these patients.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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