Could upfront temozolomide chemotherapy postpone the need for radiotherapy in young patients with high-risk low-grade gliomas?

Ze-Yang Li[1], Shi-Wen Yuan[2], Yan-Yan Song[3], N.U. Farrukh Hameed[1], Hong Chen[4], Dong-Xiao Zhuang[1], Jun-Feng Lu[1], Fang-Yuan Gong[1], Abudumijit Aibaidula[1], Zhi-Feng Shi[1], Shuai Wu[1], Qi-Hao Guo[5], Jin-Song Wu[1]

[1]Department of Neurosurgery, Huashan Hospital, Fudan University, Shanghai 200040, China;
[2]Department of Human Behavior and Psychiatry, Butler Hospital, Brown University, Providence, RI, USA;
[3]Department of Biostatistics, Medical School of Shanghai Jiaotong University, Shanghai 200025, China;
[4]Department of Neuropathology, Huashan Hospital, Shanghai Medical College, Fudan University, Shanghai 200040, China;
[5]Department of Geriatrics, Shanghai 6th People's Hospital, Shanghai 200233, China.

Gliomas are progressive and infiltrating primary brain tumors. National Comprehensive Cancer Network points out that for low-grade gliomas (LGGs) patients in a high-risk group (<40 years old and subtotal resection), standard strategies are maximum safe resection with radiotherapy and adjuvant chemotherapy; however, the guidelines do not address the question whether patients need adjuvant therapy immediately after diagnosis because of RTOG 9802.[1] Temozolomide (TMZ) is one of the first-line regimens used in LGGs chemotherapy, and results of EORTC 22033-26033 have shown that compared to TMZ chemotherapy, radiotherapy did not prolong progression-free survival (PFS) in LGGs patients significantly, and overall survival (OS) outcomes remain unknown.[2] A 12-year follow-up for patients <40 years showed that radiotherapy could cause significant treatment-related side effects such as cognitive dysfunction.[3]

In young patients, the goal is to avoid cognitive impairments; therefore, immediate post-operative radiotherapy is questionable. We initiated an interventional study (NCT02209428) and focused on response indicators and neurocognitive function changes related to TMZ chemotherapy to investigate whether we can use TMZ to postpone radiation and delay potential cognitive impairments.

NCT02209428 was initiated in 2014, as a prospective, one-arm, open-label study in a single tertiary specialized center (Glioma Surgery Division, Neurological Surgery Department of Huashan Hospital, Fudan University) in Shanghai, China. We enrolled LGGs patients under 40 years old with sub-total resected tumors in the eloquent areas. Chemotherapy was started within 2 weeks to 3 months after surgery and continued for six cycles. Metronomic TMZ regimen was administrated from day 1 to day 21 at a dose of 75 $mg \cdot m^{-2} \cdot d^{-1}$, repeated every 28 days. Patients were followed up by magnetic resonance imaging for tumor volume and neuropsychological evaluation. The primary endpoint is objective response rate (ORR), and objective response includes complete response (CR), partial response (PR), and minor response (MR).[4] Secondary endpoints include: (1) intensity of response (IOR), defined as the ratio of maximum volume reduction to residual volume after operation; (2) duration of response (DOR) is used instead of PFS; (3) malignant progression-free survival (MPFS), cognitive function results, and the safety of chemotherapy. We estimated 54 patients were sufficient to provide 80% power and a significance level of 5% to a detect difference in ORR between isocitrate dehydrogenase (IDH) mutant and wildtype groups. Fisher exact test was used for comparisons for ORR, and Wilcoxon-Mann-Whitney *U* test was performed for comparison of IOR. Kaplan-Meier method was used for DOR. A repeated mixed model was used for comparison among cognitive test scores, which could handle missing values. Unpaired *t*-test with Welch correction was used for comparing our cognitive test data with that in historical literature. For all analyzes, a *P* value of <0.05 was regarded as significant. Statistical analysis was done with SPSS version 19.0 (IBM Corp., Armonk, NY, USA).

The final follow-up was completed on December 30th, 2019. A total of 65 patients receiving adjuvant TMZ only

Access this article online

Quick Response Code:

Website: www.cmj.org

DOI: 10.1097/CM9.0000000000001434

Ze-Yang Li and Shi-Wen Yuan contributed equally to this work.

Correspondence to: Dr. Jin-Song Wu, Glioma Surgery Division, Department of Neurological Surgery, Huashan Hospital, Shanghai Medical College, Fudan University, Mid Wulumuqi Road 12, Jing'an District, Shanghai 200040, China
E-Mail: wujinsong@huashan.org.cn

Chinese Medical Journal 2021;134(11)
Received: 04-11-2020 **Edited by:** Yuan-Yuan Ji

were recruited with a median follow-up of 39.6 months, and 50 patients had a long-term evaluation with extensive serial neuropsychological batteries. ORR was 37/65 (56.9%), including 22/65 (33.9%) PR and 15/65 (23.1%) MR, while there was 2/65 (3.1%) stable disease and 26/65 (40.0%) progression disease. No CR occurred. IDH mutant patients had a more obvious ORR compared to IDH wild-type patients (64.3% *vs.* 11.1%, $P = 0.004$). No correlation was seen between ORR and other biomarkers such as 1p/19q codeletion, MGMT promoter methylation, α-thalassemia mental retardation syndrome X-linked (ATRX) loss, and telomerase reverse transcriptase (TERT) mutation ($P = 0.112$, 0.291, 0.732, and 0.245, respectively). IOR of IDH mutant patients was more obvious than that of IDH wildtype patients ($P = 0.023$), and IOR of 1p/19q codeletion patients was more obvious than that of 1p/19q retain patients ($P = 0.002$). There was no statistical difference in IOR for MGMT promoter methylation, ATRX loss, and *TERT* mutation ($P = 0.188$, 0.464, and 0.577, respectively).

Based on the 2016 World Health Organization Classification, diffuse astrocytoma, IDH-mutant and oligodendroglioma, IDH-mutant, and 1p/19q-codeleted can be classified as IDH-mutant group, and diffuse astrocytoma, IDH-wildtype as IDH-wildtype group. We found that the IDH-mutant group had longer DOR than the IDH-wildtype group (median DOR, 52.4 *vs.* 25.8 months; log-rank $P = 0.0007$). 1p/19q codeletion group also had a longer duration of response than 1p/19q retain group (median DOR, 52.4 *vs.* 37.5 months; log-rank $P = 0.049$). For histological features, both diffuse astrocytoma, IDH-mutant and oligodendroglioma, IDH-mutant, and 1p/19q-codeleted had a longer duration of response than diffuse astrocytoma, IDH-wildtype (median DOR, log-rank *P*: 44.5 *vs.* 25.8 months, 0.004; 52.4 *vs.* 25.8 months, 0.0003).

Malignant progression rate for IDH-mutant was 6/34 (17.7%), and that for diffuse astrocytoma, IDH-wildtype was 44.4%. Malignant progression rate for oligodendroglioma, IDH-mutant, and 1p/19q-codeleted patients was 2/22 (9.1%). Oligodendroglioma, IDH-mutant, and 1p/19q-codeleted also had a longer MPFS than diffuse astrocytoma, IDH-wildtype (median MPFS, unreached *vs.* 43.7 months; log-rank $P = 0.025$). MPFS for diffuse astrocytoma, IDH-mutant was unreached.

The OS follow-up time of the patients was not reached, and gliomas recurred in 26 of 65 patients. Three patients received TMZ chemotherapy for six cycles again and the tumor remained stable. Eleven patients received radiotherapy when the tumor recurred, with two patients eventually dying. Eleven patients received radiotherapy and chemotherapy after re-surgery, with four eventual deaths. One patient received re-surgery without radio-chemotherapy and the tumor remained stable.

We analyzed the cognitive data at 5-time points: before chemotherapy, after chemotherapy, 1 year after surgery, 2 years after surgery, and 3 years after surgery. Results are presented in Table 1. The mean Hopkins Verbal Learning Test-Revised (HVLT-R) score for each group is 14.5, 17.6, 20.5, 22.4, 23.9, and scores of 2 years and 3 years after surgery were statistically higher than those of 1 year after and before surgery. Although the mean HVLT-R score of 3 years after surgery was higher than that of 2 years after surgery, there was no statistical difference. There was no statistical difference in the HVLT-R percentage of retention among every group, implying that there was no testing effect bias due to patient recall of testing material. For Trail Making Test (TMT) time A, the mean time consumption for each group was 54.4, 37.8, 37.0, 31.8, and 31.5 s. For TMT time B, the mean time consumption for each group was 180.7, 107.2, 92.0, 94.1, and 80.1 s. Both TMT times A and B during follow-up showed that the time to complete tests decreased gradually, and the patients completed tests in a much shorter time compared to their performance before chemotherapy. For Multilingual Aphasia Examination Controlled Oral Word Association (COWAT), the mean number of animal naming for each group was 13.5, 16.3, 17.8, 18.4, and 19.1, and that for furniture naming was 12.7, 14.9, 16.4, 16.8, and 17.5. At the same time, the mean number for switch naming was

Table 1: Cognitive test of young patients with high-risk low-grade gliomas at 5-time points.

	Follow-up time point (mean)					*P*-value									
Items	(1)	(2)	(3)	(4)	(5)	(1)(2)	(1)(3)	(1)(4)	(1)(5)	(2)(3)	(2)(4)	(2)(5)	(3)(4)	(3)(5)	(4)(5)
HVLT-R															
Score	14.5	17.6	20.5	22.4	23.9	0.0004	<0.0001	<0.0001	<0.0001	0.0016	<0.0001	<0.0001	0.0492	<0.0001	0.1999
POR	0.41	0.17	0.11	0.12	0.11	0.8970	0.2979	0.3969	0.2291	0.6708	0.8893	0.6364	0.9949	0.9889	0.9230
TMT test															
TMT A	54.4	37.8	37.0	31.8	31.5	0.0001	<0.0001	<0.0001	<0.0001	1.0000	0.4741	0.0014	0.2871	0.0172	0.8346
TMT B	180.7	107.2	92.0	94.1	80.1	<0.0001	<0.0001	<0.0001	<0.0001	0.1892	0.7349	0.3929	0.7938	0.9991	0.7854
COWAT															
Animal	13.5	16.3	17.8	18.4	19.1	0.0005	<0.0001	<0.0001	<0.0001	0.2525	0.0769	0.0522	0.9067	0.6494	0.9435
Furniture	12.7	14.9	16.4	16.8	17.5	0.0185	<0.0001	<0.0001	<0.0001	0.3202	0.2475	0.0959	0.9979	0.7239	0.8863
Switch	12.3	15.6	17.1	17.4	18.0	<0.0001	<0.0001	<0.0001	<0.0001	0.2589	0.4120	0.1073	1.0000	0.8527	0.6244
MMSE	26.8	28.2	28.9	28.7	29.1	0.0047	0.0001	0.0002	<0.0001	0.0053	0.0488	0.0144	0.9455	1.0000	0.9419

Follow-up time point: (1) Before chemotherapy, (2) After chemotherapy, (3) 1 year after surgery, (4) 2 years after surgery, (5) 3 years after surgery. *P* value: Mixed model. HVLT-R: Hopkins Verbal Learning Test-Revised; POR: Percentage of retention; TMT: Trail Making Test; COWAT: Multilingual Aphasia Examination Controlled Oral Word Association; MMSE: Mini-Mental State Examination.

12.3, 15.6, 17.1, 17.4, and 18.4. COWAT showed that during follow-up, the number of naming had statistically increased as compared to that before chemotherapy. The mean Mini-Mental State Examination (MMSE) score for each group was 26.8, 28.2, 28.9, 28.7, 29.1, and scores of 1, 2, and 3 years after surgery were statistically higher than those of before and after chemotherapy. Although the mean MMSE score of 1, 2, and 3 years after operation increased gradually, there was no statistical difference among these three groups. We compared our patients with patients undergoing early radiotherapy (NCCTG protocol 86-72-51), the cognitive dysfunction was significantly lessened after chemotherapy.[5] (MMSE $P = 0.0200$; Auditory Learning Test [AVLT]/HVLT-R total $P = 0.0023$, TMT time Part A $P < 0.0001$; TMT time Part B $P < 0.0001$). Additionally, we compared cognitive results of patients receiving chemotherapy alone with that of 11 patients receiving post-operative radiotherapy with or without adjuvant chemotherapy for patients' choice or other pathologies. The results showed an obvious improvement in MMSE score, AVLT/HVLT-R total, and TMT time Part B tests (MMSE $P = 0.0242$; AVLT/HVLT-R total $P = 0.0022$; TMT time Part B $P = 0.0108$) [Supplementary Table 1, http://links.lww.com/CM9/A500].

The TMZ chemotherapy was well tolerated by all recruited patients, and all adverse effects could be relieved after treatment. And no discontinuation of chemotherapy occurred among all patients except one patient for Grade 3 thrombocytopenia. No patient had an alkylating agent-related secondary tumor.

In our study, we found that *IDH* mutation and 1p/19q codeletion are associated with better chemotherapy response and better prognosis, and 64.29% of LGG patients with *IDH* mutation can achieve partial or MR after TMZ chemotherapy. This suggested that both *IDH* mutation and 1p/19q codeletion are meaningful prognostic markers, which can help decide whether the patient needs to receive only chemotherapy at an early stage to delay radiotherapy. We recommend that providers engage with close follow-up of patients on upfront TMZ chemotherapy after surgery, and cautiously decide the addition of radiotherapy based on their response. Based on the median DOR, it is possible that for the majority of *IDH* mutant patients, TMZ chemotherapy alone can control tumor progression for 4 years or longer. For the *IDH* wild-type group, IOR and DOR showed poor response and prognosis. This group of tumors biologically and clinically resemble glioblastomas and therefore may need concurrent chemo and radiotherapy at an early stage.

In our study, TMT time A and B and COWAT showed that executive function, visual-spatial perception ability, language proficiency, and plasticity of patients improved at the end of chemotherapy. MMSE showed cognitive function had statistically improved even 1 year after surgery, and HVLT-R showed memory and attentional function had statistically improved even 2 years after surgery. This suggests that TMZ chemotherapy might not cause obvious neurotoxicity, which leads to cognitive impairment. Cognitive function can improve compared with the time before chemotherapy. Comparison between our results to the prospective study with the similar group of patients undergoing radiotherapy (NCCTG protocol 86-72-51) suggests that chemotherapy might protect neurocognitive function better than radiotherapy. Thus, it is worth considering upfront adjuvant TMZ chemotherapy in biologically favorable groups early after tumor resection to control tumor progression and delayed radiotherapy intervention to prevent early potential cognition decline in young high-functioning patients. To investigate whether there is a difference in cognitive function protection between radiotherapy and chemotherapy, we need to carry out further clinical research.

We conclude that *IDH* mutation is a predictive factor for better TMZ response and a prognostic factor for longer survival. It might be possible that young patients with *IDH* mutation could use upfront chemotherapy to postpone radiotherapy until progression to avoid potential cognitive impairments.

Acknowledgements

The authors thank all investigators in the centers who did a tremendous job to collect data, especially for Zhong Yang performing Magnetic Resonance Imaging and Yan Zhou performing cognitive tests.

Funding

This work was supported by the Chinese Society of Clinical Oncology (No. CSNO-2015-MSD06), and Shi-Wen Yuan's effort was supported by the National Institute of Mental Health (No. R25MH101076).

Conflicts of interest

None.

References

1. Shaw EG, Wang M, Coons SW, Brachman DG, Buckner JC, Stelzer KJ, *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; 30:3065–3070. doi: 10.1200/JCO.2011.35.8598.
2. Baumert BG, Hegi ME, Mj VDB, Von DA, Gorlia T, Hoangxuan K, *et al*. Temozolomide chemotherapy versus radiotherapy in high-risk low-grade glioma (EORTC 22033–26033): a randomised, open-label, phase 3 intergroup study. Lancet Oncol 2016;17:1521–1532. doi: 10.1016/S0140-6736(17)31442-3.
3. Douw L, Klein M, Fagel SS, van den Heuvel J, Taphoorn MJ, Aaronson NK, *et al*. Cognitive and radiological effects of radiotherapy in patients with low-grade glioma: long-term follow-up. Lancet Neurol 2009;8:810–818. doi: 10.1016/s1474-4422(09)70204-2.
4. Bent MVD, Wefel JS, Schiff D, Taphoorn M, Jaeckle K, Junck L, *et al*. Response assessment in neuro-oncology (a report of the RANO group): assessment of outcome in trials of diffuse low-grade gliomas. Lancet Oncol 2011;12:583–593. doi: 10.1016/S1470-2045(11)70057-2.
5. Laack NN, Brown PD, Ivnik RJ, Furth AF, Ballman KV, Hammack JE, *et al*. Cognitive function after radiotherapy for supratentorial low-grade glioma: a North Central Cancer Treatment Group prospective study. Int J Radiat Oncol Biol Phys 2005;63:1175–1183. doi: 10.1016/j.ijrobp.2005.04.016.

How to cite this article: Li ZY, Yuan SW, Song YY, Hameed NU, Chen H, Zhuang DX, Lu JF, Gong FY, Aibaidula A, Shi ZF, Wu S, Guo QH, Wu JS. Could upfront temozolomide chemotherapy postpone the need for radiotherapy in young patients with high-risk low-grade gliomas? Chin Med J 2021;134:1356–1358. doi: 10.1097/CM9.0000000000001434