Editorial

Temozolomide—the jack of all gliomas? Reviewing the interim results of the CATNON trial for 1p/19q non-co-deleted anaplastic glioma

Mateo Ziu, Jeffrey I. Traylor

Seton Brain and Spine Institute, Department of Surgery and Perioperative Care, Dell Medical School, University of Texas at Austin, Austin, TX, USA
Correspondence to: Mateo Ziu, MD. Seton Brain and Spine Institute, 1601 Trinity St, Suite 704, Austin, TX 78712, USA. Email: mateo.ziu@inova.org.
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.

Submitted Mar 05, 2018. Accepted for publication Mar 12, 2018.
doi: 10.21037/tcr.2018.03.25
View this article at: http://dx.doi.org/10.21037/tcr.2018.03.25

Gliomas are the most common primary neoplasm of the brain parenchyma with a prevalence of 6.0 per 100,000 (1) and are categorized by the glial cells from which they are thought to be derived, including astrocytes, ependymal cells, and oligodendrocytes. In the most recent World Health Organization (WHO) Classification of Central Nervous System (CNS) Tumors, gliomas were classified not only by their histological characteristics, but on their genetic and molecular markers as well (2). Of these, co-deletion of chromosomes 1p and 19q (referred to simply as 1p/19q co-deletion) specific to oligodendroglial tumors, has been found to correlate with improved survival and response to chemotherapy (3). Specifically, anaplastic oligodendrogliomas with 1p/19q co-deletion are classified by the WHO as grade III and are associated with shorter median survival (4), though this is based on data collected prior to the 2016 update of WHO classification criteria. Although 1p/19q co-deleted anaplastic gliomas have shown to be responsive to adjuvant procarbazine, lomustine, and vincristine chemotherapy, a 2013 study revealed no overall survival (OS) benefit when using this regimen to treat anaplastic gliomas without the 1p/19q co-deletion (5), further illustrating the need for reliable, effective chemotherapeutic agents to manage these patients.

Temozolomide (TMZ) is an alkylating agent shown to be efficacious in the treatment of different intracranial malignancies, including glioblastoma (6), high risk low grade glioma (7) and oligodendroglioma (8). In the EORTC phase III trial in Europe, combined TMZ and radiation therapy (RT) was shown to have a clinically meaningful and statistically significant survival benefit in glioblastoma (9). Another translational study that year observed an association of *MGMT* promotor gene methylation (i.e., 'silencing') with a substantial survival benefit in those patients treated with combined TMZ and RT (10). Though studies have clearly demonstrated the efficacy of TMZ in the treatment of glioblastoma and 1p/19q co-deleted glioma (8), its role in the management of other intracranial malignancies is less clear.

The CATNON trial thus investigated the use of adjuvant TMZ combined with RT in patients with non-1p/19q co-deleted anaplastic glioma compared to RT alone, concurrent RT and TMZ, and adjuvant and concurrent TMZ to determine if chemotherapy offered any additional survival benefit (11). The interim results were released in 2017 as the authors claimed preliminary data confirmed an association between adjuvant TMZ chemotherapy and improved survival, obligating them to publish their preliminary findings. Indeed, these interim results demonstrated a higher OS at 5 years and longer progression-free survival (PFS) for those who received adjuvant TMZ versus those who did not. The median follow-up was 27 months. Up to the date of the interim analysis, 221 (30%) had died; 129 (35%) in the groups that did not receive adjuvant TMZ and 92 (25%) in the groups that did receive adjuvant TMZ. Age was a significant risk factor for survival. In the group of patients that received adjuvant TMZ, median PFS increased from 19 to 42.8 months and 5-year OS increased from 44%

to 56% (11).

The study was designed as a phase 3, randomized, intergroup trial spread over 137 institutions in 12 countries. Utilizing a 2×2 factorial design, all patients with newly diagnosed 1p/19q non-co-deleted anaplastic glioma were included. The study sought to answer the question of whether RT with adjuvant TMZ chemotherapy improves OS adjusted by several stratification factors. Secondary end points were univariate analysis of OS, PFS, health-related quality of life outcomes, adverse events, and cognitive effects. Patients with 1p/19q non-co-deleted anaplastic gliomas (n=1,400) were randomized in 4 groups: RT alone, RT and concurrent TMZ, RT and adjuvant TMZ, and RT with concurrent and adjuvant TMZ. For this interim analysis though, the study investigators reported patients divided in only 2 groups, patients that received RT alone and RT with concurrent TMZ in one group (group of no-adjuvant-TMZ) and patients that received RT with adjuvant TMZ and those that received RT with concurrent and adjuvant TMZ in another group (group of adjuvant-TMZ). For the interim results, the authors analyzed the outcome of 372 patients in no-adjuvant-TMZ and 373 in the adjuvant-TMZ group. Recruitment started in 2007 and on April 2015 the study was locked for the interim analysis. The study investigators randomized patients in 4 groups, however in this report of preliminary results they discuss findings in 2 groups; patients that received adjuvant TMZ versus the ones that did not (11). It is important to keep in mind that RT alone and RT with concurrent TMZ constitute different treatment options and we certainly look forward to the publication of the final results where the outcome for all four groups should be reported separately.

The authors of the interim results for the CATNON trial detail a rigorous statistical analysis and achieve a power of 83% at an overall significance level of 5% (11). The data are effectively illustrated using a Kaplan-Meier curve, contrasting the overall and PFS for those who received adjuvant TMZ, and those who did not. These methods were appropriate to analyze the association between the adjuvant therapy with TMZ and OS and substantiate the conclusion of a 'significant survival benefit' (11) for patients with non-co-deletion anaplastic glioma treated with TMZ.

Though inadequate organ function and previous treatment with experimental agents were exclusion criteria for this trial, previous surgery for low-grade glioma (LGG) was not, nor was it a stratified variable in the randomization schedule. Surgery has remained the mainstay of therapy for glioblastoma, LGGs and anaplastic gliomas alike and studies have demonstrated an improved OS with this therapeutic option based on extent of resection (12). Research has also revealed shorter progression time (to higher grade) for residual disease following less than gross total neurosurgical tumor resection (13). Thus, surgery for a previous LGG in some patients possibly introduces confounding variables, which can be eliminated with proper randomization. Most of the patients in this trial (n=347) underwent partial resection (PR) of the tumor, 228 patients underwent gross total resection of the tumor (GTR) and 149 underwent biopsy alone. The authors did not stratify for this important factor in treatment of these tumors (11).

There is a documented association between GTR and OS for high grade glioma (14). Buckner *et al.* considered patients younger than 40 years of age that had undergone GTR as low risk in RTOG 9802 (15). Shaw *et al.* reported in their preliminary results of RTOG 9802 that 2-year survival of LGG patients was higher for patients that had undergone GTR or PR instead of biopsy alone (16). It will be helpful if van den Bent and the investigators of the CATNON study evaluate whether GTR, PR, or biopsy would have any impact on outcomes when they report their final results.

On another note, tumor burden is another factor that should be considered when determining chemotherapy and RT efficacy. Would a small tumor respond better to chemotherapy and RT than a large one? In the RTOG Phase II study on LGG reported by Shaw *et al.*, pre-operative diameter of >4 cm and post-operative residual >2 cm were found to be poor prognostic factors for survival among other factors (13). It will be of great value to know whether the size of primary tumor and residual tumor can be used as predictors for survival in anaplastic glioma as well.

Additionally, the authors mention their study was amended in 2011 to include prospective analysis of TMZ efficacy on *IDH1* and *IDH2* tumor status, which are molecular markers associated with better prognosis (17). Though it is not an oversight on the authors' part as the associations of these markers with improved prognosis were not discovered until after recruitment for the trial had begun, the interim results for the CATNON trial are not based on proper randomization of patients based on the *IDH* marker, which can inflate figures for OS. In fact, the authors state themselves that "future trials should involve only patients with either mutated or wild-type *IDH1* and *IDH2* grade II and III gliomas" (11). We anticipate the final results of this trial will further analyze TMZ efficacy based on *IDH1* and *IDH2* tumor marker and *MGMT* promotor

methylation status.

In conclusion, this report of the interim results of the CATNON trial has showed that RT with adjuvant TMZ improves 5-year OS in patients with 1p/19q non-co-deleted anaplastic glioma, however, we will need to wait for the final results of the trial to determine which treatment regimen is more efficacious for these patients: adjuvant therapy or concurrent therapy or use of concurrent and adjuvant TMZ. We hope the authors would consider the type of surgical resection as a stratifying factor and report on whether the size of the residual tumor would make any difference in these patients' survival. Furthermore, since the investigators have the *IDH* and *MGMT* promotor methylation data for all patients enrolled from 2011, it will certainly be of great interest to see in the future analysis whether patients should be treated differently depending on the *IDH* and *MGMT* promotor methylation status. As the authors stated on this publication (11), with 30% of patients having died and 46% having had disease progression, follow up is still immature and we must wait for the final report to draw definitive conclusions on these treatment regimens.

Several studies now have confirmed that addition of chemotherapy to surgery and/or RT improves OS and PFS in patients with low grade and high-grade glioma (7,9,15). Furthermore, these studies have all used TMZ as the chemotherapeutical drug of choice in treatment of many types of gliomas because of the perceived impression that TMZ has a better toxicity pattern than other chemotherapeutic agents. However, studies that directly compare the OS, PFS and toxicity spectrum between TMZ and other chemotherapeutics are needed.

Nevertheless, TMZ has been shown to improve OS and PFS in LGG and glioblastoma, (7,9,15) and it would seem this study confirms that even patients with non-co-deleted anaplastic gliomas can benefit from its use (11). We can certainly conclude that TMZ is becoming the drug of choice for all gliomas. However, we hope that in the near future, we will see other treatment options apart from TMZ added to our armamentarium to increase further OS and PFS in patients with glioma.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned and reviewed by the Section Editor Xian-Xin Qiu (Shanghai Proton and Heavy Ion Center (SPHIC), a.k.a. the Proton and Heavy Ion Center of Fudan University Shanghai Cancer Center (FUSCC), Shanghai, China).

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tcr.2018.03.25). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. Porter KR, McCarthy BJ, Freels S, et al. Prevalence estimates for primary brain tumors in the United States by age, gender, behavior, and histology. Neuro Oncol 2010;12:520-27.
2. Louis DN, Perry A, Reifenberger G, et al. The 2016 World Health Organization Classification of Tumors of the Central Nervous System: a summary. Acta Neuropathol 2016;131:803-20.
3. Cairncross JG, Ueki K, Zlatescu MC, et al. Specific genetic predictors of chemotherapeutic response and survival in patients with anaplastic oligodendrogliomas. J Natl Cancer Inst 1998;90:1473-79.
4. Ostrom QT, Gittleman H, Liao P, et al. CBTRUS Statistical Report: Primary brain and other central nervous system tumors diagnosed in the United States in 2010-2014. Neuro Oncol 2017;19:v1-v88.
5. van den Bent MJ, Brandes AA, Taphoorn MJ, et al. Adjuvant procarbazine, lomustine, and vincristine chemotherapy in newly diagnosed anaplastic oligodendroglioma: long-term follow-up of EORTC brain tumor group study 26951. J Clin Oncol 2013;31:344-50.

6. Brada M, Hoang-Xuan K, Rampling R, et al. Multicenter phase II trial of temozolomide in patients with glioblastoma multiforme at first relapse. Ann Oncol 2001;12:259-66.
7. Fisher BJ, Hu C, Macdonald DR, et al. Phase 2 study of temozolomide-based chemoradiation therapy for high-risk low-grade gliomas: preliminary results of Radiation Therapy Oncology Group 0424. Int J Radiat Oncol Biol Phys 2015;91:497-504.
8. Mikkelsen T, Doyle T, Anderson J, et al. Temozolomide single-agent chemotherapy for newly diagnosed anaplastic oligodendroglioma. J Neurooncol 2009;92:57-63.
9. Stupp R, Mason WP, van den Bent MJ, et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. N Engl J Med 2005;352:987-96.
10. Hegi ME, Diserens AC, Gorlia T, et al. MGMT gene silencing and benefit from temozolomide in glioblastoma. N Engl J Med 2005;352:997-1003.
11. 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.
12. Smith JS, Chang EF, Lamborn KR, et al. Role of extent of resection in the long-term outcome of low-grade hemispheric gliomas. J Clin Oncol 2008;26:1338-45.
13. Shaw EG, Berkey B, Coons SW, et al. Recurrence following neurosurgeon-determined gross-total resection of adult supratentorial low-grade glioma: results of a prospective clinical trial. J Neurosurg 2008;109:835-41.
14. Lacroix M, Abi-Said D, Fourney DR, et al. A multivariate analysis of 416 patients with glioblastoma multiforme: prognosis, extent of resection, and survival. J Neurosurg 2001;95:190-98.
15. Buckner JC, Shaw EG, Pugh SL, et al. Radiation plus procarbazine, CCNU, and vincristine in low-grade glioma. N Engl J Med 2016;374:1344-55.
16. Shaw EG, Wang M, Coons SW, et al. Randomized trial of radiation therapy plus procarbazine, lomustine, and vincristine chemotherapy for supratentorial adult low-grade glioma: initial results of RTOG 9802. J Clin Oncol 2012;30:3065-70.
17. Sanson M, Marie Y, Paris S, et al. Isocitrate dehydrogenase 1 codon 132 mutation is an important prognostic biomarker in gliomas. J Clin Oncol 2009;27:4150-54.

Cite this article as: Ziu M, Traylor JI. Temozolomide—the jack of all gliomas? Reviewing the interim results of the CATNON trial for 1p/19q non-co-deleted anaplastic glioma. Transl Cancer Res 2018;7(Suppl 4):S484-S487. doi: 10.21037/tcr.2018.03.25

