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CLINICAL STUDY – PATIENT STUDY

Temozolomide during and after radiation therapy for WHO grade III gliomas: preliminary report of a prospective multicenter study

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Abstract This prospective study was performed to determine the efficacy, safety, and tolerability of concurrent chemoradiotherapy (CCRT) followed by adjuvant chemotherapy with temozolomide (TMZ) in the treatment of patients with WHO grade III gliomas. Thirty-three adult patients with WHO grade III glioma and aged >17 years were enrolled from three institutions between 2003 and 2008. The median age was 41 years (range, 17–60 years). The pathological diagnoses were anaplastic astrocytomas in 21 patients and anaplastic oligodendrogliomas in 12 patients. The preoperative Karnofsky performance scale score was >60 for all patients. The patients received fractionated focal irradiation in daily fractions of 2 Gy administered five days per week for six weeks, for a total of 60 Gy, in combination with continuous daily TMZ, followed by six cycles of adjuvant TMZ. The median dose of radiotherapy was 59.4 Gy (range, 28.8–61.2 Gy) and the duration of CCRT was 7.0 weeks (range, 3.1–8.3 weeks). A median of 6.2 cycles (range, 2–12 cycles) of TMZ chemotherapy were performed during the period of adjuvant chemotherapy. The response rate was 61% and the tumor-control rate was 82%. Mean progression-free survival (PFS) was 48.7 months (95% CI, 36.0–61.4) and the 12, 24, and 36-month PFS was 74%, 60%, and 50%, respectively. Mean overall survival (OS) was 66.4 months (95% CI, 56.4–76.4) and the 12 and 24-month OS was 97% and 77%, respectively. The extent of surgical resection was a significant prognostic factor for PFS and OS (hazard ratio, 0.24; 95% CI, 0.02–0.73; and hazard ratio, 0.12; 95% CI, 0.01–0.88, respectively; $P < 0.001$). However, there was no significant difference in the PFS and OS of patients regarding loss of heterozygosity in chromosomes 1p and 19q and methylation of O^6-methylguanine-DNA methyltransferase promoter, because of the small number of

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patients available. Only five cases (15%) receiving CCRT with TMZ and three cases (9%) receiving adjuvant chemotherapy had hematological toxicity greater than grade 3. All these patients, however, tolerated the therapy well enough to continue treatment. No opportunistic infections were noted. This protocol for WHO grade III gliomas was relatively safe and tolerable. It showed the possibility of achieving favorable results compared with those of historical controls. A randomized controlled study with a long-term follow-up may be mandatory to evaluate its efficacy.

Keywords Temozolomide · Concurrent · Chemoradiotherapy · Anaplastic astrocytoma · Anaplastic oligodendroglioma

Introduction

Anaplastic gliomas, which correspond to WHO grade III gliomas, include anaplastic astrocytomas (AA), anaplastic oligodendrogliomas (AO), and mixed lineages. Histologically, these tumors have nuclear atypia and mitotic activity, but are not associated with necrosis. This is in contrast with what is observed for glioblastoma (GBM; WHO grade IV) [1]. The overall prognosis for patients with WHO grade III gliomas is poor. Patients with AA have a median survival time of <3 years from diagnosis; patients with AO have a longer survival time than those with AA, of approximately 5 years [2].

The standard treatment for WHO grade III gliomas is maximum surgical resection to the extent that is safely feasible, followed by adjuvant radiotherapy (RT) [3–5]. The efficacy and safety of additional chemotherapy remain controversial. Adjuvant chemotherapy for anaplastic gliomas, however, is not only justified by trials showing a small long-term survival benefit but is also clearly associated with increased toxicity [3, 6–8]. Stupp et al. [9, 10] reported that the concurrent administration of temozolomide (TMZ) and fractionated RT followed by adjuvant TMZ therapy for newly diagnosed GBM resulted in a clinically meaningful and significant survival benefit, with minimum additional toxicity. Recently, many trials have been attempted to prove that concurrent and adjuvant chemoradiotherapy with TMZ for anaplastic gliomas has longer survival benefits and minimal toxicity and risk [11–16].

We applied this concurrent chemoradiotherapy (CCRT) with TMZ protocol prospectively to patients with WHO grade III gliomas. The purpose of this prospective study was to evaluate the efficacy and safety of this protocol for treatment of WHO grade III gliomas and to compare these results with historical data reported previously. This is the preliminary report from an ongoing study conducted at three institutions, including the Seoul National University Hospital, the Seoul National University Bundang Hospital, and the Pusan National University Hospital.

Materials and methods

Patients

Our series consisted of 33 consecutive patients over the age of 17 years enrolled between September 2003 and September 2008, with pathological findings of WHO grade III gliomas that included AA and AO. The histology was considered anaplastic if the tumor had at least three of the histopathological features increased cellularity, marked cytological atypia, high mitotic activity, microvascular proliferation, and absence of necrosis [17].

All patients were required to have a Karnofsky performance scale (KPS) score ≥60 and adequate hematological, renal, and hepatic function, defined as an absolute neutrophil count ≥1,500/μL, a platelet count ≥100,000/μL, hemoglobin ≥10 g/dL, serum creatinine and total serum bilirubin levels <1.5 times the upper limit of the normal range, aspartate aminotransferase and alanine aminotransferase levels <2.5 times the upper limit of the normal range, and alkaline phosphatase levels <2 times the upper limit of the normal range. Patients were not eligible if they were in poor medical condition, which could interfere with the oral administration of TMZ. All patients signed a form giving their fully informed consent to take part in the study, which was approved by the institutional review boards of the three institutions previously mentioned.

Fluorescence in-situ hybridization was performed to assess the status of chromosomes 1p and 19q. The DNA methylation status of CpG islands at the MGMT promoter was determined by chemical modification of unmethylated (but not methylated) cytosine to uracil and subsequent polymerase chain reaction (PCR) using primers specific for either methylated or modified unmethylated DNA, as described previously [18–20].

Treatment protocols

Patients that were eligible for the study were treated with CCRT with TMZ, using the protocol proposed by Stupp et al. in 2002 [10] and 2005 [9]. According to this protocol, the RT component of the CCRT consisted of fractionated focal irradiation at a dose of 2 Gy per fraction given once a day, five days a week, for a period of six weeks, for a total dose of 60 Gy. TMZ was delivered at a dose of 75 mg/m^2/day, seven days per week, from the first to the last day of RT, but, not for longer than 49 days. TMZ was

administered daily 1 h before RT, or in the morning on days without RT.

After a four-week break, the patients then received up to six cycles of adjuvant TMZ, according to the standard five-day schedule, every 28 days. The dose of TMZ was 150 mg/m^2 for the first cycle and increased to 200 mg/m^2 at the beginning of the second cycle if no hematological toxicity occurred. Prophylaxis for *Pneumocystis jiroveci* pneumonia was recommended during CCRT, or if lymphocyte counts decreased below 500/mm^3.

Patient evaluations

Preoperative evaluations were performed for each patient and included a detailed patient history, physical and neurological examination, KPS score, hematological and serological evaluation, and brain magnetic resonance (MR) images with gadolinium enhancement. MR scans were performed before the first adjuvant treatment cycle and then every two or three months during the first year, and every three months during the second year. The response of patients to treatment was categorized into four groups: complete response (CR: complete disappearance of the targeted lesion), partial response (PR: >50% decrease in the product of the maximum perpendicular diameters of the targeted lesion), stable disease (SD: no clinical progression, with <50% reduction or <25% increase in the product of the maximum perpendicular diameters of the targeted lesion), and progressive disease (PD: >25% increase in the volume of the targeted lesion or development of a new lesion), using the initial baseline measurements as a reference.

The toxic effects of CCRT were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 3.0), with a score of 1 indicating mild adverse effects, 2 indicating moderate adverse effects, 3 indicating severe adverse effects, 4 indicating life-threatening adverse effects, and 5 indicating death related to the adverse effect.

Statistical analysis

The primary end point was overall survival (OS) and secondary end points were progression-free survival (PFS), safety, and KPS score. OS and PFS were measured from the date of diagnosis. PFS was measured until the date of brain MR imaging that showed progression of the disease, and OS was measured until the date of death or last follow-up examination. PFS and OS were estimated using the Kaplan–Meier method. Differences with regard to survival and disease progression were tested for significance using the two-sided log rank test. The Cox proportional hazards model was fitted to adjust for stratification factors and other confounding variables. All these analyses were performed using the SPSS statistical software package (release 12.0, 2004; SPSS, Chicago, IL, USA). Toxicity of TMZ was reported separately for the CCRT period and the adjuvant chemotherapy period.

Results

Patients and delivery of treatment

From September 2003 to September 2008, 33 patients from three institutions were enrolled in the study; their characteristics are outlined in Table 1. There were 15 male patients (45%) and 18 female patients (55%). Their median age was 41 years (range 17–60 years). Nineteen patients (58%) underwent removal of over 75% of the mass, including gross total removal (GTR), near total removal (NTR), and subtotal removal (STR), and 14 patients (42%) underwent partial removal or biopsy only. The histological examination corresponded to AA in 21 patients (65%) and AO in 12 patients (35%). Evaluation of the loss of heterozygosity (LOH) at chromosomes 1p and 19q and of methylation of the MGMT promoter in 15 and 20 tumors, respectively, revealed that eight patients had deletion of 1p/19q and 11 patients had MGMT promoter methylation.

In this trial, 31 patients (93.9%) completed the CCRT schedule. Table 2 summarizes the details of the treatment administered to these 31 patients. The remaining two patients were excluded because of loss at follow-up. The median therapeutic radiation dose was 59.4 Gy (range, 28.8–61.2 Gy) and the median duration of CCRT was 7.0 weeks. After CCRT, 22 patients (71.0%) started adjuvant TMZ and received a median of 6.2 cycles (range, 2–12 cycles); 16 patients (51.6%) completed six cycles. Two patients were given PCV chemotherapy (which is composed of procarbazine, lomustine (CCNU), and vincristine) instead of TMZ, and the remaining seven patients were not given adjuvant chemotherapy. Of these patients, two patients could not complete six cycles of adjuvant TMZ because of disease progression, and the remaining patients did not begin or complete adjuvant TMZ therapy for economic reasons. The total duration of CCRT and adjuvant chemotherapy with TMZ was 30.9 weeks (range, 15.3–52.3 weeks).

Survival and progression

After CCRT with TMZ, nine patients showed CR, eleven patients exhibited PR, seven patients had SD, four patients showed PD, and data were unavailable for two patients. The objective response rate (CR and PR) was 61%, and the

Table 1 Demographic characteristics of the 33 patients at baseline

Characteristic	Value (%)
Sex	
Male	15 (45)
Female	18 (55)
Age (years)	
Median (range)	41 (17–60)
≥50	9 (27)
<50	24 (73)
KPS (LPS) at diagnosis	
60	1 (3)
70	3 (9)
80	1 (3)
90	16 (49)
100	12 (36)
KPS (LPS) after CCRT	
60	4 (12)
70	1 (3)
80	1 (3)
90	16 (49)
100	11 (33)
Extent of surgery	
Gross total removal	7 (21)
Near total removal	1 (3)
Subtotal removal	11 (33)
Partial removal	2 (6)
Biopsy only	12 (36)
Time to diagnosis to radiotherapy (week)	
Median (range)	4.9 (1.4–9.9)
Corticosteroid therapy	
During CCRT	9 (27)
During adjuvant chemotherapy	6 (18)
LOH at chromosomes 1p and 19q	
Yes	8 (24)
No	7 (21)
Data not available	18 (55)
Methylation of MGMT promoter	
Yes	11 (33)
No	9 (27)
Data not available	13 (39)

KPS (LPS) Karnofsky performance scale (Lansky play performance scale), *CCRT* concurrent chemoradiotherapy, *LOH* loss of heterozygosity, *MGMT* O^6-methylguanine-DNA methyltransferase

Table 2 Details and intensities of the treatment

Variable	Value
Dose of RT (Gy)	
Median	59.4
Range	28.8–61.2
Duration of CCRT (weeks)	
Median	7.0
Range	3.1–8.3
Duration of CCRT + adjuvant TMZ (weeks)	
Median	30.9
Range	15.3–52.3
Cycles of adjuvant TMZ	
Median	6.2
Range	2–12
Response to CCRT (%)	
Complete remission	9 (27)
Partial remission	11 (33)
Stable disease	7 (21)
Progressive disease	4 (12)
Data not available	2 (6)

RT radiotherapy, *CCRT* concurrent chemoradiotherapy, *TMZ* temozolomide

Table 3 PFS and OS of patients with WHO grade III gliomas

Variable	Value[a]
PFS (months; $n = 31$)	
Mean	48.7 (36.0–61.4)
At 12 months	74.2% (58.8–89.6)
At 24 months	60.2% (42.6–77.8)
At 36 months	50.0% (30.5–69.6)
OS (months; $n = 31$)	
Mean	66.4 (56.4–76.4)
At 12 months	96.8% (90.6–100.0)
At 24 months	77.1% (62.2–92.0)

PFS progression-free survival, *OS* overall survival

[a] Range, 95% confidence interval

tumor control rate (CR, PR, and SD) was 82%. At the time of analysis, seven patients (23%) had died and 24 patients (77%) were alive. The median follow-up duration was 25 months (range, 9–72 months).

The Kaplan–Meier method was used to establish that the mean PFS of these patients was 48.7 months (95% confidence interval (CI), 36.0–61.4) and that 12, 24, and 36-month PFS was 74.2% (95% CI, 58.8–89.6), 60.2% (95% CI, 42.6–77.8), and 50.0% (95% CI, 30.5–69.6), respectively. The mean OS was 66.4 months (95% CI, 56.4–76.4) and 12 and 24-month OS was 96.8% (95% CI, 90.6–100.0) and 77.1% (95% CI, 62.2–92.0), respectively. The PFS and OS values are summarized in Table 3 and the Kaplan–Meier survival curves of the patients with WHO grade III gliomas are illustrated in Fig. 1.

Prognostic factors, including the extent of surgical resection, LOH at chromosomes 1p and 19q, and methylation of the MGMT promoter were analyzed in these patients. The mean PFS and OS of the GTR, NTR, and

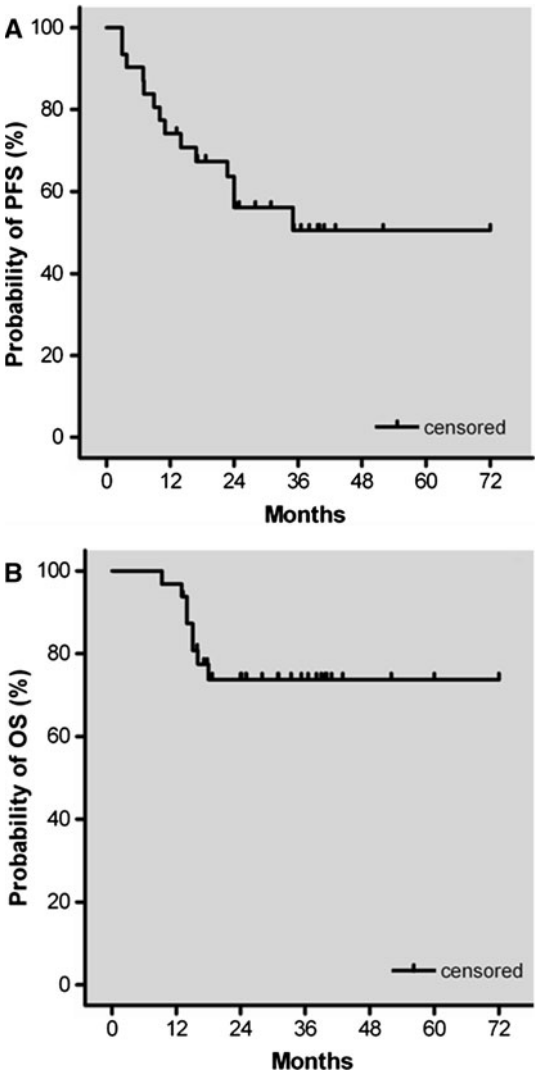

Fig. 1 Kaplan–Meier estimates of **a** progression-free survival (PFS) and **b** overall survival (OS) for 33 patients suffering from grade III gliomas that were treated with temozolomide during and after radiation therapy

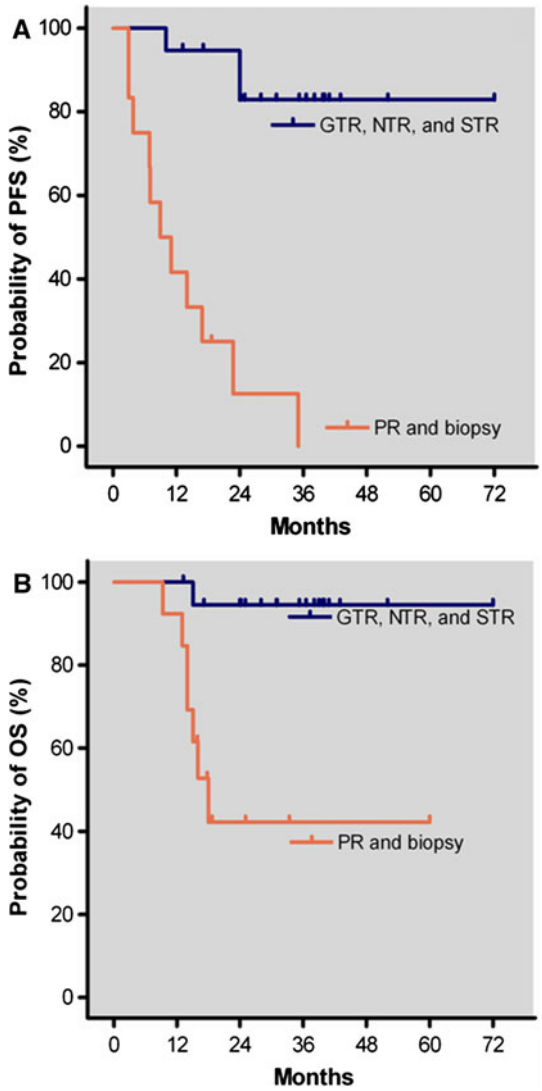

Fig. 2 Kaplan–Meier estimates. **a** Progression-free survival (PFS) and **b** overall survival (OS) were analyzed according to the extent of resection

STR groups (70.7 and 78.3 months, respectively) were longer than those of the PR and biopsy groups (13.6 and 36.2 months, respectively); this difference was significant (hazard ratio, 0.24; 95% CI, 0.02–0.73; and hazard ratio, 0.12; 95% CI, 0.01–0.88, respectively; $P < 0.001$). The Kaplan–Meier survival curves of these groups are depicted in Fig. 2. The mean PFS of the 1p19q co-deletion group and the MGMT promoter methylation group was longer than those of the other groups; there was no statistical significance ($P = 0.40$ and $P = 0.21$, respectively). Comparison of OS in the 1p19q co-deletion group and 1p19q no-deletion group was impossible because of the small number of available patients. The survival data for these groups are summarized in Table 4.

Toxicity

During CCRT with TMZ, five patients (16.1%) showed hematological toxicity and eight patients (25.8%) exhibited nonhematological toxicity >grade 3. There were two leukocytopenias, one neutropenia, one thrombocytopenia, and one anemia in the hematological toxicity category, and three gastrointestinal symptoms (including nausea and vomiting), three skin problems, one insomnia, and one vertigo in the nonhematologic toxicity category. During adjuvant chemotherapy with TMZ, three patients (12.5%) experienced hematological toxicity and five patients (20.8%) experienced nonhematological toxicity >grade 3. There were two leukocytopenias and one neutropenia in the

Table 4 PFS and OS associated with prognostic factors including extent of surgical resection, LOH at chromosomes 1p and 19q, and methylation of the MGMT promoter

	Hazard ratio (95% CI)	Mean (months; 95% CI)	1 year (%; 95% CI)	2 years (%; 95% CI)
Progression-free survival				
Extent of resection				
PR and biopsy ($n = 12$)	1.0	13.6 (7.3–19.8)	41.7 (13.8–69.6)	12.5 (0–33.7)
GTR, NTR, and STR ($n = 19$)	0.2 (0.0–0.7)*	70.7 (59.2–82.1)	94.7 (84.7–100)	88.8 (74.2–100)
LOH of 1p and 19q				
No ($n = 7$)	1.0	31.6 (19.0–44.2)	85.7 (59.8–100)	53.6 (14.2–92.9)
Yes ($n = 8$)	0.7 (0.1–9.0)	42.0 (36.6–47.3)	100	80.0 (44.9–100)
MGMT promoter				
Unmethylated ($n = 9$)	1.0	25.7 (17.5–33.8)	77.8 (50.6–100)	51.9 (17.4–86.3)
Methylated ($n = 11$)	0.6 (0.1–2.7)	29.8 (21.1–38.5)	81.8 (59.0–100)	72.7 (46.4–99.1)
Overall survival				
Extent of resection				
PR and biopsy ($n = 12$)	1.0	36.2 (23.0–49.3)	91.7 (76.0–100)	48.6 (19.6–77.6)
GTR, NTR, and STR ($n = 19$)	0.1 (0.0–0.8)*	78.3 (71.7–85.0)	100	94.7 (84.7–100)
LOH of 1p and 19q				
No ($n = 7$)	1.0	41.4 (33.1–49.7)	100	85.7 (59.8–100)
Yes ($n = 8$)	NA	NA	100	100
MGMT promoter				
Unmethylated ($n = 9$)	1.0	49.7 (37.8–61.6)	100	77.8 (50.6–100)
Methylated ($n = 11$)	0.9 (0.1–6.9)	69.0 (53.0–85.0)	90.9 (73.9–100)	81.8 (59.0–100)

PFS progression-free survival, *OS* overall survival, *LOH* loss of heterozygosity, *MGMT* O^6-methylguanine-DNA methyltransferase, *GTR* gross total removal, *NTR* near total removal, *STR* subtotal removal, *PR* partial removal, *NA* not available

* $P < 0.001$

hematological toxicity category, and four nausea/vomiting and one skin problem in the nonhematological toxicity category. In this series, there was no lymphocytopenia during both CCRT and adjuvant chemotherapy with TMZ. All complications corresponded to grade 3 toxicity, with the exception of one leukocytopenia during CCRT and one neutropenia during adjuvant chemotherapy. All patients that experienced toxicity from the chemotherapeutic agent tolerated them well during the therapy. No opportunistic infections, for example *Pneumocystis jiroveci*, were noted. The distribution of the toxicity associated with chemotherapy is presented in Table 5.

Table 5 Toxic effects over grade 3

Toxicity	CCRT with TMZ		Adj with TMZ	
	Grade 3	Grade 4	Grade 3	Grade 4
Hematological				
Leukopenia	1	1	1	0
Neutropenia	1	0	1	1
Thrombocytopenia	1	0	0	0
Anemia	1	0	0	0
Nonhematological				
Nausea/vomiting	3	0	4	0
Skin problems	3	0	1	0
Other	2[a]	0	0	0

CCRT concurrent chemoradiotherapy, *TMZ* temozolomide, *Adj* adjuvant chemotherapy

[a] Including insomnia and vertigo

Discussion

TMZ is a novel, second-generation, oral alkylating agent that is an imidazotetrazine derivative. Its mechanism of action is methylation of guanine residues in the DNA of tumor cells, thus creating a mismatch that the repairing enzyme system cannot fix, because it cannot find a base complementary to the methylated guanine. This ultimately leads to cell-cycle arrest [1, 15]. TMZ has demonstrated antitumor activity in the treatment of malignant gliomas and has been approved for treatment of recurrent malignant glioma and newly diagnosed GBM [10, 21–23].

A randomized prospective study reported in 2005 revealed that concomitant TMZ and RT was more effective than RT alone in patients with newly diagnosed GBM [9]. This randomized study compared RT plus concomitant

TMZ with RT alone in patients with newly diagnosed GBM and confirmed the effectiveness of CCRT with TMZ for GBM patients. On the basis of this pilot study, we proceeded to apply CCRT using the same protocol to patients with WHO grade III gliomas and GBM, starting in 2003. In 2008 we reported that CCRT with TMZ for newly diagnosed high-grade gliomas was effective and safe [13]. At present, CCRT followed by a single-agent adjuvant treatment with the alkylating agent TMZ is widely accepted as the current standard care for patients with GBM [16, 24, 25].

Unlike GBM, there is no definite consensus regarding the standard treatment protocol for WHO grade III gliomas, for example AA and AO. To date, the standard treatment for patients with anaplastic gliomas has been maximum surgical resection followed by adjuvant RT [3]. Although WHO grade III gliomas have been regarded as at least as chemosensitive as GBMs, on the basis of observations from previous trials, the effectiveness of concomitant or adjuvant chemotherapy with RT regarding longer survival and PFS compared with RT alone remains controversial. Representative trials of postsurgical treatment of WHO grade III gliomas are summarized in Table 6.

Traditionally, AO is generally thought of as exquisitely chemosensitive, primarily on the basis of the high rates of radiographic response in several trials after treatment with PCV, which is composed of procarbazine, lomustine (CCNU), and vincristine [26, 27]. The LOH of chromosomes 1p and 19q in AO is regarded as a good prognostic factor because of the chemosensitivity. However, the results of a large clinical trial investigating the use of sequential CCRT in patients with AO revealed an absence of a substantial survival advantage over RT alone. The study reported by Cairncross et al. randomized 289 patients with newly diagnosed anaplastic oligodendrocytic tumors to either RT alone or neoadjuvant PCV followed by RT [7]. In these trials, although no significant difference in OS between the PCV plus RT group and the RT alone group (4.9 and 4.7 years, respectively) was detected, the former group had improved PFS compared with the latter group (2.6 vs. 1.7 years, $P = 0.008$). Grade 3/4 toxicity, however, was observed in 65% of patients treated with PCV, resulting in one death. Adjuvant chemotherapy with PCV has showed a PFS benefit together with significantly unacceptable toxicity.

In particular, the efficacy found with adjuvant chemotherapy to RT for AA remains more doubtful than that for AO. A retrospective analysis by Prados et al. revealed no improvement in survival of 432 patients with newly diagnosed AA treated with RT followed by either carmustine (BCNU) or PCV [28]. In 2001, a prospective, randomized phase III study performed by the United Kingdom Medical Research Council was designed to establish whether PCV adjuvant chemotherapy provided a survival benefit in the treatment of malignant gliomas [29]. In this trial, 117 (17%, 117/674) patients treated with RT alone or with RT plus adjuvant PCV chemotherapy after surgery were

Table 6 Trials of postoperative treatments for WHO grade III gliomas

	Author	Year	Dx	No	Protocol	OS	PFS
RT	Walker et al. [3]	1978	AG	303	Supportive	4	NA
					BCNU	6	NA
					RT	9	NA
					BCNU + RT	10	NA
RT versus RT + CTx	Cairncross et al. [7] (RTOG9402)	2006	AO	289	RT	56	20
					PCV → RT	59	31
	Bent et al. [33] (EORTC)	2006	AO	368	RT	30	13
					RT → PCV	40	23
	Combs et al. [8]	2008	AA	60	RT	13	7
					TMZ + RT	15	6
	Wick et al. [31] (NOA-04)	2009	AG	274	RT	72	31
					PCV or TMZ	82	32
CTx only	Brandes et al. [14] (GICNO)	2006	AO	67	TMZ	31	NA
	Talinsky-Aronov et al. [11]	2006	AO	20	TMZ	NA	24
	Mikkelsen et al. [12]	2008	AO	48	TMZ	77	28
Recent trials	Vogelbaum et al. [34] (RTOG BR0131)	2009	AO	42	TMZ → RT + TMZ	NA	NA
	Kim et al. (present study)	2010	AG	33	RT + TMZ → TMZ	66	49

RT radiotherapy, *CTx* chemotherapy, *Dx* histological diagnosis, *No* number of patients, *OS* mean overall survival (months), *PFS* mean progression-free survival (months), *AG* anaplastic glioma, *AO* anaplastic oligodendroglioma, *AA* anaplastic astrocytoma, *PCV* combinations of procarbazine, lomustine, and vincristine, *TMZ* temozolomide, *NA* not available

analyzed. No significant survival benefit was found for adjuvant PCV in any subgroup, compared with RT alone.

Recently, many trials have been attempted to evaluate the efficacy and toxicity of TMZ as a therapeutic substitute for PCV. In a phase II trial by Yung et al. 162 patients with AA were treated with TMZ (150–200 mg/m^2/day on days 1–5, every 28 days) at first relapse [30]. The six-month PFS was 46%, a 35% objective response rate was noted, and the regimen was well tolerated, with an acceptable safety profile. These results suggest that TMZ has modest antitumor activity with minimum toxicity in relapsed AA. However, Combs et al. revealed in 2008 that CCRT with TMZ for WHO grade III astrocytic tumors had no survival benefit compared with RT alone [8]. In these trials, the median OS and PFS in the CCRT group were 15 and 6 months, respectively, and those in the RT group were 13 and 7 months, respectively. There was no significant difference between treatment groups.

Consequently, it seemed that the adjuvant chemotherapy to radiotherapy for WHO grade III gliomas had no survival benefit, based on previous trials. The causes for the increased insufficient therapeutic effect of chemotherapy in WHO grade III gliomas compared with GBMs may include differences in biological characteristics between two categories of cancers, for example growth rate (which is regarded as a critical aspect of chemosensitivity). Therefore, longer cycles of chemotherapy or denser doses of drugs compared with those used in the usual protocols for GBM may be necessary for effective control of WHO grade III gliomas. TMZ, which is superior to other chemotherapeutic agents (e.g. PCV) in terms of minimum toxicity, could be the drug of choice for treatment of these cancers. Nevertheless, there has been no large prospective randomized trial of the efficacy and safety of CCRT and adjuvant chemotherapy with TMZ followed by RT for WHO grade III gliomas. Recently, several phase II or III trials have evaluated the benefit of CCRT and adjuvant chemotherapy with TMZ followed by RT [11, 12, 14, 15].

Therefore, we designed this study of the timing and dose of chemotherapy with TMZ, as was done in recent trials. In this trial, the objective response rate was 61% (17/28) and the mean OS and PFS were 58.5 and 43.4 months, respectively. Moreover, CCRT and adjuvant chemotherapy with TMZ was well tolerated, so there was no need to withhold chemotherapy because of toxicity. These results imply that trials including larger doses of adjuvant chemotherapy are possible, if needed. The outcome of this study was favorable compared with those of many other reports (Table 6), suggesting that CCRT and adjuvant chemotherapy with TMZ offers good clinical outcomes in the treatment of WHO grade III gliomas. There is a significant possibility that CCRT and adjuvant chemotherapy with TMZ for anaplastic gliomas would be effective and safe if the study had a longer follow-up period and more patients were recruited; in addition, the study should be redesigned as a randomized controlled trial in the future.

Age at diagnosis, KPS score, extent of surgical resection, measures of tumor cell proliferation, and gene alterations are well-established favorable prognostic factors for anaplastic gliomas [1]. In particular, trials published recently demonstrated that allelic loss of chromosomes 1p and 19q, methylation of MGMT, and IDH1 mutation have biological and clinical importance in the survival prognosis of patients, especially those with oligodendrocytic tumors [7, 11, 12, 14, 31]. In our trial, both the PFS and OS of the GTR, NTR, and STR groups, which corresponded to maximum resection of tumors, were significantly longer than those observed for the PR and biopsy groups ($P < 0.001$). Keles et al. reported that residual tumor volume is the most significant predictor of OS in patients with AA [32]. We confirmed that maximum surgical resection of WHO grade III gliomas was a significant prognostic factor compared with GBM (WHO grade IV). In this trial, however, we did not report the effects on patient survival of deletion of chromosomes 1p and 19q or methylation of the MGMT promoter, because of the small numbers of patients available. In the future, additional data regarding biological factors, for example the status of chromosomes 1p and 19q or methylation of the MGMT promoter, should be collected to reach a significant conclusion.

Conclusion

The objective of this prospective multicenter study was to demonstrate the efficacy and safety of TMZ during and after RT for treatment of WHO grade III gliomas, for example AA and AO. On the basis of our preliminary results, CCRT with TMZ for WHO grade III gliomas showed the possibility of achieving a favorable outcome. Thus, a large prospective randomized controlled trial with a long-term follow-up should be mandatory for this protocol.

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