

## Clinical Practice of Chemotherapy with Temozolomide in China

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### Abstract

The treatment for malignant tumors in the central nervous system (CNS) mainly consists of surgical resection followed by adjuvant radiation and chemotherapy. Temozolomide (TMZ), a second-generation of oral alkylating agent, plays an increasingly important role in the treatment of malignant glioma in China. However, the history of TMZ use in China, has not been well reviewed. In this study, an extensive literature search of Pubmed and major Chinese electronic databases was performed to identify clinical reports on TMZ use in mainland China. We found that TMZ is a standard addition to postoperative RT for glioblastoma, followed by 6 cycles of adjuvant treatments as Chinese and NCCN guidelines recommended. But since TMZ is relatively expensive to most Chinese patients, especially in undeveloped areas, some other regimens are still commonly used. It is also indicated for relapsed or Grade III glioma, with some potential value in brain metastasis and primary central nerve lymphoma. Extended use or combination therapy including TMZ may benefit more for glioma patients. As the clinical trials have been paid more attention in the recent years, effort and collaboration should be made to conduct well-designed multicenter randomized clinical trials on TMZ, with the aim of improving the prognosis of patients with CNS tumor in mainland China.

**Keywords** Central Nervous System tumor; Chemotherapy; Temozolomide; China

status of TMZ chemotherapy for treating patients with brain tumor in China.

### Introduction

Chemotherapy for central nervous system (CNS) tumor first became available in the 1950s and reports from the related clinical studies appeared in the early 1970s in China [1]. The traditional chemotherapy agents consist of small molecule drugs that are highly lipid soluble and penetrate to the blood brain barriers (BBB) [2], such as carmustine (BCNU), lomustine (CCNU), nimustine (ACNU) and semustine (MeCCNU). However, the application of these agents attained only modest effect on improving patient survival [3]. On the other hand, these alkylating agents appeared severe toxicities such as myelosuppression and gastrointestinal reaction, which limit application of chemotherapy. Temozolomide (TMZ) is an orally administered alkylating agent used for treatment of glioblastoma multiforme (GBM) with significantly improved efficacy and safety, which is presently the first-line chemotherapy for patients with malignant glioma in China. It is a standard addition to postoperative RT for GBM, followed by 6 cycles of adjuvant TMZ. Nowadays it is also indicated for relapsed high-grade glioma and not indicated for, and replacing the older (and less well tolerated) PCV (Procarbazine-Lomustine-Vincristine) regimen for oligodendroglioma in some places. The standard treatment scheme for TMZ in China, is 75 mg/m<sup>2</sup> daily concurrent temozolomide during the course of radiotherapy, then 150-200 mg/m<sup>2</sup> post-radiotherapy on a 5-day schedule every 28 days, and has been confirmed to reduce the recurrence rates and prolong the survival of the patients [4]. However, as a relatively new agent, the history of TMZ chemotherapy in CNS tumor in China has not been assessed. This article is to review the

### Methodology

We reviewed the literatures and identified clinical studies reporting outcomes of CNS tumor patients treated with chemotherapy in mainland China. The electronic databases of Pubmed, China Knowledge Resource Integrated Database, Chinese Medical Association Digital Periodicals and VIP Database for Chinese Technical Periodicals were searched. Keywords searched included "CNS tumor", "glioma", "lymphoma", "brain metastasis" and 'temozolomide'. There were no language restrictions for the searched articles. Titles and abstracts were first examined to exclude irrelevant diseases and treatment, and duplicates were excluded. Studies selected were in accordance with the following criteria: i) A clinical study had been conducted on temozolomide for CNS tumor in mainland China; ii) The number of patients was  $\geq 5$ ; iii)  $>70\%$  of patients were adults ( $\geq 18$  years). Information of publications, patient and chemotherapy information was extracted. Collected data were analyzed and reviewed.

### Results

A total of 383 potentially eligible publications were found using the search strategy and by screening titles and abstracts from Jan 2003 to Oct 2013. A total of 165 articles were identified to be in line with the selection criteria, of which 138 (83.6%) were retrospective and 27(16.4%) were prospective.

There were 6836 patients with CNS tumor were enrolled in the 165 studies. The median age of patients was 34-56 years and the male/female ratio was 1.5:1. Most of TMZ papers focused on gliomas (93.9%, 155/165), including the verification of the efficacies and side

effects in high or low-grade glioma, the responses of combinations of other drugs or radiation, extensive use in high-grade glioma. Besides glioma patients, TMZ also used for other CNS tumors such as brain metastasis and CNS lymphoma. Side effects were acceptable, including gastrointestinal adverse reactions (34.4%), mild neutropenia (46.9%), fatigue (86.9%), and alopecia (46.9%). Grade III-IV Neutropenia were found in 9.4% patients.

## Discussion

### General status of TMZ usage in China

Studies on TMZ began at the beginning of the 2003 in mainland China, for treating the glioma patients. In 2003, a group from Tianjin Medical School published preliminary studies on the efficacy of TMZ in gliomas. This retrospective study introduced an experience of adjuvant TMZ in 17 high-grade glioma patients, with an objective response rate of 47.1% and a 6-month survival rate of 58.8%, demonstrated the antitumor activity of TMZ in Chinese glioma patients with mild side-effects. In the following years, publications of glioma chemotherapy in mainland China increased significantly. Before 2010, an increasing number of publications have been published (Figure 1), but the number of publications has been decreased in 2012 and 2013.

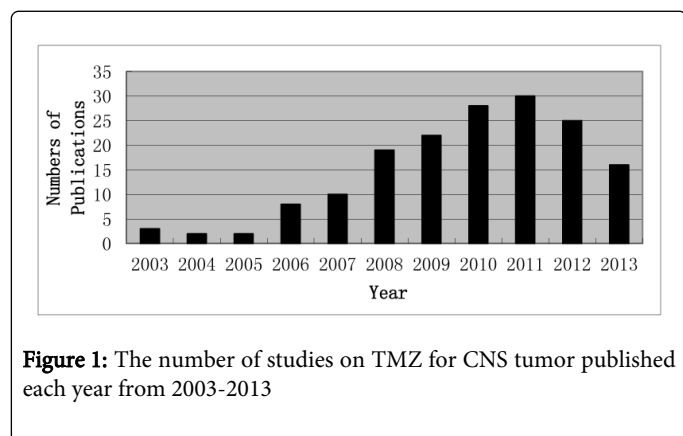


Figure 1: The number of studies on TMZ for CNS tumor published each year from 2003-2013

Multiple disciplines were involved in TMZ treatment. Of the 165 studies, 88 (53.3%) were performed in the department of neurosurgery, 46 (27.9%) in the department of medical oncology and 20 (12.1%) in the department of radiotherapy (Figure 2). According to a previous analysis of the chemotherapy for the glioma, there may be two reasons for this phenomenon [2]. On one hand, since the neuro-oncologists were lacking in mainland China, most of brain tumor patients were followed up by the neurosurgeons. As a result, neurosurgeons prescribed TMZ which was convenient and easy, directly after the surgery. On the other hand, compared to other departments, neurological complications during chemotherapy and disease progression could be managed by neurosurgeons with more confidence and efficiency. With the development of neuro-oncology in mainland China in the past 10 years, physicians with expertise of oncology have been trained for chemotherapy for CNS tumor patients. The increasing number of neuro-oncologists in mainland China will provide glioma patients with better and more specialized care and focus on both clinical and translational research in the field of neuro-oncology.

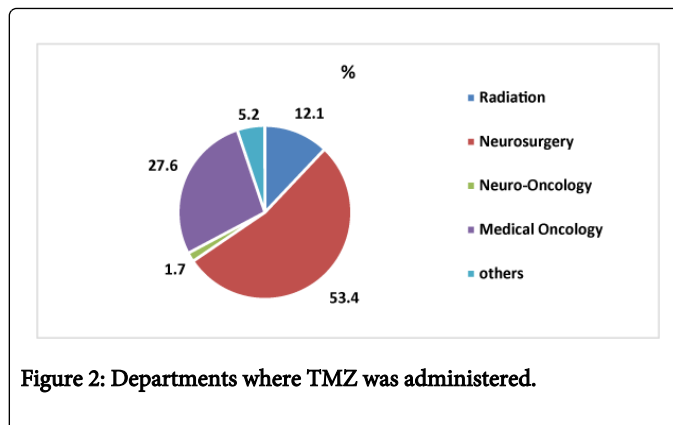


Figure 2: Departments where TMZ was administered.

The combination treatment is extensively used in China. Firstly, the concurrent radiation and TMZ is the most frequently used. According to a meta analysis depending on the domestic evidence, treatment of malignant glioma with postoperative radiotherapy plus temozolomide can improve effective rate and the survival [5]. The inter- and intra-tumoral heterogeneity of gliomas suggests that a combination regimen may be efficacious in producing lasting anti-tumor effect and overcoming drug resistance. For example, a synergistic antitumor effect between TMZ and interferon- $\beta$  (IFN- $\beta$ ) was reported in malignant glioma cells. Yang et al recently initiated a randomized phase II study to evaluate the clinical effectiveness of combination therapy with TMZ and IFN- $\beta$  in recurrent high-grade glioma [6]. It showed that the combinations treatment has moderate activity for recurrent high-grade glioma, which thus worth further investigation. Other publications showed that the combination including TMZ, such as TMZ+ CPT-11, TMZ+DDP were comparable in efficacy to TMZ alone but more toxic and poorly tolerated.

However, the substantial cost of TMZ restricts its widespread use, especially in health resource-limited regions in China. Wu conducted an economic analysis to evaluate the cost-effectiveness of TMZ in China [7]. The baseline analysis in the overall cohort showed that the TMZ strategy increased the cost and quality-adjusted life years (QALY) relative to the RT strategy by \$25,328.4 and 0.29, respectively; and the TMZ strategy increased the cost and QALY relative to the other chemotherapy drugs such as nitrosourea (NT) strategy by \$23,906.5 and 0.25, respectively. Therefore, the incremental cost effectiveness ratio (ICER) per additional QALY of the TMZ strategy, relative to the RT strategy and the NT strategy, amounts to \$87,940.6 and \$94,968.3, respectively. This cost-effectiveness consistent with the actual situation that Chinese physicians and patients often face dilemmas regarding the use of expensive therapies. The results indicated that better outcomes could be achieved by decreasing the cost of TMZ, and it is appropriate to recommend the TMZ to the insurance system.

### TMZ for glioma

Similar to the situation in western countries, chemotherapy for glioma in mainland China was mainly administered with TMZ. Before the advent of using TMZ, radiation was followed by chemotherapy with nitrosourea-based drugs for newly diagnosed glioma patients post-operation. The combinations of the traditional chemotherapy agent with topoisomerase II inhibitor such as teniposide (VM-26), or platinum drugs such as cisplatin(CDDP), were often applied with nitrosourea based drugs [2]. For example, the regimens usually

included the alkylating drugs 90 mg/m<sup>2</sup> on day 1 and VM-26 60 mg/m<sup>2</sup> on day 1 to 3, 4-6 weeks for a cycle [8]. Clinical studies demonstrate that combination therapies with radiotherapy and TMZ chemotherapy are superior to either treatment alone [4,9,10]. Currently, studies on TMZ chemotherapy account for 40% and this proportion is increasing in China [2], and it has been demonstrated that optimized treatment strategies with TMZ are most suitable for Chinese patients. A meta analysis including 7 papers were included and 438 Chinese patients indicated the effects of temozolomide was significantly better than other traditional chemotherapy drugs in newly diagnosed high-grade glioma [11]. Another meta analysis includes 8 randomised clinical trials involving 864 patients showed that compared with other chemotherapy drugs for the patients of postoperative radiotherapy, TMZ could increase the overall treatment effect, extend survival time, reduce adverse side effects, and thus improve quality of life of glioma patients [12].

Currently, the standard treatment for glioma becomes common in mainland China. National society, such as Chinese Association of Neurosurgery-Brain Tumor Board and Chinese Society of Neuro-oncology, published guidelines including "Chinese guideline of diagnosis & treatment for glioma patients", "Clinical Practice Guidelines for Central Nervous System Tumors". Currently, postoperative synchronization chemotherapy with TMZ is a widely employed treatment scheme for GBM in China, and has been confirmed to reduce the recurrence rates and prolong the survival of the patients [4]. Also, TMZ is recommended for WHO III glioma patients. However, since TMZ is relatively expensive to most Chinese patients, especially in remote areas, the traditional regimens are still commonly used as chemotherapy.

In recent years, more and more reports on the efficacy of TMZ with newly diagnosed or recurrent low-grade glioma (LGG). For example, The high response rate of confirms that TMZ chemotherapy is a valid option in the treatment of progressive LGG [13]. Some evidence showed that patients with chemosensitive LGG as predicted by heterozygotic loss of chromosomal arms 1p and 19q or methylation of the promoter of the MGMT-gene in the genome of the glioma cells respond to TMZ. It also showed a relevant clinical benefit during TMZ treatment, with gaining seizure control and QoL improvement [14]. Since the potential benefit of LGG. We have conducted a phase III clinical trial to compare the patient survival of the standard radiation with or without TMZ in LGG (data not published yet).

Referring to the recurrent glioma, the optimal chemotherapy regimens are still not defined. Currently, combination therapies of TMZ with targeted agents, such as bevacizumab and natalizumab, other drugs such as cisplatin or interferon, or switching to non-conventional TMZ regimens including dose dense (150 mg/m<sup>2</sup> on days 1 to 7, repeated on day 15, or 75 to 100 mg/m<sup>2</sup> on days 1 to 21, 28 days for a cycle) or metronomic (50 mg/m<sup>2</sup> continuously on days 1 to 28, 28 days for a cycle) regimens have been tested for the treatment of recurrent tumors [15,16].

In the elderly (≥ 60 years old) or younger (≤ 14 years old) patient, there was no strong evidence from clinical trial to use TMZ. In the clinics, TMZ should only be used carefully in elderly patients with unfavorable KPS (<70). It was reported that standard radiotherapy plus concomitant TMZ may be an advantageous treatment option for elderly patients with newly diagnosed GBM who present with good prognostic factors [17]. In future, the randomized controlled clinical trials are necessary to confirm the efficacy and the toxicity for the elderly and younger patients.

Although the 6-cycle regimen of TMZ has been used for gliomas as a standard chemotherapy, more and more data show that the cycles may not be strong enough to consolidate the efficacy as the adjuvant treatment. A group in southern China shared their experience to extend TMZ chemotherapies from 7 to 24 cycles in 32 glioma patients [18]. And the result showed that extended use of TMZ based on MGMT expression pattern was safe to patients with gliomas, which may improve response rates (overall response rate was 81.5 %) and PFSs (6 month PFS and 12 month PFS were 100% and 71% respectively) compared to conventional regimens.

When compared to the side effect, there was no significant change in quality of life (QOL) compared to baseline over the course of 6-12 cycles of TMZ, no matter in the low-grade or high-grade glioma. However, patients with right-hemisphere tumors, which spared the dominant side, report higher physical or social realm scores [14]. Tumor location and laterality have been shown to correlate with specific symptom, not depending on the duration of TMZ.

### TMZ for brain metastasis

Brain metastasis accounts for the majority of the CNS tumor. The most common primary tumors, which metastasize to the brain, are lung cancer [19,20], breast cancer [21,22] and melanoma [23]. The optimal systemic therapy for patients is still controversial. However, many clinical investigations had been discouraged by the concern that although chemotherapy drugs would have efficacy against the primary tumor, they would not cross the blood-brain barrier. Even though some evidence showed that the blood-brain barrier was disrupted when brain metastasis were present and chemotherapy could be effective against brain metastases from chemosensitive solid tumors [24], chemotherapy would not be as active against the metastatic brain disease as other metastatic organs. However, some papers showed that compared to other traditional chemotherapy drugs, TMZ may benefit more for brain metastasis patients [25-45]. The therapeutic benefit of temozolomide depends on its ability to alkylate/methylate DNA, which most often occurs at the N-7 or O-6 positions of guanine residues. This methylation might also show great potential to treat brain metastases. Studies combining TMZ with whole-brain radiotherapy reported more favorable response rates ranging from 0.176 to 0.959 with median overall survival ranging from 4.1 to 12 months. In these trials, TMZ might be shown to possess a radiosensitizing effect [24,46]. Studies that combined TMZ with other drugs had also been reported in patients with brain metastases. For example, Pegylated liposomal doxorubicin had the ability to accumulate in both brain tissue and tumor tissue within the brain [47,48]. As an active cytotoxic drug in solid tumors, cisplatin might enhance the anti-tumour activity of TMZ by reducing the activity of the DNA repair enzyme. So randomized controlled phase III studies are necessary to be conducted to evaluate the effects of TMZ combined with other drugs in brain metastasis.

### TMZ for primary central nervous system lymphoma (PCNSL)

PCNSL is rare, accounting for only 2%-3% of non-Hodgkin lymphoma (NHL) cases but the prognosis is relatively poorer than other subtypes of NHL. The first-line chemotherapy is HD-MTX based treatment. As the NCCN guideline recommends, TMZ can be considered for the relapsed PCNSL patients. In a study conducted by Tongji Medical College in Wuhan, 12 relapsed elderly patients were observed with TMZ treatment by 7 days on/ 7 days off and weekly use

of CD-20 antibody Rituximab [49]. The overall survival was 9 months with mild toxicities, which indicated that combination chemotherapy including TMZ may improve the long-term survival with moderate toxicity for the treatment of elderly relapsed PCNSL.

## Conclusion

There are still challenges in TMZ usage for CNS tumor in mainland China. Most of the studies were retrospective with a small sample size, which may result in bias and weaken the scientific strength of the studies. However, the qualities of the clinical studies in China have been improved a lot since the clinical trials have been paid more attention in recent years. This review of TMZ for CNS tumor in mainland China shows that the role of TMZ in the management of glioma is well-recognized, and the indication has gradually expanded to the relapsed and other CNS tumor such as brain metastasis and PCNSL. TMZ is still the best choice in China to treat brain tumors according to the meta analysis, but more and more data showed that combination of TMZ with radiotherapy, non-cross resistance drug or target therapy may improved the efficacy not only for glioma, but also other brain tumors, especially brain metastasis. Much effort and collaboration should, therefore, be made to conduct well-designed multicenter randomized clinical trials on TMZ, with the aim of improving the prognosis of patients with CNS tumors.

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