the intensified 3-week on/1-week off TMZ regimen for recurrent GBM after the first line chemotherapy with TMZ. In addition to differences in the preceding alkylating agent, i.e. TMZ or nitrosourea, TMZ dose settings and time since the last cycle of the previous chemotherapy, this finding raises the question of whether methods to be used for detection of MGMT status influence these correlation analyses, and might suggest a potential pitfall to the use of the MSP assay for analysing MGMT status.

Several methods have been used to determine MGMT status in glioma tissues; a MSP assay for methylation status of the *MGMT* gene promoter region (15,16), reverse-transcription (RT)–PCR for MGMT mRNA expression (36), IHC (37), DNA repair enzymatic activity assays for MGMT (37,38) and a quantitative protein expression assay using western blotting as shown herein. These assays, however, have not been standardized or validated for clinical use, because contradicting results have been reported regarding the correlation between MGMT promoter methylation and MGMT protein expression (21,39,40). The MSP assay requires small quantities of DNA, and the presence of a methylated MGMT allele can be attributed solely to the neoplastic cells, thus contamination of non-neoplastic tissue would have little influence (22). However, the MSP assay has potential technical difficulties, since its success rate with biopsied material was low in the study by Hegi et al. (15). Furthermore, promoter methylation status does not always reflect protein expression, thus limiting its application to use as an epigenetic marker, rather than as a substitute for MGMT enzymatic activity. Indeed, a recent study by Maxwell et al. (37) showed not only no correlation between MSP results and MGMT enzymatic activity, but also a substantial disagreement between the grouping of patients by IHC and MSP based on the assigned prognostic criteria. IHC is a feasible method to detect MGMT protein even in archived paraffin-embedded samples. Although it has the advantage of allowing tumor cells to be identified from non-neoplastic brain components, its major disadvantages include low sensitivity leading to an underestimation of MGMT positivity (41), and wide variation in the positive rate and threshold level among studies (37) rendering meaningful comparison difficult. While requiring a large amount of starting material, the MGMT enzymatic activity assay would be the best in terms of a theoretical connection with the resistance mechanism. A good correlation was reported between MGMT activity and MGMT protein expression quantified by both IHC (37) and western blotting (42). Considering the laborious nature of the activity assay, these findings suggest that the quantification of MGMT protein expression by western blotting may well substitute for the MGMT activity assay for predictions of the response to TMZ treatment. A western blot analysis can be performed with a relatively small amount of starting material (~20 μg tumor lysate), and the expression level is easily standardized using the lysate of a glioma cell line with known MGMT expression and sensitivity to nitrosoureas and TMZ such as T98G (26). The observation that the MGMT status of gliomas determined by either the MGMT activity assay or IHC showed a good correlation indicates that potential contamination by a small amount of normal cells in tumor tissues may not significantly affect the result of the assays (37). Accordingly, we show a correlation, for the first time, between the tumor MGMT protein expression level and the OS or PFS of patients with recurrent GBM after TMZ treatment, whereas MSP was not associated with survival or response to TMZ (20). Further investigation of the relationship among MGMT assays in our cohort of patients is ongoing.

Since gliomas with a high MGMT expression level may respond to TMZ poorly, attempts to increase the antitumor activity of TMZ have been encouraged. One such approach is to administer TMZ via dose-dense regimens, which have been shown to effectively deplete cellular MGMT activity (43). The 7-day on/7-day off schedule at 150 mg/m^2/day or the 21-day on/7-day off schedule at 75 mg/m^2/day provides theoretically a 2.1- or 1.5-fold greater dose of TMZ, respectively, than the cumulative dose obtained with the standard 5-day regimen (20,44). These treatments achieved a 30–48% PFS rate at 6 months with acceptable safety profiles in patients with recurrent GBM (20,44), which were higher than the values obtained in our series. However, patients with low MGMT expression had a significantly higher response rate to the 7-day on/7-day off TMZ regimen, than those with high MGMT expression (17), suggesting that the depletion of MGMT may be still insufficient. Another approach is the use of MGMT-depleting agents other than TMZ itself. One of the most potent agents, O^6-benzylguanine, has been investigated in combination with TMZ in a couple of phase I studies with evidence of activity against refractory malignant gliomas (45,46). Similarly, clinical trials to evaluate the activity of procarbazine or cisplatin combined with TMZ have been conducted in patients with recurrent GBM (47,48). Whether these approaches can overcome resistance to TMZ through down-regulation of MGMT activity needs to be verified in comparison with the standard TMZ regimen in patients with GBM having high MGMT expression.

Another factor found to be significantly favorable for survival in the multivariate analysis was re-resection at relapse of the tumor. Although a recent study has demonstrated that the extent of resection at initial surgery correlates with OS in patients with newly diagnosed GBM (49), this finding might have resulted from potential selection bias, because re-resection is usually considered only when the recurrent tumor bulk is located outside of the eloquent areas, not infiltrating into deep brain structures and contralateral parenchyma, reflecting a better prognosis from the beginning.

In conclusion, the standard 5-day TMZ regimen resulted in moderate antitumor activity with an acceptable safety profile in patients with recurrent GBM even after pretreatment with nitrosourea. This study also provides additional evidence that MGMT protein expression is an important prognostic factor for patients treated with TMZ even after

recurrence. Further prospective studies are needed to determine subgroups of patients for whom the standard 5-day TMZ regimen may be beneficial, or those who require more intensive TMZ regimens to overcome TMZ resistance.

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Conflict of interest statement

None declared.

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ORIGINAL ARTICLE

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Pharmacokinetic study of temozolomide on a daily-for-5-days schedule in Japanese patients with relapsed malignant gliomas: first study in Asians

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Abstract
Background. Temozolomide (TMZ) is widely used in Europe and the United States. For the safe use of TMZ in the Japanese, as representative of Asians, the pharmacokinetics of TMZ was investigated in Japanese patients and compared to that in Caucasians.
Methods. The pharmacokinetics and safety of TMZ following oral administration of 150 and 200 mg/m^2 per day for the first 5 days of a 28-day treatment cycle were investigated in six Japanese patients with relapsed gliomas.
Results. The time-to-maximum plasma concentration (tmax) of TMZ was about 1 h and the elimination half-life of terminal excretion phase ($t_{1/2}\lambda z$) was about 2 h. A dose-dependent increase was observed in maximum plasma concentration (Cmax) and AUC, while values for $t_{1/2}\lambda z$, apparent total body clearance (CL/F), and apparent distribution volume (Vz/F) were independent of dose. After administration for 5 days, changes in pharmacokinetics and accumulation were not observed. The plasma 5-(3-methyl)1-triazen-1-yl-imidazole-4-carboxamide (MTIC) concentration changed in parallel with the TMZ plasma concentration, and the Cmax and AUC of MTIC were about 2% of those of TMZ. The pharmacokinetic parameters of TMZ and MTIC in Japanese patients in this study were comparable to those previously determined in Caucasian subjects. Adverse events occurred in all patients, but toxicities were mostly mild or moderate, and continuation of administration was possible by adjusting the dose and by delaying the start of the next treatment cycle.
Conclusion. The pharmacokinetic and safety profile of TMZ in Japanese patients was comparable to that in Caucasians. The treatment regimen used in Europe and the United States will be suitable for Asian patients, including Japanese.

Key words Malignant gliomas · Temozolomide · Pharmacokinetics · Japanese

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Introduction

The treatment of patients with malignant glioma remains the biggest challenge for the neuro-oncologist. Despite maximal safe surgical debulking and radiotherapy, overall survival for the average patient remains poor. In 1999, temozolomide (TMZ) was approved in the United States for refractory anaplastic astrocytoma and in the European Union for recurrent or progressed malignant glioma. In 2005, TMZ was additionally approved in the United States and the European Union for newly diagnosed glioblastoma multiforme, in combination with radiotherapy followed by monotherapy.

TMZ is an oral anticancer drug classified as an alkylating agent. In plasma, under physiological conditions, TMZ undergoes hydrolysis by rapid reaction with an alkaline base, and is transformed into 5-[(1Z)-3-methyltriaz-1-en-1-yl]-1H-imidazole-4-carboxamide (MTIC).[1–5] MTIC rapidly undergoes degeneration to the active form, methyldiazonium ion (DNA alkylating molecule)[3,5] and the inactive compound 5-aminoimidazole-4 carboxamide (AIC). TMZ has relatively high permeability through the blood-brain barrier as an unchanged drug.[6] These features contribute to its efficacy in patients with malignant gliomas.

Biological factors, including individual and ethnic differences, are considered to have little effect on the pharmacokinetics of TMZ. This consideration is based on the following findings: the bioavailability of TMZ with oral administration is nearly 100%,[7] linearity in pharmacokinetics is observed over a wide dose range,[8,9] the bioavailability of TMZ is not substantially affected by physiological conditions such as meals and gastric pH,[8,10] and the biotransformation from TMZ to MTIC and the formation of

methyldiazonium ion from MTIC are both nonenzymatic decomposition reactions.[1-5] Although TMZ is already being used in Taiwan and South Korea, no results have been reported of a pharmacokinetic study of TMZ in Asians.

We therefore investigated the pharmacokinetics of TMZ in Japanese patients, as representing Asians, to confirm its safety in Asian patients.

Patients and methods

Patient eligibility

Male and female patients with histologically proven relapsed gliomas with evidence of recurrence confirmed by magnetic resonance imaging (MRI) and whose Karnofsky performance status (KPS) was 50 or more were eligible for participation in this study. All pathology slides were reviewed by an independent central neuropathologist (Professor Yoichi Nakazato, Department of Human Pathology, Gunma University Graduate School of Medicine) based on WHO classification.[11] Patients also had to be 18 to less than 75 years in age, with male patients weighing at least 50 kg and female patients weighing at least 45 kg.

As prior treatment, patients must have undergone radiotherapy and chemotherapy. If the tumor was surgically resected at the time of relapse, MRI should have been conducted within 72 h after surgery and at least 8 days must have elapsed between the day of the surgery and the start of TMZ administration in the first cycle.

Patients also had to have an assessable tumor site confirmed by MRI, and the results of hematology and biochemistry tests had to meet defined criteria. Clinical laboratory values (performed within 14 days prior to TMZ [Temozolomide; Schering-Plough, Tokyo, Japan] administration, including the day of initial administration) had to be as follows: neutrophil count, $\geq 1500/mm^3$; platelet count, $\geq 100000/mm^3$; hemoglobin, ≥10.0 g/dl; blood urea nitrogen, <1.5 times the upper limit of laboratory standard value; serum creatinine, <1.5 times the upper limit of laboratory standard value; serum total bilirubin, ≤upper limit of laboratory standard value; transaminase, <3 times the upper limit of laboratory standard value; alkaline phosphatase, <2 times the upper limit of laboratory standard value.

Patients also had to have a life expectancy of at least 12 weeks.

This study was conducted after obtaining approval from the institutional review board at each study site. Written informed consent, according to the principles of the Declaration of Helsinki and the rules of Good Clinical Practice was obtained from all patients.

Clinical endpoints

Pharmacokinetics

To examine the pharmacokinetics of TMZ in Japanese patients, pharmacokinetic parameters were calculated based on TMZ plasma concentrations, MTIC plasma concentrations, and TMZ urinary concentrations. The pharmacokinetic parameters of TMZ and MTIC plasma concentrations were then compared with those obtained in Caucasian patients.

Safety

Laboratory values (hematology, blood biochemistry, and urinalysis), body weight, body temperature, blood pressure, and pulse rate were measured, and adverse events and adverse reactions were investigated, according to the National Cancer Institute (NCI) common toxicity criteria (Version 2.0). The appropriateness of the safety evaluation made by the investigator was evaluated by an Efficacy and Safety Evaluation Committee (Yukitaka Ushio, Director of Otemae Hospital; Kazuo Tabuchi, Director of Koyanagi Memorial Hospital; and Professor Yuta Shibamoto, Department of Quantum Radiotherapy, Nagoya City University Graduate School of Medical Sciences).

Treatment

One treatment cycle consisted of once-daily oral administration of TMZ on an empty stomach (2 h before breakfast) for 5 consecutive days, followed by 23 days without treatment, in a 28-day treatment cycle. The dose was $150 mg/m^2$ per day in the first cycle, and the dose in subsequent cycles was 100, 150, or $200 mg/m^2$ per day, based on the criteria for dose adjustment (Table 1). If adequate recovery had not occurred, the start of the next cycle was delayed until the criteria were met.

Plasma and urine sampling

Collection of plasma samples

Immediately before TMZ administration (0 h) and at 15, 30, and 45 min, and 1, 1.5, 2, 3, 4, 6, 8, 12, and 24 h after administration on days 1 and 5 in the first cycle ($150 mg/m^2$) and second cycle ($200 mg/m^2$), 5 ml of venous blood was collected using a pre-chilled heparinized vacuum tube, and blood samples were cooled in an ice-water bath from immediately after sampling and centrifuged (4°C, 3000 rpm, 10 min) to separate plasma within 5 min of blood collection. For the determination of TMZ plasma concentrations, 1.0 ml of plasma sample immediately after centrifugation was placed in a polypropylene tube to which 50 µl of 8.5% phosphoric acid solution (stabilizer) had been pre-added. The acidified plasma was vortexed, and the tube was then sealed and stored frozen at −20°C or below until analysis. For determination of MTIC plasma concentrations, about 1 ml of plasma sample was dispensed immediately after centrifugation to a pre-cooled polypropylene tube. The tube was then sealed and frozen immediately on dry ice-methanol. The sample was stored frozen at −80°C or below until analysis.

Table 1. Dose adjustment criteria based on neutrophil count, platelet count, and onset of adverse events

	Grade	Dose adjustment criteria based on neutrophil count and platelet count		
		1	2	3
		Nadir neutrophil count >1500/mm^3 Nadir platelet count >100000/mm^3	Nadir neutrophil count 1000–1500/mm^3 Nadir platelet count 50000–100000/mm^3	Nadir neutrophil count <1000/mm^3 Nadir platelet count <50000/mm^3
Dose adjustment criteria based on onset of adverse events	CTC Grade 0, 1	Increase by 50 mg/m^2 per day	No change	Reduce by 50 mg/m^2 per day
	CTC Grade 2	No change	No change	Reduce by 50 mg/m^2 per day
	CTC Grade 3, 4	Reduce by 50 mg/m^{2}per day	Reduce by 50 mg/m^2 per day	Reduce by 50 mg/m^2 per day

Collection of urine samples

Urine was collected before TMZ administration and in 0–4, 4–8, and 8- to 24-h blocks after administration on days 1 and 5 in both the first and second cycles. The total volume of urine accumulated up to each prescribed time point was collected in plastic urine collection containers to which 2 ml of 8.5% phosphoric acid solution (stabilizer) had been pre-added. These plastic containers were refrigerated throughout the urine accumulation time period. The pH of the urine in the plastic container was determined after each voiding. If the pH was 4 or more, 8.5% phosphoric acid solution was added again. Each urine sample was collected in a polypropylene tube (total, 20 ml) and the tubes were sealed and stored frozen at –20°C or below until analysis.

Assay method

TMZ and MTIC plasma concentrations were both determined by validated high-performance liquid chromatography-tandem mass spectrometry. The lower limits of quantitation of temozolomide and MTIC were 0.020 μg/ml and 5.00 ng/ml, respectively. Urinary temozolomide concentration was determined by validated high-performance liquid chromatography. The lower limit of quantitation was 1.00 μg/ml.

Pharmacokinetic analysis

The pharmacokinetic analysis of TMZ and MTIC plasma concentrations was performed by noncompartmental analysis[12] and pharmacokinetic parameters, including the maximum plasma concentration (Cmax), time-to-maximum plasma concentration (tmax), the area under the plasma concentration-time curve (AUC) up to the final observation point (AUC_{0-t}), AUC up to 24 h after administration (AUC_{0-24}), AUC up to infinite time ($AUC_{0-\infty}$), elimination half-life of terminal excretion phase ($t_{1/2}\lambda z$), apparent total body clearance (CL/F), apparent distribution volume (Vz/F), and accumulation index (R) were calculated by patient. With TMZ urinary concentrations, the amount of urinary excretion (Ae), the urinary excretion rate (Ae%), and renal clearance (CLr) were calculated for each patient.

Role of the funding source

The supporter of this study was responsible for the study design, quality assurance, and quality control systems to ensure that the study was done and data were generated, documented, analyzed, and reported in compliance with the protocol. The supporter had no role in the interpretation of the data. The corresponding author had full access to all data in the study, including those for safety, and had the final responsibility to submit the paper for publication.

Results

Patient characteristics

Table 2 shows the major background factors of all six patients. The mean age was 43.3 years, with three patients under 40 and the remaining three between 40 and 64 years. The six patients consisted of five men and one woman. The mean body weight was 63.85 kg, and the mean body mass index was 22.92 kg/m^2. KPS was assessed to be 50, 60, 70, and 80 in one patient each and 90 in two patients.

According to the results of the central pathology review, one patient had anaplastic astrocytoma (AA), three had glioblastoma multiforme (GBM), one had anaplastic oligodendroglioma (AO), and one had malignant glioma. Four patients had received surgical treatment once and two had received surgical treatment twice. All patients had experienced one recurrence, and the time to recurrence was less than 6 months in one patient and 6 months or more in five patients.

Pharmacokinetics

Pharmacokinetics was examined in six patients who completed administration at 150 mg/m^2 per day in the first cycle and in three patients whose dose was increased to 200 mg/m^2 per day in the second cycle.

Table 2. Demographics

Item	Classification, etc.	All subjects
Age (years) $n = 6$	Mean ± standard deviation	43.3 ± 12.4
	Median value	39.5
	Minimum value–maximum value	29–62
Age classification (years) $n = 6$	<40	3 (50%)
	≥40 to <65	3 (50%)
	≥65	0
Sex $n = 6$	Male	5 (83%)
	Female	1 (17%)
Body weight (kg) $n = 6$	Mean ± standard deviation	63.85 ± 9.14
	Median value	62.1
	Minimum value–maximum value	52.6–78.0
BMI (kg/m^2) $n = 6$	Mean ± standard deviation	22.92 ± 3.71
	Median value	22.15
	Minimum value–maximum value	19.6–28.7
KPS before start of administration $n = 6$	Mean ± standard deviation	73.3 ± 16.3
	Median value	75
	Minimum value–maximum value	50–90
Central pathology judgment of lesion tissue $n = 6$	AA	1 (17%)
	Other than AA	5 (83%)
Number of operations $n = 6$	0	0
	1	4 (67%)
	2	2 (33%)
	3 or more	0
Recurrence $n = 6$	Once	6 (100%)
	2 Times or more	0
Duration from initial diagnosis to initial recurrence (months) $n = 6$	<6	1 (17%)
	≥6	5 (83%)
Steroid use $n = 6$	No	3 (50%)
	Yes	3 (50%)
Most recent steroid dose* (mg/day) $n = 3$	Mean ± standard deviation	16.13 ± 0.98
	Median value	16.7
	Minimum value–maximum value	15.0–16.7
Classification of most recent steroid dose* $n = 3$	<10 mg/day	0
	≥10 mg/day <20 mg/day	3 (100%)
	≥20 mg/day	0

*Calculated as dose of prednisolone (excluding topical steroid)

TMZ and MTIC plasma concentration-time profiles and pharmacokinetic parameters

Table 3 shows the pharmacokinetic parameters of TMZ and MTIC plasma concentrations on days 1 and 5 of TMZ administration in the first cycle (150 mg/m^2 per day) and second cycle (200 mg/m^2 per day). Figure 1 shows the mean TMZ and MTIC concentration-time profiles on days 1 and 5 of the first and second cycles.

TMZ in the six patients in the first cycle reached tmax at about 1 h after administration, with a monophasic decrease up to 12 h after administration. TMZ plasma concentrations were below the lower limit of quantitation (0.020 μg/ml) in five of six patients after 24 h. The Cmax values on days 1 and 5 were 7.87 and 8.38 μg/ml, respectively; AUC_{0-t} values were 25.7 and 25.2 μg·h/ml; AUC_{0-24} values were26.5 and 25.9 μg·h/ml; and $AUC_{0-\infty}$ values were 26.1 and 25.6 μg·h/ml. The accumulation index, based on Cmax and AUC_{0-24}, was 1.11 and 0.986, respectively, indicating no accumulation due to repeated administration. The $t_{1/2}\lambda z$ values on days 1 and 5 of administration were 2.14 and 2.29 h, respectively; CL/F values were 2.57 and 2.56 ml/min per kg; and the Vz/F values were 0.468 and 0.492 l/kg, indicating no change due to repeated administration. These coefficients of variation for AUC, $t_{1/2}\lambda z$, CL/F, and Vz/F ranged from 9% to 35%.

As with the first cycle, TMZ in the three patients in the second cycle who received 200 mg/m^2 per day reached tmax at about 1 h after administration, with a monophasic decrease up to 12 h after administration. TMZ plasma concentrations were below the lower limit of quantitation in all patients after 24 h. The Cmax values on days 1 and 5 were 15.3 and 14.0 μg/ml, respectively; AUC_{0-t} values were 35.1 and 36.0 μg·h/ml, AUC_{0-24} values were 36.4 and 37.3 μg·h/ml; and $AUC_{0-\infty}$ values were 35.7 and 36.7 μg·h/ml. The accumulation index, based on Cmax and AUC_{0-24}, was 0.868 and 1.03, respectively, indicating no accumulation due to repeated administration. The $t_{1/2}\lambda z$ values on days 1 and 5 of administration were 2.03 and 2.02 h, respectively; CL/F values were 2.37 and 2.27 ml/min per kg; and Vz/F values were 0.415 and 0.395 l/kg, indicating no change due to repeated administration, and the values were nearly the same as those observed after the administration of 150 mg/m^2 per day. The coefficients of variation for AUC, $t_{1/2}\lambda z$, CL/F, and Vz/F ranged from 4% to 9%.

The concentration-time profile of MTIC plasma concentrations in both the first cycle (150 mg/m^2 per day) and the second cycle (200 mg/m^2 per day) was nearly parallel to that

Table 3. Pharmacokinetic parameters of temozolomide and MTIC plasma concentrations in cycle 1 (150 mg/m^2 per day) and cycle 2 (200 mg/m^2 per day)

Analyte	Dose (mg/m^2)	Dosing day	Tmax (h)	Cmax (μg/ml)	$t_{1/2}\lambda z$ (h)	AUC (μg·h/ml)			CL/F (ml/min per kg)	Vz/F (l/kg)	R	
						0–t	0–24	0–∞			Cmax	AUC_{0-24}
Temozolomide	150 (n = 6)	Day 1	1.42 (52)	7.87 (38)	2.14 (25)	25.7 (15)	26.5 (14)	26.1 (14)	2.57 (18)	0.468 (23)	–	–
		Day 5	0.958 (53)	8.38 (36)	2.29 (35)	25.2 (10)	25.9 (9)	25.6 (10)	2.56 (14)	0.492 (21)	1.11 (24)	0.986 (8)
	200 (n = 3)	Day 1	0.583 (25)	15.3 (5)	2.03 (4)	35.1 (6)	36.4 (6)	35.7 (6)	2.37 (5)	0.415 (7)	–	–
		Day 5	0.917 (57)	14.0 (30)	2.02 (5)	36.0 (4)	37.3 (5)	36.7 (4)	2.27 (9)	0.395 (5)	0.868 (39)	1.03 (7)
MTIC	150 (n = 6)	Day 1	1.42 (52)	0.145 (38)	1.98 (24)	0.426 (15)	0.451 (14)	0.463 (14)	–	–	–	–
		Day 5	1.08 (43)	0.154 (28)	1.83 (12)	0.425 (12)	0.445 (13)	0.454 (13)	–	–	1.14 (29)	1.00 (16)
	200 (n = 3)	Day 1	0.750 (33)	0.272 (15)	1.93 (6)	0.594 (7)	0.622 (8)	0.632 (8)	–	–	–	–
		Day 5	0.917 (57)	0.284 (33)	1.87 (3)	0.636 (7)	0.665 (7)	0.676 (7)	–	–	1.03 (17)	1.07 (1)

Values are means, with coefficient of variation % in parentheses

Tmax, time of each plasma concentration; Cmax, maximun plasma concentration; $t_{1/2}\lambda z$, elimination half-life terminal excretion phase; AUC, area under the plasma concentration time curve; CL/F, apparent total body clearance; Vz/F, apparent distribution volume; R, accumulation index

of the TMZ plasma concentrations on day 1 as well as on day 5. The tmax and $t_{1/2}\lambda z$ values of MTIC plasma concentrations were 0.750 to 1.42 h and 1.83 to 1.98 h, respectively, which closely matched the tmax and $t_{1/2}\lambda z$ values of the TMZ plasma concentrations. After the administration of 150 and 200 mg/m^2 per day, the Cmax values were 0.145 to 0.154 and 0.272 to 0.284 μg/ml, respectively; AUC_{0-t} values were 0.425 to 0.426 and 0.594 to 0.636 μg·h/ml, respectively; AUC_{0-24} values were 0.445 to 0.451 and 0.622 to 0.665 μg·h/ml, respectively; and $AUC_{0-\infty}$ values were 0.454 to 0.463 and 0.632 to 0.676 μg·h/ml, respectively. Cmax and AUC exhibited a dose-dependent increase in relation to the administration of 150 mg/m^2 per day and 200 mg/m^2 per day. The ratios of MTIC to TMZ, based on Cmax and AUC, were 1.78% to 2.03% and 1.66% to 1.84%, respectively. The accumulation index, based on Cmax and AUC_{0-24}, was 1.03 to 1.14 and 1.00 to 1.07, indicating no accumulation due to repeated administration, as in the case of TMZ plasma concentrations. The coefficients of variation for AUC and $t_{1/2}\lambda z$ ranged from 3% to 24%.

TMZ urinary excretion rate

Table 4 shows the amount of urinary excretion, excretion rate, and renal clearance by urine accumulation intervals to 24 h after the administration of TMZ on days 1 and 5 in the first cycle (150 mg/m^2 per day) and second cycle (200 mg/m^2 per day). One of the three patients in the second cycle mistakenly discarded the 0- to 4-h urine after administration on day 5, and the cumulative urinary excretion data for this patient on day 5 of the administration of 200 mg/m^2 per day was considered missing.

The cumulative urinary excretion rates of TMZ (up to 24 h after administration) were 7.42% and 5.93% on days 1 and 5, respectively, at 150 mg/m^2 per day, and 4.81% and 5.21% on days 1 and 5, respectively, at 200 mg/m^2 per day. The renal clearance of TMZ was 0.193 and 0.155 ml/min per kg on days 1 and 5, respectively, at 150 mg/m^2 per day, and 0.114 and 0.119 ml/min per kg on days 1 and 5, respectively, at 200 mg/m^2 per day. No change due to the difference in dose or to repeated administration was observed in the urinary excretion rate or renal clearance of TMZ. Calculation of the proportion of renal clearance to total body clearance (2.27–2.57 ml/min per kg) indicated a value of 4.81% to 7.51%.

Safety

Adverse events occurred in all patients; most of these events were either mild or moderate.

The adverse events observed at an incidence of 50% or more were: constipation in 67% (four patients), nausea in 67% (four patients), increased alanine aminotransferase in 67% (four patients), increased aspartate aminotransferase in 67% (four patients), and increased blood alkaline phosphatase in 50% (three patients). These adverse events also corresponded to the adverse events for which a causal rela-

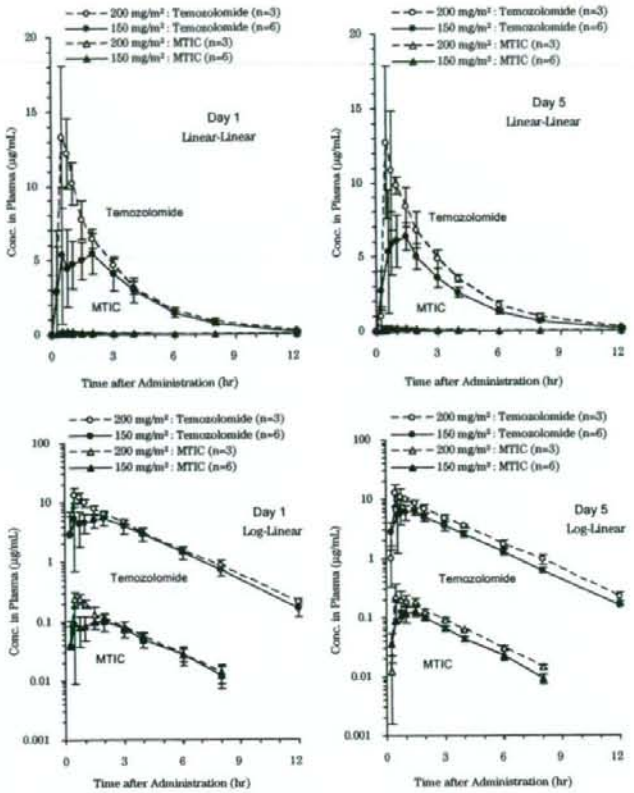

Fig. 1. Time-course change in mean plasma temozolomide and 5-(3-methyl)1-triazen-1-yl-imidazole-4-carboxamide (*MTIC*) concentrations on days 1 and 5 in cycle 1 (150 mg/m^2 per day) and cycle 2 (200 mg/m^2 per day)

Table 4. Amount of urinary temozolomide excretion (Ae), excretion rate (Ae%), and renal clearance (CLr) by urine accumulation intervals in cycle 1 (150 mg/m^2 per day) and cycle 2 (200 mg/m^2 per day)

Parameter	Dose (mg/m^2)	Administration day	Time after administration		(Urine accumulation interval) (h)	
			0–4	4–8	8–24	0–24
Ae (mg)	150	Day 1	11.1 (25)	5.64 (59)	1.49 (82)	18.2 (22)
	$n = 6$	Day 5	10.3 (43)	3.37 (46)	0.915 (55)	14.6 (26)
	200	Day 1	12.8 (53)	3.42 (62)	0.178 (173)	16.4 (53)
	$n = 3$	Day 5	12.8[a]	3.93 (32)	1.00 (89)	17.7[a]
Ae% (%)	150	Day 1	4.51 (29)	2.32 (65)	0.593 (80)	7.42 (28)
	$n = 6$	Day 5	4.20 (48)	1.36 (47)	0.366 (55)	5.93 (33)
	200	Day 1	3.75 (57)	1.00 (66)	0.0524 (173)	4.81 (57)
	$n = 3$	Day 5	3.75[a]	1.15 (36)	0.300 (90)	5.21[a]
CLr (ml/min per kg)	150	Day 1	–	–	–	0.193 (33)
	$n = 6$	Day 5	–	–	–	0.155 (42)
	200	Day 1	–	–	–	0.114 (60)
	$n = 3$	Day 5	–	–	–	0.119[a]

Values are means, with coefficient of variation % in parentheses
[a] $n = 2$

tion to TMZ could not be ruled out (adverse reactions) that were observed at an incidence of 50% or more.

As myelosuppression-related adverse events, a decrease in neutrophil count (grade 2), platelet count (grade 1), and leukocyte count (grade 2) occurred in one patient each (17%). Grade 3 toxicity observed in hematology tests was a decreased lymphocyte count in one patient, and no other grade 3 or 4 toxicity was observed. Leukocyte count, platelet count, and neutrophil count were within normal ranges. No grade 3 or 4 toxicities were observed in biochemistry tests or urinalysis, except for a grade 3 increase in alanine aminotransferase in two patients.

Two adverse events resulted in death. The first was brain damage in one patient, resulting in death 23 days after the final administration in the first cycle. The second was a decreased level of consciousness in one patient who discontinued participation in the study 23 days after the final administration in the first cycle and who died about 3 months after discontinuation. The study was also discontinued in another patient 24 days after the final administration in the sixth cycle due to progression of the primary disease, and this patient died about 3.5 months after discontinuation due to aggravation of the primary disease. Three deaths occurred in this study, but the cause of death in all three patients was attributed to the primary disease.

Discussion

We investigated the pharmacokinetics of TMZ in Japanese patients to determine whether or not the treatment regimen used in the United States and Europe could be used in Japan.

After the oral administration of 150 and 200 mg/m^2 per day, TMZ plasma concentration reached tmax about 1 h after administration, followed by a monophasic decrease. Although a dose-dependent increase in Cmax and AUC was observed, these values did not increase after 5 days of repeated administration (accumulation index was about 1), indicating no accumulation of this drug. The elimination of TMZ from plasma was rapid, and no change due to difference in the dose or to repeated administration was observed in CL/F or Vz/F. The coefficients of variation for AUC, $t_{1/2}\lambda z$, CL/F, and Vz/F were small, at 4% to 35%, suggesting that the interpatient difference in pharmacokinetics was small. Plasma MTIC concentrations were observed to change in parallel with TMZ plasma concentrations at both 150 and 200 mg/m^2 per day, and tmax and $t_{1/2}\lambda z$ values generally corresponded to those of TMZ plasma concentrations. The Cmax and AUC of MTIC plasma concentration were 1.8% to 2.0% and 1.7% to 1.8% of those of TMZ plasma concentrations. With TMZ, no accumulation was observed with repeated administration. These results suggested that the plasma MTIC concentration is dependent on the plasma TMZ concentration and that the reaction rate from MTIC to AIC is clearly more rapid than that from TMZ to MTIC. Based on the results obtained by the administration of 150 and 200 mg/m^2 per day, no marked change in pharmacokinetics due to the difference in dose or to repeated administration was noted. The cumulative urinary excretion rate of TMZ was 4.8% to 7.4% (up to 24 h after administration). The renal clearance of TMZ was 0.114 to 0.193 ml/min per kg, accounting for 4.8% to 7.5% of total body clearance. It is possible, however, that actual renal clearance was underestimated because of the possible effect of decomposition during the retention of urine in the bladder. The above plasma and urinary pharmacokinetic profile of TMZ in Japanese was essentially the same as that already observed in Caucasians.[8-10]

The pharmacokinetic parameters of TMZ and MTIC plasma concentrations in Japanese patients obtained in this study were compared with those obtained in pharmacokinetic studies (Schering-Plough data on file)[8,10,12] conducted

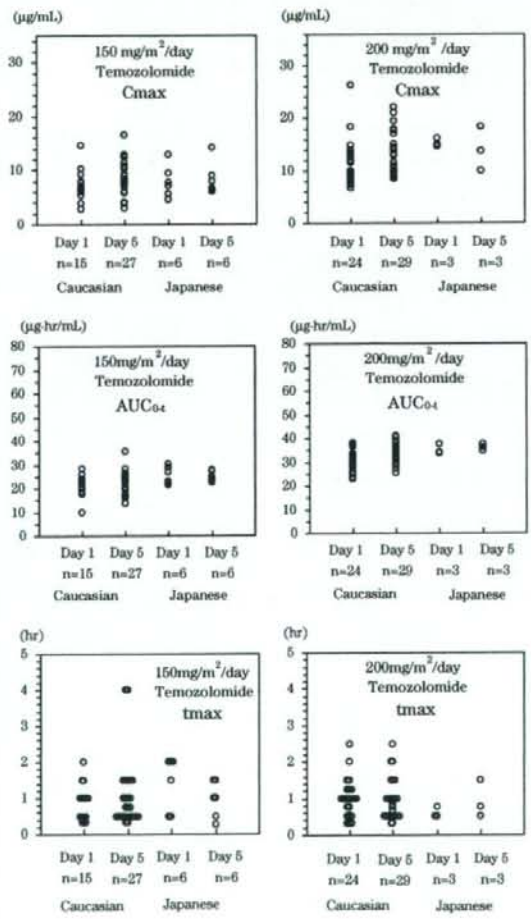

Fig. 2. Maximum plasma concentration (*Cmax*), area under the plasma concentration-time curve up to the final observation point ($AUC_{0\text{-}t}$), and time-to-maximum plasma concentration (*tmax*) of temozolomide: comparison between Japanese and Caucasians. Data of Caucasians are cited from Schering-Plough data on file[8,10,12]

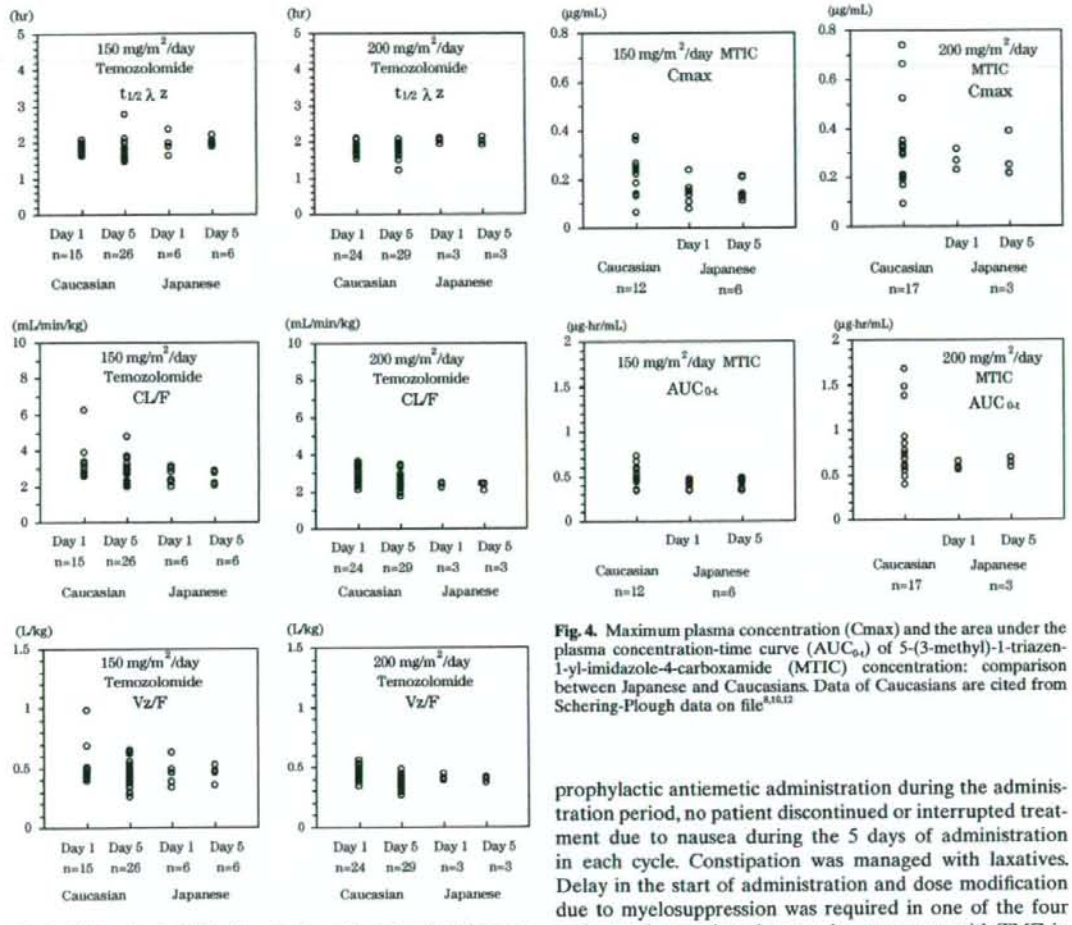

Fig. 3. Elimination half-life of terminal excretion phase ($t_{1/2}\lambda z$), apparent total body clearance (*CL/F*), and apparent distribution volume (*Vz/F*) of plasma temozolomide: comparison between Japanese and Caucasians. Data of Caucasians are cited from Schering-Plough data on file[8,10,12]

Fig. 4. Maximum plasma concentration (Cmax) and the area under the plasma concentration-time curve (AUC_{0-t}) of 5-(3-methyl)-1-triazen-1-yl-imidazole-4-carboxamide (MTIC) concentration: comparison between Japanese and Caucasians. Data of Caucasians are cited from Schering-Plough data on file[8,10,12]

in Caucasians in the United States. As shown in Figs. 2 to 5, the pharmacokinetic parameters (Cmax, tmax, AUC_{0-t}, $t_{1/2}\lambda z$, CL/F, and Vz/F) of plasma TMZ concentration and the pharmacokinetic parameters (Cmax, tmax, AUC_{0-t}, and $t_{1/2}\lambda z$) of plasma MTIC concentration obtained from Japanese patients all fell in the range of data obtained from Caucasian patients. These results confirm the assumption that there is little possibility that the pharmacokinetics of TMZ would be affected by biological factors including ethnic differences.

Adverse events occurred in all patients, but most were judged to be mild or moderate in severity. Continued administration was therefore possible with dose adjustment and delay in the start of administration of the next cycle. The incidence of nausea and constipation was high, but with prophylactic antiemetic administration during the administration period, no patient discontinued or interrupted treatment due to nausea during the 5 days of administration in each cycle. Constipation was managed with laxatives. Delay in the start of administration and dose modification due to myelosuppression was required in one of the four patients who continued to receive treatment with TMZ in the second cycle. The safe continuation of treatment was considered possible by monitoring for adverse reactions and adjusting the dose. No increase of myelosuppression with increased dose was observed.

The treatment regimen in this study was generally well tolerated in Japanese patients with relapsed gliomas.

The confirmation of the safety of TMZ in Japanese patients in this study contributes greatly to the assurance of safety in Asians, including patients in Taiwan and South Korea, where TMZ is already being used. The possibility is very high that the treatment regimen in the United States and Europe is applicable to all ethnic groups.

Conflict of interest

All authors declare no conflict of interest.

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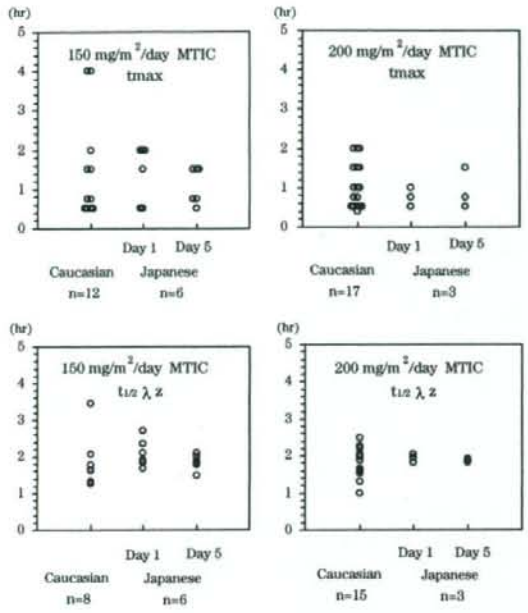

Fig. 5. Values for time of each plasma concentration (tmax) and terminal excretion phase ($t_{1/2}\lambda z$) of plasma 5-(3-methyl)-1-triazen-1-yl-imidazole-4-carboxamide (MTIC) concentration: comparison between Japanese and Caucasians. Data of Caucasians are cited from Schering-Plough data on file[8,10,12]

ticipate in this study, and to the study nurse and data managers for their collaboration.

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● 原 著 ●

初回再発の退形成性星細胞腫患者に対するTemozolomide単剤投与の有効性および安全性の検討

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Efficacy and Safety of Monotherapy with Temozolomide in Patients with Anaplastic Astrocytoma at First Relapse—A Phase II Clinical Study: Ryo Nishikawa[*1], Soichiro Shibui[*2], Motohiko Maruno[*3], Kazuhiko Sugiyama[*4], Shinya Sato[*5], Takamitsu Fujimaki[*6], Hideaki Takahashi[*7], Toshihiko Wakabayashi[*8], Jun Takahashi[*9], Masato Kochi[*10], Hideo Nakamura[*11], Yutaka Sawamura[*12], Jun Ikeda[*13], Tomokatsu Hori[*14], Tomokazu Aoki[*15] and Masao Matsutani[*1] ([*1]*Dept. of Neurosurgery, Saitama Medical University,* [*2]*Neurosurgery Division, National Cancer Center Hospital,* [*3]*Dept. of Neurosurgery, Osaka University Graduate School of Medicine,* [*4]*Dept. of Neurosurgery, Graduate School of Biomedical Sciences, Hiroshima University,* [*5]*Dept. of Neurosurgery, Yamagata University Faculty of Medicine,* [*6]*Dept. of Neurosurgery, Teikyo University School of Medicine,* [*7]*Dept. of Neurosurgery, Brain Research Institute, Niigata University,* [*8]*Center for Genetic and Regenerative Medicine, Nagoya University Hospital,* [*9]*Dept. of Neurosurgery, Kyoto University Graduate School of Medicine,* [*10]*Dept. of Neurosurgery, Faculty of Medical and Pharmaceutical Sciences, Kumamoto University (currently with Sanai Hospital),* [*11]*Dept. of Neurosurgery, Faculty of Medical and Pharmaceutical Sciences, Kumamoto University,* [*12]*Dept. of Neurosurgery, Hokkaido University Faculty of Medicine,* [*13]*Dept. of Neurosurgery, Hokkaido University Faculty of Medicine (currently with Hokkaido Cancer Center Hospital),* [*14]*Dept. of Neurosurgery, Neurological Institute, Tokyo Women's Medical University,* [*15]*Dept. of Neurosurgery, Brain Tumor Center, Kitano Hospital*)

Summary

The efficacy and safety of temozolomide were evaluated in 32 patients with anaplastic astrocytoma at first relapse. Temozolomide was administered orally once daily for the first five days of a 28-day cycle, at a dose of 150 or 200 mg/m²/day. The response rate determined by independent central review of MRI was 34% (95% confidence interval: 18.6%-53.2%), with 3 complete response and 8 partial response. The rate of "no change or better" was 91% (95% confidence interval: 75.0%-98.0%). Progression-free survival (PFS) at 6 months was 40.6%, and the median PFS was 4.1 months.

The incidence of constipation (50%) and nausea (25%) was high, but these events were all mild or moderate in severity except in one subject with constipation, and could be managed with standard laxatives and antiemetics. The main laboratory test abnormalities (total incidence and incidence of grade 3/4 change) were lymphocytopenia (50%, 25%), neutropenia (47%, 6%), leukopenia (38%, 3%), thrombocytopenia (31%, 9%), and increased GPT

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(25%, 3%).

Temozolomide was shown to have good efficacy and tolerability in patients with anaplastic astrocytoma at first relapse. Key words: Anaplastic astrocytoma, Temozolomide, Phase II study (*Received May 26, 2006/Accepted Jul. 18, 2006*)

要旨 初回再発の退形成性星細胞腫患者32名を対象としたtemozolomideの多施設共同第II相試験を行い，有効性と安全性を評価した。temozolomideは28日間を1クールとし，各クールの初めの5日間に150または200 mg/m²/日を1日1回連日経口投与した。全登録例における奏効率は34%（11/32）（95%信頼区間18.6%～53.2%）で，奏効例の内訳は著効3例，有効8例であった。不変以上であった症例の割合は91%（29/32）（95%信頼区間75.0%～98.0%）であった。また，6か月無増悪生存率は40.6%，無増悪生存期間の中央値は4.1か月であった。

自他覚症状の有害事象においては便秘（50%），悪心（25%）の発現頻度が高かったが，これらは便秘の1例を除いてすべて中等度以下の重症度で，標準的な緩下剤あるいは制吐剤でコントロール可能であった。主たる臨床検査値異常変動は，リンパ球数減少（50%，grade 3以上25%），好中球数減少（47%，grade 3以上6%），白血球数減少（38%，grade 3以上3%），血小板数減少（31%，grade 3以上9%），GPT増加（25%，grade 3以上3%）であった。temozolomideは初回再発の退形成性星細胞腫に対して優れた奏効率と忍容性を示した。

はじめに

神経膠腫は脳腫瘍の25%を占める[1]。神経膠腫に対する治療方法は確立されているとはいえず，治療成績も1980年代からほとんど進歩していない。特に退形成性星細胞腫（anaplastic astrocytoma: AA）や膠芽腫（glioblastoma: GBM）といったWHO脳腫瘍悪性度grade III/IVに相当するいわゆる悪性神経膠腫の治療成績は不良で，それぞれの5年生存率は24%と7%でしかない[1]。temozolomideは初発膠芽腫患者における生存期間延長効果が，第III相試験によって確認されている唯一の薬剤である[2]。2005年に発表されたこの第III相試験の結果，世界的には悪性神経膠腫の標準治療薬となりすでに77か国で承認されている（2005年8月現在）が，本邦では未承認である。

temozolomideはアルキル化剤に分類される抗腫瘍薬で，血漿中など生理的条件下で容易に加水分解され，5-[(1 *Z*)-3-methyltriazen-1-yl]-1 *H*-imidazole-4-carboxamide(MTIC)に変換される[3-7]。MTICは速やかに分解され，活性本体であるメチルジアゾニウムイオンを生成し，DNAのアルキル化分子として作用する[5,7]。temozolomideは未変化体のまま血液脳関門を通過することが確認されている[8]。temozolomideの脳腫瘍に対する効果は，血中で生成され循環するMTICによる抗腫瘍作用に加えて，未変化体のtemozolomideが血液脳関門を通過し，標的部位に移行した後に局所で生成されるMTICによる抗腫瘍作用の両者の寄与が考えられている。

今回，本邦における初回再発AAの患者を対象として，temozolomideの有効性および安全性を検討するための多施設共同第II相試験を2003～2005年に，各実施医療機関の治験審査委員会での承認を経た上で実施した。薬剤投与後6か月時点における結果を報告する。本試験実施医療機関，中央病理診断医および効果安全性評価委員会は表1のとおりである。

I．対象と方法

1．対　象

初回手術時に組織学的にAAと確認されている患者で，MRIによって腫瘍の再発または再増大が確認され，登録時のKarnofsky performance status (KPS)が70%以上，年齢18歳以上の患者を対象とした。組織学的診断は中央病理診断医（表1）によって再検討を行った。また，初発時に放射線治療およびnitrosourea系薬剤を含む治療レジメンによる化学療法が施行されていることを必要条件とした。

2．評価項目

1）有効性

MRI画像で腫瘍径が最大であるスライスを用いて2方向測定法により腫瘍縮小効果を判定した[9]。MRI画像上すべての腫瘍が消失したものを著効，測定可能病変の径の積の総和が50%以上減少し，新病変の出現が認められないものを有効，測定可能病変の径の積の総和が25%以上増大するか新病変が出現したものを進行，これらのいずれにも該当しないものを不変とした。また，ステロイドの使用状況と神経学的改善度を加味して総合的腫瘍縮小効果を判定した（表2）。腫瘍縮小効果と総合的腫瘍縮小効果は効果安全性評価委員会（表1）が判定した。さらに，薬剤投与開始6か月後までの無増悪生存（progression free survival: PFS）を評価した。

2）安全性

体重，体温，血圧，脈拍数の測定および臨床検査（血液学的検査，血液生化学検査，尿検査）を施行し有害事象と副作用を調査した。有害事象は可能な限りNational Cancer Institute-Common Toxicity Criteria (NCI-

表 1 試験実施医療機関，中央病理診断医および効果安全性評価委員会

試験実施医療機関	国立大学法人北海道大学病院	
	国立大学法人山形大学医学部附属病院	
	東京女子医科大学病院	
	帝京大学医学部附属病院	
	国立がんセンター中央病院	
	埼玉医科大学病院	
	国立大学法人新潟大学医歯学総合病院	
	名古屋大学医学部附属病院	
	京都大学医学部附属病院	
	財団法人田附興風会北野病院	
	大阪大学医学部附属病院	
	兵庫医科大学病院	
	広島大学病院	
	国立大学法人愛媛大学 愛媛大学医学部附属病院	
	国立大学法人熊本大学 熊本大学医学部附属病院	
	国立大学法人鹿児島大学医学部・歯学部附属病院	
	医療法人医仁会中村記念病院	
中央病理診断医	群馬大学大学院医学系研究科病態病理学	中里 洋一
効果安全性評価委員会	国家公務員共済組合連合会大手前病院	生塩 之敬
	佐賀大学医学部	田渕 和雄
	(現在の所属: 医療法人社団博文会小柳記念病院)	
	名古屋市立大学大学院医学研究科量子放射線医学分野	芝本 雄太

表 2 総合的腫瘍縮小効果の判定基準

判定	判定基準
著効	1か月以上の間隔をおいた連続するMRIで，すべての腫瘍が消失し，長期治療により必要とされた生理学的用量のステロイド投与を除いてステロイド投与を中止し，かつ神経学的に安定しているか，または改善している
有効	1か月以上の間隔をおいて実施された連続するMRIで，2方向測定可能病変の積の総和が50%以上（100%未満）減少する，かつステロイド使用量が前回のMRI検査時に投与した用量と同用量または，それより低用量で各MRI検査前7日間におけるステロイド使用量の安定がみられ，さらに神経学的安定または改善がみられる。新病変の出現が認められないもの
進行	MRIで評価可能な病変について，2方向測定可能病変の積の総和が25%以上増大するか，新病変が出現したもの，ステロイド使用量が前回のMRI検査時に投与した用量と同用量または，それより高用量で各MRI検査前7日間におけるステロイド使用量の安定がみられる。さらに神経学的増悪を伴うかまたは伴わないもの
不変	その他の状況すべて

CTC) Version 2.0[10]に従って判定し，NCI-CTCに規定されていない事象に関しては，症状が認められるが日常的活動が妨げられず処置を要さないものを軽度（grade 1），不快感のために日常的活動が妨げられる，または臨床状態に影響が認められるもので，処置を要するものを中等度（grade 2），日常的活動が不能となる，または臨床状態に重大な影響が認められるものを重度（grade 3）と分類した。

3．試験方法

temozolomideは5日間連続で1日1回空腹時に経口投与し，その後23日間休薬する28日間を1クールとした。第1クールではtemozolomide 150 mg/m²/日を投与し，第2クール以降は用量調節判定基準（表3）に従い100，150または200 mg/m²/日から選択した用量を投与した。また，各クールの開始に際して開始を延期する基準を設定した。すなわち，好中球数が1,500/mm³未満あるいは血小板数が100,000/mm³未満であった場合，それぞれが1,500/mm³あるいは100,000/mm³以上に回復するまで次クールの投与を開始しないこと，grade 2でtemozolomideとの因果関係が否定できない有害事象（悪心・嘔吐，脱毛，血液学的検査値を除く）が出現した場合は投与前の状態に戻るまで，またgrade 3/4でtemozolomideとの因果関係が否定できない有害事象（悪心・嘔吐，脱毛，血液学的検査値を除く）が出現した場

表 3 好中球数および血小板数ならびに有害事象の発現に基づく用量調節判定基準

		好中球数または血小板数		
		grade 1	grade 2	grade 3
		好中球数の最低値 ≧1,500/mm³ 血小板数の最低値 ≧100,000/mm³	好中球数の最低値 1,000～1,500/mm³ 血小板数の最低値 50,000～100,000/mm³	好中球数の最低値 <1,000/mm³ 血小板数の最低値 <50,000/mm³
好中球数と血小板数以外の有害事象	grade 0～2	1日 50 mg/m²増量あるいは用量変更なし	用量変更なし	1日 50 mg/m²減量
	grade 3, 4	1日 50 mg/m²減量あるいは用量変更なし（減量しない理由のコメントが必要）	1日 50 mg/m²減量あるいは用量変更なし（減量しない理由のコメントが必要）	1日 50 mg/m²減量あるいは投与中止

合は grade 2 以下に回復するまで次クールの投与を開始しないこととした。

II. 結 果

1. 患者背景

登録症例数は 32 例であった。年齢中央値は 52.5 歳（31～71 歳）で，18 例（56%）が男性，薬剤投与開始前の KPS の中央値は 90%であった。中央病理診断によって AA と診断された症例は 22 例（69%），AA 以外は 10 例（31%）で，その内訳は退形成性乏突起星細胞腫（anaplastic oligoastrocytoma: AOA）6 例，乏突起星細胞腫（oligoastrocytoma: OA）1 例，GBM 1 例，GBM 疑い 1 例，rosetted glioneuronal tumor 1 例であった（表 4）。

2. 有効性

効果安全性評価委員会によって判定された第 6 クール終了時点までの腫瘍縮小効果は著効 3 例，有効 8 例，不変 18 例，進行 2 例，判定不能 1 例で，奏効率（著効＋有効）34%（95%信頼区間 18.6～53.2%）であった。中央病理診断によって AA と確認された症例に限ってみると著効 2 例，有効 5 例，不変 12 例，進行 2 例，判定不能 1 例で，奏効率は 32%（95%信頼区間 13.9～54.9%）であった。判定不能症例とは神経症状の悪化により状態が悪く効果判定のための MRI が施行できなかった 1 例である。

ステロイド剤の使用状況と神経学的改善度を加味した総合的腫瘍縮小効果（表 2）では，著効 1 例，有効 9 例，不変 19 例，進行 2 例，判定不能 1 例で，奏効率は 31%（95%信頼区間 16.1～50.0%）であった。中央病理診断で AA と確認された 22 症例においては，総合的腫瘍縮小効果における著効はなく，有効 6 例，不変 13 例，進行 2 例，判定不能 1 例で，奏効率は 27%（95%信頼区間 10.7%～50.2%）であった。腫瘍縮小効果あるいは総合的腫瘍縮小効果が不変以上であった症例はいずれも 29 例（91%，95%信頼区間 75.0～98.0%）で，中央病理診断によって AA と確認された 22 例においては，腫瘍縮小効果あるいは総合的腫瘍縮小効果が不変以上であった症例はいずれも 19 例（86%，95%信頼区間 65.1～97.1%）であった。

中央病理診断において AA 以外と判定された症例においては，AOA 6 例の奏効率 33%（有効 2 例），OA 1 例は不変，GBM 1 例は有効，GBM の疑い 1 例が著効，rosetted glioneuronal tumor 1 例は不変であった。

32 症例の PFS の Kaplan-Meier 曲線を図 1 に示した。PFS の中央値は 4.1 か月，6 か月無増悪生存率は 40.6%（95%信頼区間 23.6%～57.6%）であった。これも中央病理診断において AA と確認された 22 例に限ってみると，PFS 中央値 3.9 か月，6 か月無増悪生存率は 31.8%（95%信頼区間 12.4～51.3%）であった。6 か月間に死亡した症例は原疾患の悪化による 1 例のみであった。

3. 安全性

32 症例のうち 25 例で第 2 クール以降のいずれかの時点で 200 mg/m²/日に増量し，第 6 クール終了または治験中止時まで減量しなかった。1 例では第 2 クールから 200 mg/m²/日に増量したが，第 4 クールからは 150 mg/m²/日に減量した。100 mg/m²/日に減量した症例はなかった。第 5 クール終了までに試験中止となった症例は 9 例で，原疾患の悪化 6 例，敗血症 1 例，脳室内出血 1 例，転居による転院 1 例であった。

32 症例すべてにおいて何らかの有害事象を認めたが，56%の症例では軽度または中等度であった（表 5）。生命を脅かすか活動不能に至る重症度（grade 4）の有害事象は 3 例（9%）に発現したが，その内容は汎血球減少症に伴う敗血症から播種性血管内凝固症候群，呼吸不全ならびに急性腎不全に至った症例 1 例，脳室内出血 1 例，低血糖と低カリウム血症 1 例であった。発現頻度が 20%以

表 4 主要な被験者背景

年齢（歳），n=32	平均値±標準偏差	51.5±13.3
	中央値	52.5
	最小値～最大値	31～71
年齢区分，n=32	40歳未満	9（28%）
	40歳以上50歳未満	5（16%）
	50歳以上65歳未満	11（34%）
	65歳以上	7（22%）
性別，n=32	男性	18（56%）
	女性	14（44%）
体重（kg），n=32	平均値±標準偏差	56.23±9.83
	中央値	57.05
	最小値～最大値	35.6～79.8
中央病理判定結果，n=32	退形成性星細胞腫	22（69%）
	退形成性乏突起星細胞腫	6（19%）
	乏突起星細胞腫	1（3%）
	膠芽腫	1（3%）
	膠芽腫疑い	1（3%）
	rosetted glioneuronal tumor	1（3%）
前治療での nitrosourea 系薬剤の使用，n=32	なし	0
	あり	32（100%）
ステロイド使用，n=32	なし	21（66%）
	あり	11（34%）
直近のステロイド使用量*（mg/日），n=11	平均値±標準偏差	19.63±11.76
	中央値	16.7
	最小値～最大値	4.2～50
直近のステロイド使用量*区分，n=11	10 mg/日未満	1（9%）
	10 mg/日以上20 mg/日未満	5（45%）
	20 mg/日以上	5（45%）
治験薬投与開始前の KPS n=32	平均値±標準偏差	87.5±11.1
	中央値	90
	最小値～最大値	70～100
治験薬投与開始前の KPS 区分，n=32	70	6（19%）
	80	6（19%）
	90	10（31%）
	100	10（31%）
初発時の手術内容，n=32	全摘出	8（25%）
	部分摘出	15（47%）
	生検	9（28%）
放射線療法の種類，n=32	標準線量	32（100%）
	過分割照射	0
	加速分割照射	0
初回診断から初回再発までの期間（か月），n=32	平均値±標準偏差	27.36±30.60
	中央値	17
	最小値～最大値	3.1～128.1
初回診断から初回再発までの期間区分（か月），n=32	3か月未満	0
	3か月以上6か月未満	8（25%）
	6か月以上9か月未満	1（3%）
	9か月以上12か月未満	3（9%）
	12か月以上	20（63%）
初回再発時の手術施行の有無，n=32	なし	27（84%）
	全摘出	0
	部分摘出	4（13%）
	生検	1（3%）

*: prednisolone 換算値（外用剤を除く）

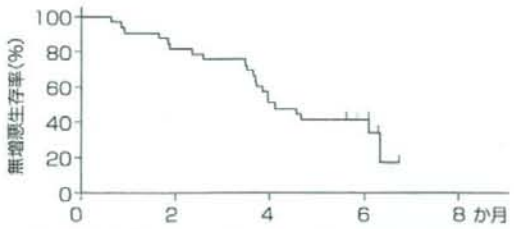

図 1 全登録症例 32 例における無増悪生存期間の Kaplan-Meier 曲線
横軸は治療開始からの期間

表 5 発現頻度が 10%以上の有害事象

	軽度	中等度	重度	生命*1	合計
有害事象発現症例数*2	1 (3%)	18 (56%)	10 (31%)	3 (9%)	32 (100%)
臨床検査*3	4 (13%)	13 (41%)	9 (28%)	2 (6%)	28 (88%)
リンパ球数減少*4	0	8 (25%)	8 (25%)	0	16 (50%)
好中球数減少	5 (16%)	8 (25%)	1 (3%)	1 (3%)*5	15 (47%)
白血球数減少	2 (6%)	9 (28%)	0	1 (3%)*5	12 (38%)
血小板数減少	5 (16%)	2 (6%)	3 (9%)*5	0	10 (31%)
GPT 増加	4 (13%)	3 (9%)	1 (3%)	0	8 (25%)
GOT 増加	4 (13%)	0	1 (3%)	0	5 (16%)
ヘモグロビン減少	2 (6%)	3 (9%)	0	0	5 (16%)
血中ブドウ糖増加	1 (3%)	2 (6%)	1 (3%)	0	4 (13%)
胃腸障害*3	10 (31%)	16 (50%)	1 (3%)	0	27 (84%)
便秘	2 (6%)	13 (41%)	1 (3%)	0	16 (50%)
悪心	6 (19%)	2 (6%)	0	0	8 (25%)
上腹部痛	2 (6%)	2 (6%)	0	0	4 (13%)
下痢	4 (13%)	0	0	0	4 (13%)
嘔吐	3 (9%)	1 (3%)	0	0	4 (13%)
感染症および寄生虫症*3	6 (19%)	9 (28%)	2 (6%)	1 (3%)	18 (56%)
鼻咽頭炎	5 (16%)	6 (19%)	0	0	11 (34%)
神経系障害*3	4 (13%)	8 (25%)	2 (6%)	1 (3%)	15 (47%)
痙攣	0	6 (19%)	0	0	6 (19%)
頭痛	5 (16%)	1 (3%)	0	0	6 (19%)
全身障害および投与局所様態*3	11 (34%)	0	2 (6%)	0	13 (41%)
倦怠感	5 (16%)	0	0	0	5 (16%)
疲労	4 (13%)	0	0	0	4 (13%)
代謝および栄養障害*3	8 (25%)	1 (3%)	0	0	9 (28%)
食欲不振	8 (25%)	1 (3%)	0	0	9 (28%)

*1: 生命を脅かすか，または活動不能に至る重症度
*2: 発現した有害事象の最高 grade による症例数
*3: 各分類の有害事象発現数は，複数の事象を発現した症例があるために示された個別の有害事象数の計とは一致しない
*4: 日和見感染によるものではない
*5: 好中球数減少 1 件，白血球数減少 1 件，血小板数減少 1 件は同一の症例で認められ，これらの異常を含めた播種性血管内凝固症候群および汎血球減少症の有害事象名で報告されたが，ここでは個々の臨床検査値異常を有害事象として記載した

上であった有害事象は便秘（16 例: 50%），鼻咽頭炎（11 例: 34%），食欲不振（9 例: 28%），悪心（8 例: 25%），リンパ球数減少（16 例: 50%），好中球数減少（15 例: 47%），白血球数減少（12 例: 38%），血小板数減少（10 例: 31%），アラニンアミノトランスフェラーゼ（GPT）増加（8 例: 25%）であった。血液学的検査において grade 3/4 の有害事象の頻度は，好中球数減少 2 例（6%），血小板数減少 3 例（9%），リンパ球数減少 8 例（25%），白血球数減少 1 例（3%）であった（表 5）。死亡に至った有害事象は発現しなかった。

III. 考 察

米国においてtemozolomideの有効性と安全性が最初に示された再発AA[11]を治療対象とし，本邦における有効性と安全性を確認することを目的として本試験を行った。再発AAにおいて報告されているPFS中央値は3～5か月であるので[11-13]，本試験においては6か月時点での総合的腫瘍縮小効果と安全性の評価を主要評価項目としPFSは副次評価項目として解析を行った。

米国の第II相試験は再発AAおよび再発AOAを対象とし，本試験とほぼ同じデザインで1995年から実施された。腫瘍縮小効果による奏効率は35%，CR症例は8%と報告されているが，これは本試験における奏効率34%，CR症例9%とほぼ同等である。また，PFS中央値と6か月無増悪生存率も米国第II相試験ではそれぞれ5.4か月（46%），本試験では4.1か月（40.6%）で，これもほぼ同等の成績であった[11]。

本試験では再発AAとして32症例が登録されたが，中央病理診断によってAAと確認された症例は22例であった。AA以外と診断された10例のうち6例はAOAであった。米国のデータは再発AAと再発AOAを対象としたものであるから，結果として米国の試験とほぼ同様の腫瘍型を対象とした試験となり，結果も同等であった。中央病理診断によってAAと確認された22例における腫瘍縮小効果と総合的腫瘍縮小効果ならびに無増悪生存期間は，全登録症例32例における結果と比べていずれもわずかに劣っていた。しかしこれは，全登録症例に含まれていたAOA 6例の腫瘍縮小効果が優れていたからではなく，GBMの1例とGBM疑いの1例がそれぞれ有効と著効を示したことによる差と解釈された。したがって，中央病理診断によって確認されたAAの22症例と全登録症例32例における結果の差は，temozolomideの有効性において意味のあるものとは判断されなかった。

本試験において発現した有害事象も，すでに報告されているものであった。自他覚症状においては便秘(50%)および悪心（25%）の発現頻度が高かったが，標準的な緩下剤あるいは制吐剤でコントロール可能であった。また，発現頻度が高かった臨床検査値異常の主たる項目は骨髄抑制に関係するものであったが，骨髄抑制は蓄積性ではなく，投与の延期や投与量の減量を要した症例は17例（53%）であったが，投与量を調節することによって投与継続が可能であった。また遅発性の有害事象は認められなかった。

本試験によって，初回再発の退形成性星細胞腫におけるtemozolomideの有効性および忍容性が日本人においても確認され，temozolomideは再発退形成性星細胞腫に対する有効な薬剤となり得ることが示された。本邦においても他の神経膠腫を対象とした臨床試験が積極的に行われ，あるいは海外の臨床試験成績が外挿されていくことが期待される。

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悪性神経膠腫の治療戦略 2006

西川　亮

Treatment Strategies for Malignant Gliomas—2006

by

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In the treatment of glioblastoma (GBM), postoperative radiotherapy has been recognized as standard therapy, whereas the addition of chemotherapy has been a controversial issue. A meta-analysis based on 12 randomized trials suggested only a small benefit. The recent trial by the European Organisation for Research and Therapy of Cancer (EORTC) and National Cancer Institute of Canada Clinical Trial Group was the first study to demonstrate unequivocally that the addition of temozolomide to radiotherapy provides a statistically significant survival benefit in GBM. For anaplastic oligodendroglioma and oligoastrocytoma, two separate trials by EORTC and the Radiation Therapy Oncology Group clearly demonstrated that chemotherapy by procarbazine, lomustine, and vincristine, plus radiotherapy does not prolong survival but does increase the incidence of progression-free survival. The combined loss of 1p/19q identifies a favorable subgroup of oligodendroglial tumors, and no genetic subgroup could be identified that benefited with respect to survival from adjuvant PCV. In low-grade gliomas, older age, astrocytoma histology, presence of neurologic deficits, largest tumor diameter, and tumor crossing the midline were important prognostic factors for survival, and these factors can be used to identify low-risk and high-risk patients. Taken together, these evidences reported recently provide the most up-to-date treatment strategies for malignant gliomas.

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Key words : glioma, temozolomide, radiotherapy, chemotherapy, clinical study

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転換期を迎えた膠芽腫・退形成性星細胞腫の化学療法

膠芽腫・退形成性星細胞腫に対する化学療法は，1970年代に米国で行われた大規模臨床試験から始まるといって過言ではない．まず，手術後に放射線照射も化学療法も行わない群を対照としたランダム化比較試験が行われ，放射線照射あるいは化学療法単独治療による，統計学的に有意の生存期間延長効果が証明された[15]．そしてさらに放射線照射に化学療法（BCNUあるいはMeCCNU）を併用する方法が検証されたが，放射線照射単独群との間には統計学的に有意の生存期間延長効果は認められなかった[15)16)]．有意の生存期間延長効果は認められなかったわけであるが，実際の生存曲線をみると放射線照射にBCNUを併用した群の生存期間が最も優れていたことから，膠芽腫・退形成性星細胞腫においては，放射線照射にBCNUを併用する方法が手術後の治療として推奨されることになった．わが国においても，術後

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