

RESEARCH ARTICLE

Comprehensive Analysis of Temozolomide Treatment for Patients with Glioma

Wen-Bing Yang^{1*}, Bian-Zhi Xing², Hua Liang³

Abstract

Background: This analysis was conducted to evaluate the efficacy and safety of temozolomide based chemotherapy in treating patients with glioma. **Methods:** Clinical studies evaluating the efficacy and safety of temozolomide based regimens for patients with glioma were identified using a predefined search strategy. Pooled response rates (RRs) were calculated. **Results:** In temozolomide based regimens, 5 clinical studies including 152 patients with advanced glioma were considered eligible for inclusion. Four clinical studies included temozolomide. Systematic analysis suggested that, in all patients, pooled CR was 21% (32/152), and PR was 21% (32/152). Grade 3/4 toxicity included neutropenia, thrombocytopenia, and anemia. No grade 3 or 4 renal or liver toxicity was observed. No treatment related death occurred with temozolomide based treatment. **Conclusion:** This systematic analysis suggests that temozolomide based regimens are associated with mild response rate and acceptable toxicity for treatment of glioma patients.

Keywords: Glioma - temozolomide chemotherapy - efficacy - toxicity

Asian Pac J Cancer Prev, **15** (19), 8405-8408

Introduction

Gliomas are the most common malignant brain tumors in Chinese adults (Cheng et al., 2013; Ge et al., 2013; Jiang et al., 2013; Liang et al., 2013; Yu et al., 2013; Wang et al., 2013; Luo et al., 2013; Zhu et al., 2013). Previous report revealed a statistically significant survival benefit for patients with gliomas treated with radiotherapy (RT) plus concomitant and adjuvant temozolomide (TMZ) chemotherapy, which currently represents the standard of care for newly diagnosed gliomas (Stupp et al., 2005; Stupp et al., 2007; Stupp et al., 2009). However, despite surgery, RT and TMZ, patients with gliomas always relapse and ultimately develop terminal disease. TMZ is used in the treatment of glioma and is associated with an improvement of the prognosis (Khasraw et al., 2009). TMZ is an orally administered chemotherapeutic drug that methylates DNA in a way that prevents tumor cell proliferation, and is a second-generation alkylating agent approved by the Food and Drug Administration in 1999 (Stupp et al., 2002; Stupp et al., 2005; Khasraw et al., 2009). After Stupp reported the efficacy and toxicity of TMZ, it became a common and standard regimen in the chemotherapy of malignant gliomas (Stupp et al., 2005). Since 2006, it has been approved for the standard treatment of newly diagnosed glioblastoma in conjunction with radiotherapy for Chinese patients. However, no comprehensive analysis on TMZ in treating

patients with glioma was conducted. According to this background, we hypothesize that TMZ originated regimen could be established as an optimal schedule for patients with glioma. And we should conduct this analysis.

Materials and Methods

Search strategy

We searched PUBMED, by using the following search term: (glioma) and (temozolomide). All clinical studies evaluating the impact of temozolomide on the response or survival and side effects for glioma published in English prior to July 1st of 2014 were identified. If samples of two studies overlap, only the latest one was included. Additional articles were obtained from references within the articles identified by the electronic search. We did not consider meeting abstracts or unpublished reports.

Inclusion and exclusion criteria

We reviewed abstracts of all citations and retrieved studies. The following criteria were used to include published studies: (a) clinical studies, with temozolomide; (b) The study was performed in accordance with the Helsinki Declaration (1964, amended in 1975 and 1983) of the World Medical Association. Eligibility criteria included histologically verified with glioma, the presence of at least one bidimensionally measurable lesion, a performance status (WHO) 2, age 18 years. Studies were

¹Department of Radiology, ²Department of Radiology, ³Department of Obstetrics and Gynecology, Renmin Hospital of Wuhan University, Wuhan, Hubei Province, China *For correspondence: ywb_wenbing@hotmail.com

excluded if one of the following existed: (a) duplicate data; (b) no sufficient data were reported.

Data collection and analysis

Selection of trials and data extraction: The titles and abstracts of publications identified according to the above search strategy were assessed independently for inclusion by two authors, the full text was selected for further assessment if the abstract suggests relevance. Disagreement was resolved by discussion. Data was extracted by independent authors. The following recorded data were extracted: author, publication data, and country of the first or corresponding author, the number of patients.

Results

There were 152 papers relevant to the search words by the end of July, 2014. Via steps of screening the title and reading the abstract, 5 studies were identified (Verhoeff et al., 2010; Zustovich et al., 2009; Quinn et al., 2009; Tosoni et al., 2008; Brandes et al., 2006) when TMZ was used in chemotherapy. These studies had been carried out in Europe countries, and the United States. The following outcomes were presented in all studies and extracted for combined analysis: response rate, including the rate of complete or partial response (CR or PR) and toxicities.

Characteristics of TMZ as a component of chemotherapy, studies included in this study are presented as short-term outcomes: the response rate of Verhoeff JJ et al. was 20%, of Zustovich F et al. was 29.4%, 19% for Quinn JA et al, 30% for Tosoni A et al, and 9% for Brandes AA et al. Totally, 152 patients were enrolled and 32 patients achieved CR or PR, the pooled response rate thus was 21% (32/152).

Observation on toxicities: Nausea and vom-iting, were exceedingly common. Grade 3/4 toxicities included neutropenia, thrombocytopenia, and anemia (graded according to the World Health Organization grading system). No treatment related death occurred in TMZ based treatment.

Discussion

According to 2007 World Health Organization classification on tumors of central nervous system, glioma is divided into grades I-IV. Grade I and II are defined as low grade and grade III and IV as high grade. The incidence of the tumor in China is 1-4/100, 000 (Zhou et al., 2012). Treatment strategies for malignant glioma include removing the local lesion by surgery followed by adjuvant radiation and chemotherapy (Chen et al., 2013; Yang et al., 2013). Despite considerable efforts, however, the prognosis for patients with glioma is still poor. Resistance to radiation and chemotherapy is the main reason in treatment failure of malignant glioma. On this background, chemotherapy plays an important role in this settings. Currently, concomitant radiochemotherapy with TMZ, an alkylating agent, is widely used in China, and is reported to reduce the risk of recurrence and prolong patient survival (Strik et al., 2012; Yang et al., 2013). However, clinical studies of TMZ on malignant glioma in

Chinese patients is not well documented. Thus, we conduct this comprehensive analysis on efficacy, side reactions, and clinical application of TMZ in the treatment of glioma. Compared with common used chemotherapeutic agents, effect of TMZ in treating malignant glioma is significantly improved. It was suggested that complete response and partial response rates are approximately 30% with TMZ versus only 10% with common used chemotherapeutic agents (Shen et al., 2012). Two-year survival rate is improved from 10.4% to 26.5% with the use of TMZ when the efficacy of TMZ was compared with lomustine (Shen et al., 2012; Qian et al., 2009). In a previous report, when patients were randomly divided into TMZ group and lomustine group, the response rate in TMZ and lomustine group was 35.7% and 9.1%, and clinical benefit rate was 90.5% and 75.0%, respectively. Yan evaluated the efficacy of TMZ in the treatment of recurrent glioma, the treatment effect of TMZ was modest (Yan et al., 2007). Thus they concluded that patients who were treated first with TMZ had significantly higher rates of response and 6-month progression-free survival than patients retreated with previous chemotherapy. Much of the relevant data generated in China is similar to that for studies performed in other countries, and shows that the therapeutic effect of TMZ is more effective than that of traditional chemotherapy regimens with regard to progression-free survival, overall survival, complete response rate, and clinical benefit rate in patients with malignant glioma (Yan et al., 2007). Silvani et al. (Silvani et al., 2008) analyzed the activity and safety of procarbazine and fotemustine combination in the treatment of TMZ-refractory glioblastoma patients. They obtained a low rate of toxicity: only 2% of patients had grades 3-4 haematologic toxicity and no patients required dose reduction. They demonstrated the results of efficacy: median PFS and OS were 19.3 and 28.7 weeks, respectively. The association of TMZ and fotemustine in TMZ -refractory glioblastoma was also unsuccessful in previous study due to the important toxicity of the combination (Gaviani et al., 2008); in fact, this study was stopped for relevant side-effects that occurred in the first 20 patients: 13 patients did not complete the third cycle because of grades 3-4 thrombocytopenia and 7 of 13 patients had grade 4 granulocytopenia (Gaviani et al., 2008).

In recent years, Bevacizumab, an anti-VEGF antibody, was approved by the US Food and Drug Administration in 2009 for patients with recurrent gliomas who have failed previous TMZ and radiation therapy based on prior studies (Vredenburgh et al., 2007; Friedman et al., 2009). This is because gliomas are highly vascularised brain tumors and are attractive targets for antiangiogenic therapies. Moreover, a recent clinical trial showed encouraging evidence of bevacizumab activity as well as acceptable safety among patients with recurrent grade III malignant glioma (Reardon et al., 2011). It is demonstrated that during bevacizumab therapy tumors may evade the inhibition of VEGF signaling and so the association of a cytotoxic drug might lead to more effective treatment. This could be the reason why bevacizumab would enhance the delivery of an active cytotoxic drug. But bevacizumab is

very expensive and not yet covered by medical insurance in China, thus not available for most of patients.

We analyzed the efficacy and toxicity of TMZ by a comprehensive assessment on TMZ when treating patients with glioma. The response rate of Verhoeff JJ et al. was 20%, of Zustovich F et al. was 29.4%, 19% for Quinn JA et al, 30% for Tosoni A et al, and 9% for Brandes AA et al. Totally, 152 patients were enrolled and 32 patients achieved CR or PR, the pooled response rate thus was 21% (32/152). Although TMZ is associated with a set of toxicities, most of the toxicities were grade 1 or 2 and were tolerable to patients. However, gastrointestinal troubles, e.g. nausea and vomiting, were exceedingly common. Thus, our systemic analysis suggests that TMZ based regimens are associated with mild response rate and accepted toxicities for treating patients with glioma.

References

- Athanassiou H, Synodinou M, Maragoudakis E, et al (2005). Randomized phase II study of temozolomide and radiotherapy compared with radiotherapy alone in newly diagnosed glioblastoma multiforme. *J Clin Oncol*, **23**, 2372-7.
- Brandes AA, Tosoni A, Cavallo G, et al (2006). Temozolomide 3 weeks on and 1 week off as first-line therapy for recurrent glioblastoma: phase II study from gruppo italiano cooperativo di neuro-oncologia (GICNO). *Br J Cancer*, **95**, 1155-60.
- Chen C, Xu T, Lu Y, et al (2013). The efficacy of temozolomide for recurrent glioblastoma multiforme. *Eur J Neurol*, **20**, 223-30.
- Cheng HB, Xie C, Zhang RY, et al (2013). Xeroderma pigmentosum complementation group f polymorphisms influence risk of glioma. *Asian Pac J Cancer Prev*, **14**, 4083-7.
- Gaviani P, Salmaggi A, Silvani A (2008). Combined chemotherapy with temozolomide and fotemustine in recurrent glioblastoma patients. *J Neurooncol*, **104**, 617-18.
- Ge YF, Sun J, Jin CJ, et al (2013). AntagomiR-27a targets FOXO3a in glioblastoma and suppresses U87 cell growth in vitro and in vivo. *Asian Pac J Cancer Prev*, **14**, 963-8.
- Jiang J, Quan XF, Zhang L, et al (2013). The XRCC3 Thr241Met polymorphism influences glioma risk - a meta-analysis. *Asian Pac J Cancer Prev*, **14**, 3169-73.
- Khasraw M, Bell D, Wheeler H (2009). Long-term use of temozolomide: could you use temozolomide safely for life in gliomas? *J Clin Neurosci*, **16**, 854-5.
- Liang HJ, Yan YL, Liu ZM, et al (2013). Association of XRCC3 Thr241Met polymorphisms and gliomas risk: evidence from a meta-analysis. *Asian Pac J Cancer Prev*, **14**, 4243-7.
- Luo KQ, Mu SQ, Wu ZX, et al (2013). Polymorphisms in DNA repair genes and risk of glioma and meningioma. *Asian Pac J Cancer Prev*, **14**, 449-52.
- National Cancer Institute. CTCAE v3.0. Available at <http://www.cancer.gov> (accessed on 9 August 2006).
- Ohgaki H, Kleihues P (2009). Genetic alterations and signaling pathways in the evolution of gliomas. *Cancer Sci*, **100**, 2235-41.
- Qian ZZ, Wang HQ, Liu XM, et al (2009). [A multicenter randomized controlled study of temozolomide in 97 patients with malignant brain glioma]. *Zhonghua Yi Xue Za Zhi*, **89**, 2059-62. Chinese.
- Quinn JA1, Jiang SX, Reardon DA, et al (2009). Phase II trial of temozolomide (TMZ) plus irinotecan (CPT-11) in adults with newly diagnosed glioblastoma multiforme before radiotherapy. *J Neurooncol*, **95**, 393-00.
- Reardon DA, Herndon JE, II, Peters K, et al (2011). Outcome after bevacizumab clinical trial therapy among recurrent grade III malignant glioma patients. *J Neurooncol*, **107**, 213-21.
- Santoni M, Paccapelo A, Burattini L, Onofri A, Cascinu S (2012). Twice-daily dosing of temozolomide in combination with fotemustine for the treatment of patients with refractory glioblastoma. *Anticancer Res*, **32**, 1099-01.
- Shen D, Yang QY, Chen ZP (2012). [Advances in the chemotherapy of malignant gliomas with temozolomide]. *Chin J Neurooncol*, **4**, 271-6. Chinese.
- Shen D, Yang QY, Chen ZP. Advances in the chemotherapy of malignant gliomas with temozolomide. *Chin J Neurooncol*, **4**, 271-6. Chinese.
- Silvani A, Lamperti E, Gaviani P, et al (2008). Salvage chemotherapy with procarbazine and fotemustine combination in the treatment of temozolomide treated recurrent glioblastoma patients. *J Neurooncol*, **87**, 143-51.
- Strik HM, Marosi C, Kaina B, et al (2012). Temozolomide dosing regimens for glioma patients. *Curr Neurol Neurosci Rep*, **12**, 286-93.
- Stupp R, Dietrich PY, Kraljevic S, et al (2002). Promising survival for patients with newly diagnosed glioblastoma multiforme treated with concomitant radiation plus temozolomide followed by adjuvant temozolomide. *J Clin Oncol*, **20**, 1375-82.
- Stupp R, Hegi ME, Gilbert MR, Chakravarti A (2007). Chemoradiotherapy in Malignant Glioma: Standard of Care and Future Directions. *J Clin Oncol*, **25**, 4127-36.
- Stupp R, Hegi ME, Mason WP, et al. (2009) 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 EORTCNCIC trial. *Lancet Oncol*, **10**, 459-66.
- Stupp R, Mason WP, van den Bent MJ, et al (2005). Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. *N Engl J Med*, **352**, 987-96.
- Stupp R, Mason WP, van den Bent MJ, et al. (2005) Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. *N Engl J Med*, **352**, 987-96.
- Tosoni A1, Franceschi E, Ermani M, et al (2008). Temozolomide three weeks on and one week off as first line therapy for patients with recurrent or progressive low grade gliomas. *J Neurooncol*, **89**, 179-85.
- Verhoeff JJ, Lavini C, van Linde ME, et al (2010). Bevacizumab and dose-intense temozolomide in recurrent high-grade glioma. *Ann Oncol*, **21**, 1723-7.
- Vredenburgh JJ, Desjardins A, Herndon JE, II, et al (2007). Bevacizumab plus irinotecan in recurrent glioblastoma multiforme. *J Clin Oncol*, **25**, 4722-29
- Walker MD, Green SB, Byar DP, et al (1980). Randomized comparisons of radiotherapy and nitrosoureas for the treatment of malignant glioma after surgery. *N Engl J Med*, **303**, 1323-9.
- Wang YX, Fan K, Tao DB, et al (2013). Association between genetic polymorphism of xrcc1 gene and risk of Glioma in ? Chinese population. *Asian Pac J Cancer Prev*, **14**, 5957-60.
- Yan YI, Tang WY, Deng ZX, et al (2007). [Efficacy of temozolomide in treatment of recurrent glioma]. *Cancer Res Prev Treat*, **17**, 1359-64. Chinese.
- Yang P, Wang Y, Peng X, et al (2013). Management and survival rates in patients with glioma in China (2004-2010): a retrospective study from a single-institution. *J Neurooncol*, **113**, 259-66.
- Yu CY, Liang GB, Du P, et al (2013). Lgr4 promotes glioma cell

- proliferation through activation of Wnt signaling. *Asian Pac J Cancer Prev*, **14**, 4907-11.
- Zhou LF, Wang RZ, Bao SD, et al (2012). Chinese guideline for diagnosis and treatment on central nervous system tumors. *Zhonghua Yi Xue Za Zhi*, **92**, 2309-13.
- Zhu Y, Zhuang JX, Wang Q, et al (2013). Inhibitory effect of benzyl isothiocyanate on proliferation in vitro of human glioma cells. *Asian Pac J Cancer Prev*, **14**, 2607-10.
- Zustovich F1, Lombardi G, Della Puppa A, et al (2009). A phase II study of cisplatin and temozolomide in heavily pre-treated patients with temozolomide-refractory high-grade malignant glioma. *Anticancer Res*, **29**, 4275-9.
- Zwinkels H, Roon K, Jeurissen FJ, et al (2009). Management of temozolomide toxicity by nurse practitioners in neuro-oncology. *Oncol Nurs Forum*, **36**, 225-31.