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ORIGINAL ARTICLE

Comparison of the clinical efficacy of temozolomide (TMZ) versus nimustine (ACNU)-based chemotherapy in newly diagnosed glioblastoma

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Abstract Although temozolomide (TMZ) replaced nitrosoureas as the standard initial chemotherapy for glioblastoma (GBM), no studies have compared TMZ with nimustine (ACNU), a nitrosourea agent widely used in central Europe and most Asian regions. One hundred thirty-five patients with GBM who underwent extensive tumor resection in our institution received both radiation and chemotherapy as initial treatment, 34 received TMZ and 101 ACNU-based (ACNU plus teniposide or cisplatin) chemotherapy. Efficacy analysis included overall survival (OS) and progression-free survival (PFS). The following prognostic factors were taken into account: age, performance status, extent of resection, and O^6-methylguanine-DNA-methyltransferase (MGMT) gene status. The median OS was superior in the TMZ versus the ACNU group (p=0.011), although MGMT gene silencing, which is associated with a striking survival benefit from alkylating agents, was more frequent in the ACNU group. In multivariate Cox analysis adjusting for the common prognostic factors, TMZ chemotherapy independently predicted a favorable outcome (p=0.002 for OS, hazard ratio [HR], 0.45; p=0.011 for PFS, HR, 0.56). Given that >40 % of patients in ACNU group did not receive the intensive chemotherapy cycles because of severe hematological and nonhematological toxicity, we performed a further subanalysis for patients who received at least 4 cycles of chemotherapy. Although a modest improvement in survival occurred in this ACNU subgroup, the efficacy was still inferior to that in the TMZ cohort. Our data suggest that the survival benefit of TMZ therapy is superior to that of an ACNU-based regimen in patients with extensive tumor resection, also shows greater tolerability.

Keywords Glioblastoma · Adjuvant chemotherapy · Nimustine (ACNU) · Temozolomide (TMZ) · Survival

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Introduction

Alkylator-based chemotherapy plays an important role in the treatment of glioblastoma (GBM). Nitrosoureas (nimustine [ACNU], carmustine [BCNU], and lomustine [CCNU]) were previously the most popular chemotherapeutic agents, and several meta-analyses have shown a modest but real benefit from nitrosourea-based adjuvant chemotherapy followed by radiotherapy (RT) [1, 9, 18]. After the phase III clinical trial by

Stupp et al. [13] showing that the addition of temozolomide (TMZ) to RT significantly improved survival over RT alone, TMZ protocols have been recommended as the standard-of-care treatment for patients with newly diagnosed GBM [12, 13]. However, no randomized comparisons between the two regimens have been reported; thus, there is no proof of actual superiority of TMZ over nitrosourea-based chemotherapy in terms of prolonging survival.

In central Europe and most Asian regions, ACNU rather than BCNU or CCNU has been widely used because of its comparative advantages of efficacy and availability. ACNU was usually administered with cisplatin (CDDP) or teniposide (VM26) to increase its anticancer effect [8, 17–19]. Our previous translational study involved 135 patients with GBM who received chemotherapy with TMZ or an ACNU-based regimen as initial adjuvant treatment after extensive tumor resection (at least near-total resection [NTR]) and intensity-modulated radiation therapy [15]. Herein, we comparatively analyzed the efficacy of the two adjuvant chemotherapy regimens in the GBM patients with extensive tumor resection.

Patients and methods

Patients and treatment

A total of 135 patients with newly diagnosed GBM received at least NTR surgery followed by radiation and chemotherapy as initial therapy at the Glioma Center of Beijing Tiantan Hospital from March 2005 to March 2010. Histological diagnosis was independently re-evaluated according to the 2007 World Health Organization classification criteria. The patients were included for analysis if they received at least one dose of the chemotherapy. TMZ-based chemotherapy was recommended as the first choice since March 2006. Taking into account the affordable healthcare, the patients had the autonomy according to their own financial situation and other condition. A total of 101 patients received an ACNU-based (Nindran, Sankyo Co.) regimen (82 ACNU plus VM26, 19 ACNU plus CDDP) and 34 received a TMZ (Diqing, Tasly Diyi Pharm) regimen. According to previously set criteria, NTR was defined as thin rim enhancement of the resection cavity only (resection margins at the level of tumor border) on the early MRI (within 72 h from surgery); gross-total resection (GTR) was defined as no residual enhancement (resection margins 1–2 cm from the tumor border). All patients provided written informed consent, and the study was approved by the Research Ethics Board of Beijing Tiantan Hospital.

ACNU-based chemotherapy was initiated after completion of RT: ACNU (90 mg/m^2, day 1) plus VM26 (60 mg/m^2, days 1–3) or ACNU (90 mg/m^2/day) plus CDDP (40 mg/m^2/day) infused continuously for 3 days (both schemes at 6-week intervals). Adequate hydration and diuretics were applied, and all patients were given a prophylactic anti-5HT3 receptor agent to prevent nausea and vomiting. A total of 6 cycles were administered unless the patient showed progressive disease during treatment or unacceptable toxicity or refused further treatment. Hematologic, renal, and hepatic function were measured on the day immediately following chemotherapy, 4 weeks later, and 6 weeks later just prior to the next chemotherapy. Treatment was delayed for 1 to 2 weeks in patients with a neutrophil level of $<1.5\times10^9$/L or platelet level of $<100\times10^9$/L. If a cycle was delayed for 2 weeks because of hematological toxicity, the drug dose was reduced by 25 %. In the TMZ group, the patients received the concurrent chemo-radiotherapy: TMZ (75 mg/m^2, oral) was given from the first until the last day of RT, 4 weeks off, maintenance therapy at a dose of 150 to 200 mg/m^2 daily for 5 days every 28-day cycle. TMZ was administered 6 cycles or continued up to 12 months if tolerated by the patient.

RT at a total dose of 60 Gy was administered within 4 weeks after surgery (2 Gy each dose, five fractions administered per week). The tumor volume initially treated included the contrast-enhanced lesion and surrounding edema identified by preoperative MRI plus a 2–3 cm margin. After 46 Gy had been administered, treatment was confined to the contrast-enhanced lesion only.

DNA Pyrosequencing for MGMT promoter methylation

Specimens with an estimated tumor-cell content of ≥80 % were selected. For O^6-methylguanine-DNA-methyltransferase (MGMT) promoter methylation analysis, bisulfite modification of the DNA was performed using the EpiTect Kit (Qiagen). The primers used were 5′-GTTTYGGATATGTTGGGATA-3′ and reverse: 5′-biotin-ACCCAAACACTCACCAAATC-3′. Pyrosequencing analysis of MGMT promoter methylation was carried out by Gene Tech Company Limited (Shanghai, China). The methylation values obtained were averaged across the seven tested CpG loci within the MGMT promoter. GBM samples were considered MGMT promoter methylation-positive if they had an average methylation of >10 %.

Statistical analysis

The date of diagnosis was defined as the date of first surgery. Treatment response was assessed by regular enhanced MRI scans at 3-month intervals, and progression was defined as the appearance of a new lesion or an increase in tumor size of ≥25 % [3]. When pseudo-progression or radiation necrosis was suspected, magnetic resonance spectroscopy (MRS) and/or positron emission tomography (PET) imaging would be employed and the patients would be centrally reviewed by Neuroimaging experts (X Chen), Neuro-oncologist (B Chen), and Neurosurgeon (L Chen or T Jiang). Failure to return for evaluation due to death or deteriorating condition was

considered to represent progression. The clinical end points used to measure clinical outcome were overall survival (OS) and progression-free survival (PFS). OS was calculated from the day of first surgery until death or end of follow-up; PFS was calculated from the day of first surgery until tumor progression, death, or end of follow-up.

All statistical analyses were performed using SPSS 13.0 for Windows (Chicago, IL). Correlations between two independent variables were analyzed by t tests, χ^2 tests, or Fisher's exact test. Survival curves were estimated using the Kaplan–Meier method, and statistical differences were evaluated using the log-rank test. Significant factors identified in the univariate analysis were tested by backward stepwise multivariate analysis using the Cox regression method. A p value of <0.05 (two-sided) was considered to be statistically significant.

Results

Patient characteristics

Patient demographics and baseline characteristics are listed in Table 1. The ages of the 135 patients surveyed ranged from 16 to 70 years (mean 45.7, median 46.0), including 86 men and 49 women. The preoperative Karnofsky Performance Status (KPS) score ranged from 50 to 100 (median, 80). Fifty-six of 135 patients (41.5 %) were estimated to have been treated with GTR based on the MRI results after surgery, and 79 patients (58.5 %) were treated with subtotal resection. The pretreatment clinical characteristics were well matched between the two groups.

Table 1 Comparison of clinical characteristics between the treatment groups

	ACNU	TMZ	p value
No. of patients	101	34	
Age at diagnosis (years)			
Median (range)	46.0 (17–68)	47.5 (16–70)	
Mean (IQR)	44.9 (36.5-55)	47.9 (39–57)	0.238
Sex			
Female (%)	37 (36.6)	12 (35.3)	0.888
Preoperative KPS scale			
Median (range)	80 (50–100)	80 (60–100)	0.842
Surgical			
Gross-total resection (%)	41 (40.6)	15 (44.1)	
Near-total resection (%)	60 (59.4)	19 (55.9)	0.718
No. of chemo cycles			
Mean (IQR)	3.8 (2–5)	4.8 (4–6)	0.008
MGMT promoter gene			
Methylation (%)	19/41 (46.3)	3/19 (15.8)	0.025

IQR interquartile range, *KPS* Karnofsky Performance Status

Only 59.4 % (60 of 101) patients underwent the more intensive chemotherapy (defined as ≥4 cycles) in the ACNU group (mean cycles, 3.8; interquartile range [IQR], 2–5), while the ratio was 79.4 % (28 of 34 patients) in the TMZ group (mean cycles, 4.8; IQR, 4–6). The difference was statistically significant (p=0.008, t test). There were 60 frozen tumor tissues available for the analysis of MGMT promoter status, and a statistically significant difference found was the lower ratio of MGMT promoter methylation in the TMZ group (p=0.025, Fisher's exact test) (Table 1).

Survival analysis

At a median follow-up of 39.5 months, the median OS in the TMZ and ACNU groups was 26.3 (95 % confidence interval [CI], 12.3–40.0 months) and 15.4 months (95 % CI, 12.7–18.1 months), respectively, and the curves were significantly different (p=0.011, log-rank test) (Fig. 1). The 2-year survival was 51 % in the TMZ group and 26 % in the ACNU group. The median PFS was 17.7 months in the TMZ group and 10.1 months in ACNU group (p=0.039, log-rank test). No statistically significant difference in survival was found between the ACNU plus VM26 series and the ACNU plus DDP series (data not shown). In the multivariate Cox model adjusting for age, KPS score, and extent of resection, patients who received TMZ chemotherapy had a significantly longer OS (hazard ratio [HR], 0.45; 95 % CI, 0.28–0.75; p=0.002) and PFS (HR, 0.56; 95 % CI, 0.33–0.88; p=0.011) compared with those who were treated with the ACNU-based regimen (Tables 2 and 3).

Given that >40 % of patients did not undergo the more intensive chemotherapy in the ACNU group, we further analyzed the subgroup of patients who received at least 4 cycles of chemotherapy. Kaplan–Meier survival curves illustrated modest improvement in OS and PFS with the more intensive chemotherapy, but the efficacy was still inferior to that of the TMZ cohort (p=0.075 for OS, p=0.187 for PFS; log-rank test) (Fig. 1).

Toxicity

In 31 (30.7 %) ACNU patients, the chemotherapy was interrupted because of prolonged hematological toxicity (persistent leukopenia) and in nine (8.2 %) because of severe nonhematological toxicity (fatigue, lethargy, obstinate vomiting, etc.). In four (4.0 %) patients, the chemotherapy was stopped because of tumor progression. In total, 43.4 % of patients in the ACNU group did not complete the 6 cycles of chemotherapy because of drug side effects compared with only 8.8 % (3 of 34) patients in the TMZ group (two with stubborn leukopenia and one with obstinate vomiting) (p<0.01, χ^2 test). No patient died of toxicity in either group.

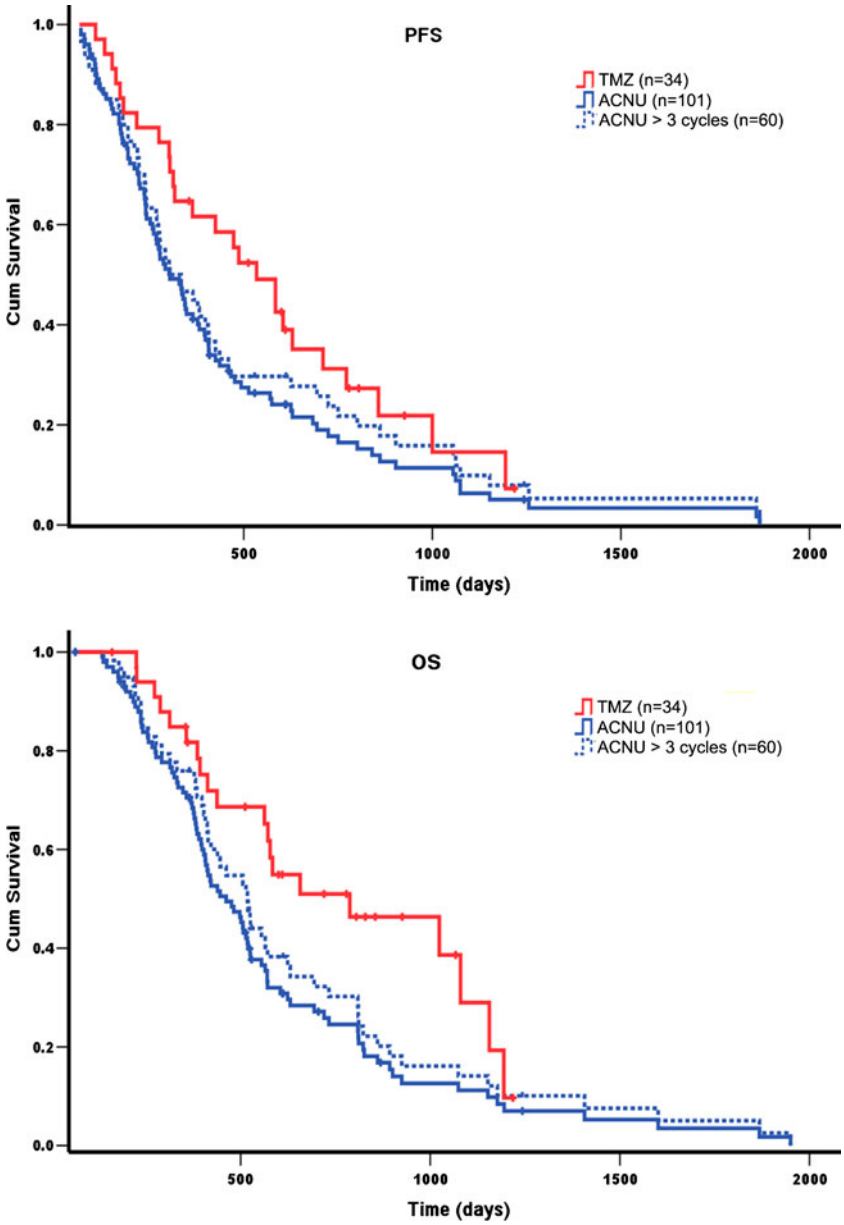

Fig. 1 Kaplan–Meier overall survival (OS) and progression-free survival (PFS) curves of patients who received radiation plus TMZ (n=34), all patients who received radiation plus ACNU (n=101), and patients who received radiation plus ACNU for ≥4 cycles of chemotherapy (n=60). The curves demonstrated that TMZ chemotherapy was associated with a longer OS and PFS compared with the ACNU-based regimen. Even though in the subgroup that received more intensive ACNU chemotherapy showed modest improved survival, the survival benefits were still inferior to those of the TMZ group

Discussion

TMZ has been recommended as the first chemotherapy of choice for patients with malignant glioma because of its ease of use and low toxicity compared with nitrosourea-based regimens [12, 13]. However, the substantial cost of TMZ restricts its widespread use, especially in health resource-limited regions such as China [19]. On the other hand, no randomized clinical trials have demonstrated the superiority of TMZ over nitrosoureas in terms of improved survival. The aim of our study was to compare the OS and PFS in patients with GBM receiving radiation plus either ACNU or TMZ as initial therapy after surgery. Our results demonstrated that among patients who underwent at least NTR surgery, those who received TMZ had a longer OS and PFS compared with those who received ACNU-based chemotherapy. In addition, in the multivariate analyses adjusting for the common prognostic factors, TMZ chemotherapy independently predicted a favorable survival. Meanwhile, we noticed that >40 % of patients in the ACNU group did not complete the planned 6 cycles of chemotherapy because of serious hematological and nonhematological toxicity. However, even though in the subgroup that received more intensive ACNU chemotherapy showed modest improved survival, the survival benefits were still inferior to those of the TMZ group.

Although our patients were not randomized, common prognostic factors such as age at diagnosis, preoperative performance status, and extent of resection were quite comparable between the groups. Although MGMT gene silencing, which interferes with the important DNA-repair enzyme in

Table 2 Variables related to overall survival (OS): univariate and multivariate analyses

Variables	Univariate analysis	Multivariate analysis	HR (95 % CI)
Age ≥50 years	$p<0.001$	$p=0.001$	1.986 (1.319–2.990)
Sex	$p=0.069$		
Preoperative KPS ≥80 %	$p<0.001$	$p=0.006$	0.534 (0.342–0.833)
Gross-total resection surgery	$p=0.001$	$p<0.001$	0.463 (0.304–0.706)
MGMT promoter methylation	$p=0.057$		
TMZ vs. ACNU chemotherapy	$p=0.011$	$p=0.002$	0.454 (0.276–0.746)

Note: significant factors identified in the univariate analysis were tested by backward stepwise multivariate analysis using the Cox regression method

MGMT expression and is thus associated with a striking survival benefit in patients treated with alkylating agents [2, 13, 16], was more frequent in the ACNU group in the current series, the actual survival benefit of ACNU chemotherapy was still inferior to that of TMZ chemotherapy. A recent retrospective analysis comparing TMZ with BCNU showed that the superior survival of TMZ-treated patients with GBM was not due to better tumor control by TMZ but was related to the use of the molecular-targeted drugs (bevacizumab) in salvage therapy [14]. However, bevacizumab had not been approved by the China FDA in the study period. This suggests that TMZ may actually be superior to ACNU-based chemotherapy in its effect on tumor progression.

Tumor resection to the maximum extent can diminish the tumor burden and thereby enhance the effects of subsequent chemotherapy and radiation in eradicating remaining tumor cells [6], and the majority of large-sample studies have considered extensive surgical resection to be a significant independent predictor of favorable survival [5, 10]. We found that, even among patients receiving at least NTR surgery, GTR remained to be a strong prognostic factor for improved survival. We presume that the limited efficacy of the ACNU-based regimen occurred partly because dose reductions and treatment delays or interruptions more frequently occurred in the ACNU group due to toxicity. In addition, chemotherapeutic agents for brain tumors are severely limited by the inability of these agents to penetrate the blood–brain barrier (BBB). TMZ can more readily cross the BBB and reach effective concentrations in the CNS with a plasma/CSF ratio of approximately 30 to 40 % [4, 11].

Table 3 Variables related to progression-free survival (PFS): univariate and multivariate analyses

Variables	Univariate analysis	Multivariate analysis	HR (95 % CI)
Age ≥50 years	$p<0.001$	$p=0.002$	1.861 (1.265–2.739)
Sex	$p=0.131$		
Preoperative KPS ≥80 %	$p<0.001$	$p=0.007$	0.565 (0.371–0.858)
Gross-total resection surgery	$p=0.005$	$p=0.006$	0.573 (0.386–0.851)
MGMT promoter methylation	$p=0.225$		
TMZ vs. ACNU chemotherapy	$p=0.039$	$p=0.011$	0.562 (0.360–0.878)

One possible limitation of this study was that the threshold for high-quality surgical resection excluded those patients who underwent biopsies or debulking surgery only. This threshold may have also excluded some older patients with GBM because most only underwent biopsies or temporary surgery. Several recent studies have shown that elderly patients may demonstrate a distinctive prognostic pattern [7]. Besides, in the current study, ACNU-based chemotherapy did not get any concomitant treatment during radiation, which might had some impact on outcome.

Altogether, the efficacy of ACNU-based therapy was inferior to that of TMZ in patients who underwent extensive tumor resection; it also showed considerable hematotoxicity. Toxicity of a therapeutic regimen is an important factor in treatment choice, especially in terms of quality of life and palliative care according to the modern trends of cancer management. On the other hand, in general clinical practice, cost-effectiveness (a pharmacoeconomic factor) is another important consideration of treatment choice, especially in health resource-limited settings. A cost-effective analysis based on Chinese clinical practice suggested that the TMZ regimen was not a cost-effective option considering its high cost and relatively limited survival benefits for patients with GBM compared with ACNU-based therapy [19]. Decreasing the price of TMZ might be one potential way to spread its use and allow more patients to benefit from it.

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Conflict of interest None.

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Comments

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There is little knowledge on any superiority of one alkylating agent over another in the treatment of glioblastomas. A randomized controlled trial to answer this important question will not be feasible these days. In China, the nitrosourea nimustine is used quite often due to a limited access to the newer alkylating agent temozolomide (TMZ). The authors retrospectively compared the clinical efficacy of TMZ versus nimustine (ACNU)-based chemotherapy in newly diagnosed glioblastoma. Although the study design is retrospective and nonrandomized, the authors could demonstrate the efficacy of ACNU-based therapy to be inferior to that of TMZ in patient cohorts that were well matched related to prognostic factors. ACNU was more toxic, and thus, >40 % of patients in the ACNU group could not complete the planned 6 cycles of chemotherapy; they experienced dose reductions and treatment delays. There are some limitations to this study which are all discussed in the paper, e.g., ACNU-based chemotherapy did not get any concomitant treatment during radiation, which might have had a worse impact on outcome.

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Dr. Wang et al. provide a retrospective analysis of two different systemic treatment options in 135 patients with newly diagnosed glioblastoma patients at a premier institution in Beijing, China. The authors compare the clinical efficacy of nimustine (ACNU)-based chemotherapy with temozolomide and radiation as initial therapy in this patient population from March 2005 to March 2010. Given the constraints of a nonrandomized patient population and absence of concomitant radiation in one cohort, the results appear to favor the use of temozolomide and radiation with respect to outcome and toxicity. The impact of the significant toxicity of ACNU is particularly relevant in a patient population whose prognosis is measured only in months. The authors do, however, make reference to a cost-benefit analysis, noting a lack of cost-effectiveness of the temozolomide regimen in the context of resource-limited Chinese clinical practice and appealing for a reduction in its pricing. These data again confirm the Stupp regimen as the current global standard with respect to efficacy in patients with newly diagnosed glioblastoma.