

# Comparative efficacy of antiangiogenic treatment for newly diagnosed glioblastoma

## A protocol for systematic review and network meta-analysis

Runting Li, MD<sup>a</sup>, Chao Li, MD<sup>a</sup>, Zhaolun Cai, MD<sup>b</sup>, Lianwang Li, MD<sup>a</sup>, Liudong Wei, MD<sup>a</sup>, Zenghui Qian, MD<sup>a</sup>, Dabiao Zhou, MD, PhD<sup>a,\*</sup>

### Abstract

**Background:** Glioblastoma is the most common malignant primary brain tumor which has highly expressed vascular endothelial growth factor. To date, various antiangiogenic drugs have been investigated in clinical trials but with no overall conclusion, especially for newly diagnosed glioblastoma (nGBM). In this study, Bayesian network meta-analysis will be used to conduct a comprehensive analysis of the results of different clinical trials, and assess the efficacy of different antiangiogenic drugs on nGBM.

**Methods:** In order to find more comprehensive information about the application of antiangiogenic drugs in nGBM patients, we searched the MEDLINE, EMBASE, Web of Science, and Cochrane Central Register of Controlled Trials for relevant randomized controlled trials. We also reviewed their reference lists to avoid omissions. Cochrane risk of bias tool (V.1.4.3) and Stata (V.15.0) will be used to assess the methodological quality of this review.

**Results:** This study will provide reliable evidence for different antiangiogenic therapies in nGBM patients.

**Conclusion:** We will evaluate the relative effectiveness of different antiangiogenic drugs and rank each intervention in nGBM patients through prognosis to provide decision-making reference on which method to choose for clinicians.

**Protocol registration number:** CRD42019146537

**Abbreviations:** GBM = glioblastoma, nGBM = newly diagnosed glioblastoma, NMA = network meta-analysis, OS = overall survival, PFS = progression-free survival, RCTs = randomized controlled trials.

**Keywords:** antiangiogenic drugs, Bayesian network meta-analysis, glioblastoma, newly diagnosed glioblastoma, overall survival, progression-free survival, protocol

## 1. Introduction

Glioblastoma (GBM) is the most common malignant primary brain tumor, accounting for about 28% of all brain tumors and 80% of malignant brain tumors. GBM is also known for its

invasive and aggressive behavior.<sup>[1,2]</sup> Patients with newly diagnosed glioblastoma (nGBM) have a poor prognosis even when treated with maximal resection followed by radiotherapy combined with temozolomide (TMZ), as well as maintenance therapy with TMZ. The median survival time is 14 to 16 months, and tumor re-growth and patient relapse still remain inevitable.<sup>[3–6]</sup> Moreover, once GBM recurs, the median overall survival (OS) time is typically 3 to 9 months, and available therapies have a limited impact on outcome.<sup>[7]</sup>

The biology of oncogenesis and the molecular mechanisms of GBM have showed that it typically overexpresses vascular endothelial growth factor, which can promote tumor angiogenesis, contributing to tumor growth and progression.<sup>[8]</sup> Therefore, antiangiogenic therapy seems to be an attractive therapeutic strategy. Drawing on the experience of positive results from antiangiogenic therapy in other solid cancers, there have recently been a number of clinical trials of antiangiogenic drugs in GBM.<sup>[9]</sup> Among those drugs, bevacizumab (BEV), a humanized monoclonal antibody against vascular endothelial growth factor, has already played a positive role when combined with standard therapy in recurrent diagnosed glioblastoma with both radiographic response and progression-free survival (PFS).<sup>[10–13]</sup> In May 2009, the Food and Drug Administration approved BEV for the first-line treatment of recurrent diagnosed glioblastoma patients.<sup>[14]</sup> Noteworthy, 2 studies in 2014 showed a longer PFS with BEV but failed to demonstrate an improvement in OS in nGBM.<sup>[15,16]</sup> Trials of various other antiangiogenic drugs were

LRT and LC contributed equally to this work as the first authors.

This study is supported by the National Natural Science Foundation of China (Grant Number 31671109).

The authors declare there are no conflicts of interest.

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

<sup>a</sup> Department of Neurosurgery, Beijing Tiantan Hospital, Capital Medical University, Beijing, <sup>b</sup> Department of Gastrointestinal Surgery, West China Hospital, Sichuan University, Chengdu 610041, Sichuan, China.

\* Correspondence: Dabiao Zhou, Department of Neurosurgery, Beijing Tiantan Hospital, Capital Medical University, No.119 South Fourth Ring West Road, Fengtai District, Beijing 100070, China (e-mail: dabiaozhou@163.com).

Copyright © 2020 the Author(s). Published by Wolters Kluwer Health, Inc. This is an open access article distributed under the Creative Commons Attribution License 4.0 (CCBY), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

How to cite this article: Li R, Li C, Cai Z, Li L, Wei L, Qian Z, Zhou D. Comparative efficacy of antiangiogenic treatment for newly diagnosed glioblastoma: a protocol for systematic review and network meta-analysis. *Medicine* 2020;99:19(e20011).

Received: 24 March 2020 / Received in final form: 27 March 2020 / Accepted: 27 March 2020

<http://dx.doi.org/10.1097/MD.00000000000020011>



### 2.9. Data synthesis and statistical methods

Time-to-event outcomes will be assessed by calculating hazard ratios. Dichotomous outcomes will be analyzed by calculating the relative risks. Results from the NMA will be presented as summary relative effect sizes (hazard ratios or relative risks) and relative 95% confidence intervals for each possible pair of treatments.

We will first conduct a standard pairwise meta-analysis of all the direct comparisons with Stata (Stata Corp), using a random-effects model. Heterogeneity variances for each pairwise comparison will be estimated by  $Q$ -test and  $I^2$  statistic.<sup>[41]</sup>

Next, we will perform the NMA using R x64 3.5.0 and Stata (StataCorp). The inconsistency of our results will be confirmed by the node-splitting method and its Bayesian  $P$ -value.<sup>[42]</sup> We will estimate the potential ranking probability of interventions by calculating the surface under the cumulative ranking curve (SUCRA) for each intervention.<sup>[43]</sup> The SUCRA value ranges between 0 and 1, and the intervention with a higher SUCRA value is considered to have better efficacy.<sup>[40]</sup>

Subgroup analysis will be performed based on O-6-methylguanine–DNA methyltransferase (MGMT) status and recursive partitioning analysis (RPA) class.

We will use comparison-adjusted funnel plots to evaluate the small study effects in the present study.<sup>[44]</sup>

### 3. Discussion

This will be the first NMA to comprehensively compare the efficacy of different antiangiogenic drugs in nGBM patients. Despite the advantages of this approach, there are some inevitable limitations. Some antiangiogenic drugs are not discussed in the literature due to the lack of RCTs or the RCT is still ongoing. The potentially high heterogeneity among different studies may also influence the final results of this NMA. However, we hope this study will uncover the best antiangiogenic treatment currently available for clinical practice and assist in directing future study design.

#### Author contributions

**Conceptualization:** Dabiao Zhou, Chao Li.

**Data curation:** Zhaolun Cai.

**Investigation:** Runting Li, Zenghui Qian.

**Methodology:** Zhaolun Cai.

**Project administration:** Dabiao Zhou, Runting Li.

**Resources:** Dabiao Zhou, Runting Li.

**Software:** Zhaolun Cai.

**Supervision:** Dabiao Zhou.

**Validation:** Zhaolun Cai.

**Writing – original draft:** Runting Li, Chao Li.

**Writing – review and editing:** Dabiao Zhou, Zhaolun Cai.

#### References

- Ostrom QT, Gittleman H, Liao P, et al. CBTRUS statistical report: primary brain and central nervous system tumors diagnosed in the United States in 2007-2011. *Neuro Oncol* 2014;16 Suppl 4:iiv1–63.
- 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.
- Norden AD, Drappatz J, Wen PY. Novel anti-angiogenic therapies for malignant gliomas. *Lancet Neurol* 2008;7:1152–60.
- Sanai N, Polley MY, McDermott MW, et al. An extent of resection threshold for newly diagnosed glioblastomas. *J Neurosurg* 2011;115:3–8.
- Stupp R, Hegi ME, Mason WP, et al. Effects of radiotherapy with concomitant and adjuvant temozolomide versus radiotherapy alone on survival in glioblastoma in a randomised phase III study: 5-year analysis of the EORTC-NCIC trial. *Lancet Oncol* 2009;10:459–66.
- Stupp R, Pavlidis N, Jelic S, et al. ESMO minimum clinical recommendations for diagnosis, treatment and follow-up of malignant glioma. *Ann Oncol* 2005;16 Suppl 1:i64–5.
- Yung WKA, Albright RE, Olson J, et al. A phase II study of temozolomide vs. procarbazine in patients with glioblastoma multiforme at first relapse. *Br J Cancer* 2000;83:588–93.
- Jain RK, di Tomaso E, Duda DG, et al. Angiogenesis in brain tumours. *Nat Rev Neurosci* 2007;8:610–22.
- Jain RK. Normalizing tumor microenvironment to treat cancer: bench to bedside to biomarkers. *J Clin Oncol* 2013;31:2205–18.
- Ferrara N, Hillan KJ, Gerber HP, et al. Discovery and development of bevacizumab, an anti-VEGF antibody for treating cancer. *Nat Rev Drug Discov* 2004;3:391–400.
- Friedman HS, Prados MD, Wen PY, et al. Bevacizumab alone and in combination with irinotecan in recurrent glioblastoma. *J Clin Oncol* 2009;27:4733–40.
- Kreisl TN, Kim L, Moore K, et al. Phase II trial of single-agent bevacizumab followed by bevacizumab plus irinotecan at tumor progression in recurrent glioblastoma. *J Clin Oncol* 2009;27:740–5.
- Vredenburgh JJ, Desjardins A, Herndon JE2nd, et al. Bevacizumab plus irinotecan in recurrent glioblastoma multiforme. *J Clin Oncol* 2007;25:4722–9.
- Johnson DR, Leeper HE, Uhm JH. Glioblastoma survival in the United States improved after Food and Drug Administration approval of bevacizumab: a population-based analysis. *Cancer* 2013;119:3489–95.
- Chinot OL, Wick W, Mason W, et al. Bevacizumab plus radiotherapy-temozolomide for newly diagnosed glioblastoma. *N Engl J Med* 2014;370:709–22.
- Gilbert MR, Dignam JJ, Armstrong TS, et al. A randomized trial of bevacizumab for newly diagnosed glioblastoma. *N Engl J Med* 2014;370:699–708.
- Chinnaiyan P, Won M, Wen PY, et al. A randomized phase II study of everolimus in combination with chemoradiation in newly diagnosed glioblastoma: results of NRG Oncology RTOG 0913. *Neurooncology* 2018;20:666–73.
- Laack NN, Galanis E, Anderson SK, et al. Randomized, placebo-controlled, phase II study of dasatinib with standard chemo-radiotherapy for newly diagnosed glioblastoma (GBM), NCCTG N0877 (Alliance): American Society of Clinical Oncology 2015; 2013-2013.
- 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;21:3610–8.
- Stupp R, Hegi ME, Gorlia T, et al. Cilengitide combined with standard treatment for patients with newly diagnosed glioblastoma with methylated MGMT promoter (CENTRIC EORTC 26071-22072 study): a multicentre, randomised, open-label, phase 3 trial. *Lancet Oncol* 2014;15:1100–8.
- Westphal M, Heese O, Steinbach JP, et al. A randomised, open label phase III trial with nimotuzumab, an anti-epidermal growth factor receptor monoclonal antibody in the treatment of newly diagnosed adult glioblastoma. *Eur J Cancer* 2015;51:522–32.
- Wick W, Gorlia T, Van Den Bent MJ, et al. Radiation therapy and concurrent plus adjuvant temsirolimus (CCI-779) versus chemoradiation with temozolomide in newly diagnosed glioblastoma without methylation of the MGMT gene promoter: American Society of Clinical Oncology 2014; 2003-2003.
- Fu P, He Y-S, Huang Q, et al. Bevacizumab treatment for newly diagnosed glioblastoma: systematic review and meta-analysis of clinical trials. *Mol Clin Oncol* 2016;4:833–8.
- Li Y, Hou M, Lu G, et al. The prognosis of anti-angiogenesis treatments combined with standard therapy for newly diagnosed glioblastoma: a meta-analysis of randomized controlled trials. *PLoS One* 2016;11:e0168264.
- Liao K-L, Huang S, Wu Y-P. The prognosis for patients with newly diagnosed glioblastoma receiving bevacizumab combination therapy: a meta-analysis. *Onco Targets Ther* 2018;11:3513–20.

- [26] Lombardi G, Pambuku A, Bellu L, et al. Effectiveness of antiangiogenic drugs in glioblastoma patients: a systematic review and meta-analysis of randomized clinical trials. *Crit Rev Oncol Hematol* 2017;111:94–102.
- [27] Su J, Cai M, Li W, et al. Molecularly targeted drugs plus radiotherapy and temozolomide treatment for newly diagnosed glioblastoma: a meta-analysis and systematic review. *Oncol Res* 2016;24:117–28.
- [28] Wang W-L, Aru N, Liu Z, et al. Prognosis of patients with newly diagnosed glioblastoma treated with molecularly targeted drugs combined with radiotherapy vs temozolomide monotherapy: a meta-analysis. *Medicine* 2019;98:e17759.
- [29] Xiao Q, Yang S, Ding G, et al. Anti-vascular endothelial growth factor in glioblastoma: a systematic review and meta-analysis. *Neurol Sci* 2018;39:2021–31.
- [30] Salanti G. Indirect and mixed-treatment comparison, network, or multiple-treatments meta-analysis: many names, many benefits, many concerns for the next generation evidence synthesis tool. *Res Synth Methods* 2012;3:80–97.
- [31] Moher D, Shamseer L, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Syst Rev* 2015;4:1.
- [32] Hutton B, Salanti G, Caldwell DM, et al. The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: checklist and explanations. *Ann Intern Med* 2015;162:777–84.
- [33] Cai Z, Yin Y, Yin Y, et al. Comparative effectiveness of adjuvant treatments for resected gastric cancer: a network meta-analysis. *Gastric Cancer* 2018;21:1031–40.
- [34] Cai Z, Yin Y, Zhao Z, et al. Comparative effectiveness of neoadjuvant treatments for resectable gastroesophageal cancer: a network meta-analysis. *Front Pharmacol* 2018;9:872.
- [35] Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *J Clin Epidemiol* 2009;62:e1–34.
- [36] Charrois TL. Systematic reviews: what do you need to know to get started? *Can J Hosp Pharm* 2015;68:144–8.
- [37] Higgins JPT, Altman DG, Gøtzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011;343:d5928.
- [38] Gs HJP. *Cochrane handbook for systematic reviews of interventions version 5.1.0 (updated March 2011)*. Naunyn-Schmiedeberg's Archiv für Experimentelle Pathologie und Pharmakologie 2014;5:S38.
- [39] Cai Z, Yin Y, Shen C, et al. Comparative effectiveness of preoperative, postoperative and perioperative treatments for resectable gastric cancer: a network meta-analysis of the literature from the past 20 years. *Surg Oncol* 2018;27:563–74.
- [40] Cai Z, Zhou Y, Wang C, et al. Optimal reconstruction methods after distal gastrectomy for gastric cancer: a systematic review and network meta-analysis. *Medicine (Baltimore)* 2018;97:e10823.
- [41] Higgins JP, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses. *BMJ* 2003;327:557–60.
- [42] Dias S, Welton NJ, Caldwell DM, et al. Checking consistency in mixed treatment comparison meta-analysis. *Stat Med* 2010;29:932–44.
- [43] Salanti G, Ades AE, Ioannidis JP. Graphical methods and numerical summaries for presenting results from multiple-treatment meta-analysis: an overview and tutorial. *J Clin Epidemiol* 2011;64:163–71.
- [44] Chaimani A, Higgins JP, Mavridis D, et al. Graphical tools for network meta-analysis in STATA. *PLoS One* 2013;8:e76654.