Received 5 December 2020 | Revised 19 May 2021 | Accepted 27 May 2021
DOI: 10.1136/ebmed-2021-111622

This article is the first in a series of articles on evidence-based medicine.
GETTING STARTED

ORIGINAL ARTICLE

Postoperative anlotinib plus radiotherapy in patients with newly diagnosed, unmethylated O^6-methylguanine-DNA methyltransferase glioblastoma: A single-arm, phase 2 study

Bian Wu MD, PhD[1,2,3,4] | Zhanjie Zhang MD, PhD[5,6,7] | Hui Ma MD, PhD[8,9] | Jing Huang MD, PhD[10,11] | Xiu Liu MD[12] | Longfang Shi MD, PhD[13,14] | Kanchun Dong MD[15] | Dongxing Lei MD, PhD[16] | Xuan Wang MD, PhD[17] | Fangfang Zhang MD, PhD[18] | Hongwei Wang MD, PhD[19] | Hong Liu MD[20] | Fengzhi Tian MD, PhD[21] | Jianxin Xue MD, PhD[22] | Ruichao Chai MD, PhD[23] | Huiyuan Wang MD, PhD[24] | Xuebin Ma MD, PhD[25] | Dongsheng Wang MD, PhD[26] | Liu Yang MD, PhD[27] | Jiaqing Liang MD, PhD[28] | Yuhong Ma MD, PhD[29] | Jia Wang MD[30] | Lu Wei MD, PhD[31] | Cao Zhang MD[32] | Zhiwen Liang PhD[1] | Zhuang Fang MD[1] | Ziyu Wu MD, PhD[1] | Yuan Ma MD, PhD[1] | Fei Ma MD[33] | Geng Peng MD, PhD[2,3,4] | Xiaobing Jiang MD, PhD[1] | Runrey Yang MD, PhD[1,2,3,4]

[1]Department of Neurosurgery, Tianjin Medical University General Hospital, Tianjin, China
[2]Tianjin Neurosurgery Institute, Tianjin Medical University, Tianjin, China
[3]Tianjin Neurosurgery Clinical Medical Center, Tianjin Medical University, Tianjin, China
[4]Department of Neurosurgery, Tianjin Medical University Cancer Hospital and Institute, Tianjin, China
[5]Department of Neuro-Oncology, Tianjin Medical University Cancer Institute and Hospital, National Clinical Research Center for Cancer, Tianjin, China
[6]Tianjin Key Laboratory of Cancer Prevention and Therapy, Tianjin, China
[7]Tianjin Clinical Research Center for Cancer, Tianjin, China
[8]Department of Neurosurgery, Tianjin Medical University Second Hospital, Tianjin, China
[9]Tianjin Medical University Second Hospital Clinical Research Institute, Tianjin, China
[10]Department of Neurosurgery, Tianjin Medical University Cancer Hospital and Institute, Tianjin, China
[11]Tianjin Medical University Cancer Institute and Hospital, National Clinical Research Center for Cancer, Tianjin, China
[12]Department of Neurosurgery, Tianjin Medical University Hospital, Tianjin, China
[13]Department of Neurosurgery, Tianjin Medical University Hospital, Tianjin, China
[14]Department of Neurosurgery, Tianjin Medical University Hospital, Tianjin, China
[15]Department of Neurosurgery, Tianjin Medical University Hospital, Tianjin, China
[16]Department of Neurosurgery, Tianjin Medical University Hospital, Tianjin, China
[17]Department of Neurosurgery, Tianjin Medical University Hospital, Tianjin, China
[18]Department of Neurosurgery, Tianjin Medical University Hospital, Tianjin, China
[19]Department of Neurosurgery, Tianjin Medical University Hospital, Tianjin, China
[20]Department of Neurosurgery, Tianjin Medical University Hospital, Tianjin, China
[21]Department of Neurosurgery, Tianjin Medical University Hospital, Tianjin, China
[22]Department of Neurosurgery, Tianjin Medical University Hospital, Tianjin, China
[23]Department of Neurosurgery, Tianjin Medical University Hospital, Tianjin, China
[24]Department of Neurosurgery, Tianjin Medical University Hospital, Tianjin, China
[25]Department of Neurosurgery, Tianjin Medical University Hospital, Tianjin, China
[26]Department of Neurosurgery, Tianjin Medical University Hospital, Tianjin, China
[27]Department of Neurosurgery, Tianjin Medical University Hospital, Tianjin, China
[28]Department of Neurosurgery, Tianjin Medical University Hospital, Tianjin, China
[29]Department of Neurosurgery, Tianjin Medical University Hospital, Tianjin, China
[30]Department of Neurosurgery, Tianjin Medical University Hospital, Tianjin, China
[31]Department of Neurosurgery, Tianjin Medical University Hospital, Tianjin, China
[32]Department of Neurosurgery, Tianjin Medical University Hospital, Tianjin, China
[33]Department of Neurosurgery, Tianjin Medical University Hospital, Tianjin, China

Correspondence:
Prof. Runrey Yang MD, PhD, Cancer Institute, Tianjin Medical University General Hospital, Tianjin, China
Prof. Geng Peng MD, PhD, Department of Neurosurgery, Tianjin Medical University Cancer Hospital and Institute, Tianjin, China
Email: runrey@tmu.edu.cn, pengg@tmu.edu.cn

Funding information:
Tianjin Medical University General Hospital Talent Cultivation Fund, 02-020-0000
Tianjin Medical University General Hospital Talent Cultivation Fund, 02-020-0000
Tianjin Medical University Cancer Institute and Hospital Talent Cultivation Fund, 02-020-0000
Tianjin Medical University Cancer Institute and Hospital Talent Cultivation Fund, 02-020-0000
Tianjin Key Medical Discipline (Specialty) Construction Project, 02-020-0000
Tianjin Medical College, Huanhu Hospital, 02-020-0000
Tianjin Medical College, Huanhu Hospital, 02-020-0000
Tianjin Medical College, Huanhu Hospital

although confirmatory magnetic resonance imaging was performed, anlotinib-induced vascular normalization may have reduced contrast enhancement, potentially masking subtle progression and inflating PFS estimates. This challenge underscores the need for advanced imaging biomarkers for anti-angiogenic therapy trials.

CONCLUSIONS

This phase 2 study demonstrated encouraging survival benefits and a manageable safety profile of anlotinib plus radiotherapy in patients with newly diagnosed, unmethylated *MGMT* GBM. Based on our data, a confirmatory randomized clinical trial will be planned to investigate whether anlotinib is a substitute for TMZ in this patient population. These results also support further evaluation of anlotinib combined with other molecularly targeted agents to improve survival outcomes in patients with unmethylated *MGMT* GBM.

AUTHOR CONTRIBUTIONS

Bian Wu: Conceptualization; investigation; writing—original draft. **Zhanjie Zhang**: Conceptualization; data curation; writing—original draft. **Hui Ma**: Formal analysis; methodology; writing—original draft. **Jing Huang**: Data curation; writing—original draft. **Xixi Liu**: Formal analysis; methodology; and writing—original draft. **Liangliang Shi**: Formal analysis; writing—original draft. **Xiaochuan Dong**: Methodology. **Deqiang Lei**: Resources. **Xuan Wang**: Resources. **Fangcheng Zhang**: Resources. **Hongyang Zhao**: Resources. **Hong Lin**: Resources. **Rong Fu**: Resources. **Zhenwei Zou**: Investigation. **You Qin**: Investigation. **Haijun Wang**: Resources. **Xuebin Hu**: Resources. **Dongxiao Yao**: Resources. **Lin Yang**: Resources. **Jinsong Yang**: Validation. **Xiaohua Hong**: Validation. **Jing Wang**: Validation. **Lu Wen**: Validation. **Can Zhang**: Validation. **Zhiwen Liang**: Investigation. **Zhiyong Yang**: Investigation. **Xin Nieb**: Investigation. **Gang Liu**: Investigation. **Fei Hu**: Resources. **Gang Peng**: Data curation; writing—review and editing; supervision. **Xiaobing Jiang**: Conceptualization; investigation; supervision; writing—review and editing. **Kunyu Yang**: Conceptualization; data curation; funding acquisition; writing—review and editing; investigation; supervision.

ACKNOWLEDGMENTS

We thank the patients and their families for their participation in this trial and CHIA TAI Tianqing Pharmaceutical Group Company, Ltd., China, for data analyses. This work was supported by the National Natural Science Foundation of China (Grant No. 82330085); and the CHIA TAI Tianqing Pharmaceutical Group Company, Ltd.

CONFLICT OF INTEREST STATEMENT

The authors disclosed no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ORCID

Bian Wu https://orcid.org/0000-0002-4024-4291
Xixi Liu https://orcid.org/0000-0003-4440-5328
Lu Wen https://orcid.org/0000-0003-2203-5119
Kunyu Yang https://orcid.org/0000-0002-2575-4736

REFERENCES

1. Tan AC, Ashley DM, López GY, Malinzak M, Friedman HS, Khasraw M. Management of glioblastoma: state of the art and future directions. *CA Cancer J Clin*. 2020;70(4):299-312. doi:10.3322/caac.21613
2. Stupp R, Mason WP, van den Bent MJ, et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. *N Engl J Med*. 2005;352(10):987-996. doi:10.1056/nejmoa043330
3. Wen PY, Weller M, Lee EQ, et al. Glioblastoma in adults: a Society for Neuro-Oncology (SNO) and European Society of Neuro-Oncology (EANO) consensus review on current management and future directions. *Neuro Oncol*. 2020;22(8):1073-1113. doi:10.1093/neuonc/noaa106
4. Weller M, van den Bent M, Preusser M, et al. EANO guidelines on the diagnosis and treatment of diffuse gliomas of adulthood. *Nat Rev Clin Oncol*. 2021;18(3):170-186. doi:10.1038/s41571-020-00447-z
5. Hegi ME, Diserens AC, Gorlia T, et al. MGMT gene silencing and benefit from temozolomide in glioblastoma. *N Engl J Med*. 2005;352(10):997-1003. doi:10.1056/nejmoa043331
6. Hegi ME, Diserens AC, Godard S, et al. Clinical trial substantiates the predictive value of O-6-methylguanine-DNA methyltransferase promoter methylation in glioblastoma patients treated with temozolomide. *Clin Cancer Res*. 2004;10(6):1871-1874. doi:10.1158/1078-0432.ccr-03-0384
7. Taylor JW, Schiff D. Treatment considerations for MGMT-unmethylated glioblastoma. *Curr Neurol Neurosci Rep*. 2015;15(1):507. doi:10.1007/s11910-014-0507-z
8. Sim HW, McDonald KL, Lwin Z, et al. A randomized phase II trial of veliparib, radiotherapy, and temozolomide in patients with unmethylated MGMT glioblastoma: the VERTU study. *Neuro Oncol*. 2021;23(10):1736-1749. doi:10.1093/neuonc/noab111
9. Omuro A, Brandes AA, Carpentier AF, et al. Radiotherapy combined with nivolumab or temozolomide for newly diagnosed glioblastoma with unmethylated MGMT promoter: an international randomized phase III trial. *Neuro Oncol*. 2023;25(1):123-134. doi:10.1093/neuonc/noac099
10. Jue TR, Nozue K, Lester AJ, et al. Veliparib in combination with radiotherapy for the treatment of MGMT unmethylated glioblastoma. *J Transl Med*. 2017;15(1):61. doi:10.1186/s12967-017-1164-1
11. Seano G, Jain RK. Vessel co-option in glioblastoma: emerging insights and opportunities. *Angiogenesis*. 2020;23(1):9-16. doi:10.1007/s10456-019-09691-z
12. Chinot OL, Wick W, Mason W, et al. Bevacizumab plus radiotherapy-temozolomide for newly diagnosed glioblastoma. *N Engl J Med*. 2014;370(8):709-722. doi:10.1056/nejmoa1308345
13. Herrlinger U, Schäfer N, Steinbach JP, et al. Bevacizumab plus irinotecan versus temozolomide in newly diagnosed O6-methylguanine-DNA methyltransferase nonmethylated glioblastoma: the randomized GLARIUS trial. *J Clin Oncol*. 2016;34(14):1611-1619. doi:10.1200/jco.2015.63.4691
14. Lee EQ, Kaley TJ, Duda DG, et al. A multicenter, phase II, randomized, noncomparative clinical trial of radiation and temozolomide with or without vandetanib in newly diagnosed glioblastoma patients. *Clin Cancer Res*. 2015;21(16):3610-3618. doi:10.1158/1078-0432.ccr-14-3220
15. Batchelor TT, Mulholland P, Neyns B, et al. Phase III randomized trial comparing the efficacy of cediranib as monotherapy, and in

combination with lomustine, versus lomustine alone in patients with recurrent glioblastoma. *J Clin Oncol*. 2013;31(26):3212-3218. doi:10.1200/jco.2012.47.2464
16. Angara K, Borin TF, Arbab AS. Vascular mimicry: a novel neovascularization mechanism driving anti-angiogenic therapy (AAT) resistance in glioblastoma. *Transl Oncol*. 2017;10(4):650-660. doi:10.1016/j.tranon.2017.04.007
17. Ahir BK, Engelhard HH, Lakka SS. Tumor development and angiogenesis in adult brain tumor: glioblastoma. *Mol Neurobiol*. 2020;57(5):2461-2478. doi:10.1007/s12035-020-01892-8
18. Reardon DA, Turner S, Peters KB, et al. A review of VEGF/VEGFR-targeted therapeutics for recurrent glioblastoma. *J Natl Compr Canc Netw*. 2011;9(4):414-427. doi:10.6004/jnccn.2011.0038
19. Daneshimehr F, Barabadi Z, Abdolahi S, et al. Angiogenesis and its targeting in glioblastoma with focus on clinical approaches. *Cell J*. 2022;24(10):555-568. doi:10.22074/cellj.2022.8154
20. Wang N, Jain RK, Batchelor TT. New directions in anti-angiogenic therapy for glioblastoma. *Neurotherapeutics*. 2017;14(2):321-332. doi:10.1007/s13311-016-0510-y
21. Syed YY. Anlotinib: first global approval. *Drugs*. 2018;78(10):1057-1062. doi:10.1007/s40265-018-0939-x
22. Wang Y, Liang D, Chen J, et al. Targeted therapy with anlotinib for a patient with an oncogenic FGFR3-TACC3 fusion and recurrent glioblastoma. *Oncologist*. 2021;26(3):173-177. doi:10.1002/onco.13530
23. Guan Y, Li J, Gong X, et al. Safety and efficacy of hypofractionated stereotactic radiotherapy with anlotinib targeted therapy for glioblastoma at the first recurrence: a preliminary report. *Brain Sci*. 2022;12(4):471. doi:10.3390/brainsci12040471
24. Xu Q, Huang K, Meng X, et al. Safety and efficacy of anlotinib hydrochloride plus temozolomide in patients with recurrent glioblastoma. *Clin Cancer Res*. 2023;29(19):3859-3866. doi:10.1158/1078-0432.ccr-23-0388
25. Brandner S, McAleenan A, Kelly C, et al. MGMT promoter methylation testing to predict overall survival in people with glioblastoma treated with temozolomide: a comprehensive meta-analysis based on a Cochrane systematic review. *Neuro Oncol*. 2021;23(9):1457-1469. doi:10.1093/neuonc/noab105
26. Uno M, Oba-Shinjo SM, Camargo AA, et al. Correlation of MGMT promoter methylation status with gene and protein expression levels in glioblastoma. *Clinics (Sao Paulo)*. 2011;66(10):1747-1755. doi:10.1590/s1807-59322011001000013
27. Han B, Li K, Wang Q, et al. Effect of anlotinib as a third-line or further treatment on overall survival of patients with advanced non-small cell lung cancer: the ALTER 0303 phase 3 randomized clinical trial. *JAMA Oncol*. 2018;4(11):1569-1575. doi:10.1001/jamaoncol.2018.3039
28. Zhou M, Chen X, Zhang H, et al. China National Medical Products Administration approval summary: anlotinib for the treatment of advanced non-small cell lung cancer after two lines of chemotherapy. *Cancer Commun*. 2019;39(1):36. doi:10.1186/s40880-019-0383-7
29. Wen PY, van den Bent M, Youssef G, et al. RANO 2.0: Update to the Response Assessment in Neuro-Oncology criteria for high- and low-grade gliomas in adults. *J Clin Oncol*. 2023;41(33):5187-5199. doi:10.1200/jco.23.01059
30. National Cancer Institute. *Common Terminology Criteria for Adverse Events (CTCAE)*. Version 4.0. 2009. NIH Publication No. 09-5410. US Department of Health and Human Services, National Institutes of Health, National Cancer Institute; 2016.
31. Alnahhas I, Alsawas M, Rayi A, et al. Characterizing benefit from temozolomide in MGMT promoter unmethylated and methylated glioblastoma: a systematic review and meta-analysis. *Neurooncol Adv*. 2020;2(1):vdaa082. doi:10.1093/noajnl/vdaa082
32. Gilbert MR, Dignam JJ, Armstrong TS, et al. A randomized trial of bevacizumab for newly diagnosed glioblastoma. *N Engl J Med*. 2014;370(8):699-708. doi:10.1056/nejmoa1308573
33. Stupp R, Taillibert S, Kanner A, et al. Effect of tumor-treating fields plus maintenance temozolomide vs. maintenance temozolomide alone on survival in patients with glioblastoma: a randomized clinical trial. *JAMA*. 2017;318(23):2306-2316. doi:10.1001/jama.2017.18718
34. Lai S, Li P, Liu X, et al. Efficacy and safety of anlotinib combined with the Stupp regimen in patients with newly diagnosed glioblastoma: a multicenter, single-arm, phase II trial. *Cancer Biol Med*. 2024;21(5):433-444. doi:10.20892/j.issn.2095-3941.2023.0373
35. Carrasco-García E, Saceda M, Martínez-Lacaci I. Role of receptor tyrosine kinases and their ligands in glioblastoma. *Cells*. 2014;3(2):199-235. doi:10.3390/cells3020199
36. Snuderl M, Fazlollahi L, Le LP, et al. Mosaic amplification of multiple receptor tyrosine kinase genes in glioblastoma. *Cancer Cell*. 2011;20(6):810-817. doi:10.1016/j.ccr.2011.11.005
37. Xie C, Wan X, Quan H, et al. Preclinical characterization of anlotinib, a highly potent and selective vascular endothelial growth factor receptor-2 inhibitor. *Cancer Sci*. 2018;109(4):1207-1219. doi:10.1111/cas.13536
38. Lin B, Song X, Yang D, Bai D, Yao Y, Lu N. Anlotinib inhibits angiogenesis via suppressing the activation of VEGFR2, PDGFRbeta and FGFR1. *Gene*. 2018;654:77-86. doi:10.1016/j.gene.2018.02.026
39. Li PJ, Lai SZ, Jin T, et al. Radiotherapy opens the blood-brain barrier and synergizes with anlotinib in treating glioblastoma. *Radiother Oncol*. 2023;183:109633. doi:10.1016/j.radonc.2023.109633
40. Huang J, Xiao J, Fang W, et al. Anlotinib for previously treated advanced or metastatic esophageal squamous cell carcinoma: a double-blind randomized phase 2 trial. *Cancer Med*. 2021;10(5):1681-1689. doi:10.1002/cam4.3771
41. Chi Y, Shu Y, Ba Y, et al. Anlotinib monotherapy for refractory metastatic colorectal cancer: a double-blinded, placebo-controlled, randomized phase III trial (ALTER0703). *Oncologist*. 2021;26(10):e1693-e1703. doi:10.1002/onco.13857
42. Jayson GC, Kerbel R, Ellis LM, Harris AL. Antiangiogenic therapy in oncology: current status and future directions. *Lancet*. 2016;388(10043):518-529. doi:10.1016/s0140-6736(15)01088-0
43. Khasraw M, Ameratunga MS, Grant R, Wheeler H, Pavlakis N. Antiangiogenic therapy for high-grade glioma. *Cochrane Database Syst Rev*. 2014(9):CD008218. doi:10.1002/14651858.CD008218.pub3
44. Yang P, Zhang W, Wang Y, et al. IDH mutation and MGMT promoter methylation in glioblastoma: results of a prospective registry. *Oncotarget*. 2015;6(38):40896-40906. doi:10.18632/oncotarget.5683
45. Woo PYM, Lee JWY, Lam SW, et al. Radiotherapy-induced glioblastoma: distinct differences in overall survival, tumor location, pMGMT methylation and primary tumor epidemiology in Hong Kong Chinese patients. *Br J Neurosurg*. 2024;38(2):385-392. doi:10.1080/02688697.2021.1881445

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Wu B, Zhang Z, Ma H, et al. Postoperative anlotinib plus radiotherapy in patients with newly diagnosed, unmethylated O^6-methylguanine–DNA methyltransferase glioblastoma: a single-arm, phase 2 study. *Cancer*. 2026;e70502. doi:10.1002/cncr.70502