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ORIGINAL ARTICLE

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A first feasibility study of temozolomide for Japanese patients with recurrent anaplastic astrocytoma and glioblastoma multiforme

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Abstract
Background. The efficacy of temozolomide has been evaluated in phase I and phase II trials in patients with recurrent malignant gliomas in the United States and the European Union. We report a feasibility study of the palliative efficacy of temozolomide for patients with recurrent anaplastic astrocytoma (AA) and glioblastoma multiforme (GBM).
Methods. Sixteen patients with at least two prior chemotherapy regimens were enrolled in the study. Nine patients were confirmed to have GBM and 7 patients were confirmed to have AA at the latest pathology review, and all had a Karnofsky performance status (KPS) of over 50%. The median age was 57 years (range, 31–65 years).
Results. No cumulative toxicity was observed at any dose level when temozolomide was administered on a once-daily, 5-day schedule. Myelosuppression occurred, with the nadir being mid-late in the cycle (day 14 or 21). National Cancer Institute common toxicity criteria (NCI-CTC) grade 3 or 4 hematological toxicity did not occur. In the 9 GBM patients, the overall response rate (complete response + partial response [CR + PR]) was 0%. The median time to progression (TTP) was 3.5 months, and the rates of progression-free survival (PFS) at 6 and 12 months were 40% and 0%. In the 7 AA patients, the overall response rate (CR + PR) was 29% and median TTP was 9 months, while PFS rates at 6 and 12 months were 80% and 30%.
Conclusion. The favorable safety profile and the efficacy of temozolomide in Japanese patients are not incompatible with the results seen with patients in the United States and the European Union.

Key words Temozolomide · Glioma · Japanese patients · Feasibility study

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Introduction

The treatment of recurrent high-grade gliomas is resistant to most therapeutic endeavors. There are no clearly established chemotherapeutic regimens.[1] Temozolomide (TMZ; Temodar; Schering-Plough, Kenilworth, NJ, USA) is a well-tolerated, orally bioavailable alkylator with activity in glioma patients.[2] It was approved for use in patients with recurrent anaplastic astrocytoma (AA) in the United States in 1999, and was approved for recurrent AA and glioblastoma multiforme (GBM) in the European Union in 2000. TMZ undergoes chemical degradation to its active metabolites, monomethyl triazenoimidazole carboxamide, at physiologic pH. The cytotoxicity of monomethyl triazenoimidazole carboxamide is primarily due to alkylation at the O^6 position of guanine.[3]

The efficacy of temozolomide has been evaluated in phase I and phase II trials in patients with recurrent malignant glioma in the United States and the European Union.[2,4] We report a feasibility study of the palliative efficacy of temozolomide in Japanese patients with recurrent AA and GBM.

Patients and methods

Eligibility

All patients enrolled in this study were adults (aged 18–70 years) with a life expectancy of at least 12 weeks, who had histologically confirmed AA and GBM, based on the most recent histology prior to enrollment, and evidence of tumor

progression shown by magnetic resonance imaging (MRI). The patients must have had at least two previous chemotherapy regimens, but they must have recovered from the toxic effects of the prior therapy, with evidence of adequate bone marrow, liver, and renal functions. Patients were excluded if they had a Karnofsky performance status of less than 50%, any other active malignancy, an active infection, any serious disease, or were pregnant. All patients were required to sign an institutional review board-approved informed consent form.

Dose escalation

To investigate the nature and incidence of dose-limiting toxicity (DLT) and the maximum tolerated dose (MTD), we administered temozolomide capsules (Schering-Plough Research Institute, Kenilworth, NJ, USA) orally to cohorts of three patients at an initial dosage of 100 mg/m^2 per day for 5 days, followed by sequential escalation to 150, 200, or 250 mg/m^2 per day, if a DLT was not observed. Intrasubject dose escalation was allowed. All patients received an antiemetic drug (ondansetron).

The DLT was defined according to the NCI-CTC as grade 4 neutropenia (absolute neutrophil count, $<0.5 \times 10^9 l^{-1}$); grade 4 anemia (hemoglobin, $<6.5\,g\,dl^{-1}$); or grade 3 thrombocytopenia (platelet count, $<50 \times 10^9 l^{-1}$); serum creatinine, more than $2.0\,mg\,dl^{-1}$; or another grade 3 or 4 adverse event (with the exception of controllable nausea or vomiting). All patients continued treatment with temozolomide until a DLT occurred or the disease progressed.

Response evaluation

Objective tumor assessment was performed by Gd-enhanced MRI, and disease response was defined according to Response Evaluation Criteria in Solid Tumors (RECIST) criteria.[5] The best response for each patient was derived from the objective tumor response at each cycle. A complete response (CR) was defined as the disappearance of contrast-enhanced tumor, on examinations done not less than 4 weeks apart. A partial response (PR) was defined as more than a 70% decrease in the maximum diameter of an enhanced lesion, an examinations done not less than 4 weeks apart. Stable disease was defined less than as a 70% decrease or less than a 20% increase in the maximum diameter of an enhanced lesion. Progressive disease (PD) was defined as more than a 20% increase in the maximum diameter of a lesion, or the appearance of a new lesion.

Results

Patients' characteristics

From July 17, 2001, to August 10, 2002, 16 patients were enrolled in the trial. The characteristics of patients with GBM and AA at the latest pathology review who were eligible for the temozolomide trial are given in Table 1. The median age was 57 years (range, 31–65 years). All patients had a KPS of over 50%. All patients had received conventional radiation and two or more adjuvant chemotherapy regimens. All patients had single lesions that were measurable. Tumor size (maximum diameter of enhanced lesion) ranged from 2 to 6 cm. Four patients underwent surgery at the time of relapse.

Table 1. Patients' characteristics

	No. of patients
Total no. of patients	16
Age (years)	
<40	5
40–60	9
>60	2
Sex	
Male	11
Female	5
KPS	
100%, 90%	0
80%, 70%	4
60%, 50%	12
No. of prior chemotherapy regimens	
0	0
1	8
2	8
Histology at latest diagnosis	
Glioblastoma multiforme	9
Anaplastic astrocytoma	7

KPS, Karnovsky performance status

Table 2. Hematological toxicity

Dose level (mg/m^2)	100	150	200	250
Number of cycles	3	16	13	2
NCI-CTC grade				
0	2	12	8	2
1	1	1	3	0
2	0	3	2	0
3	0	0	0	0
4	0	0	0	0

NCI-CTC, National Cancer Institute common toxicity criteria

Toxicity

A total of 84 cycles were given to the 16 patients, and the mean number of cycles per patient was 5.3 (range, 1–18 cycles). No cumulative toxicity was observed at any dose level when temozolomide was administered on a once-daily, 5-day schedule. Myelosuppression occurred, with the nadir being mid-late in the cycle (day 14 or 21), and recovered smoothly. CTC grade 3 or 4 hematological toxicity did not occur (Table 2). The most common nonhematological toxicities were nausea and vomiting (CTC grade 1–2; 22% and 5%, respectively). These rates, however, represent rates of emesis occurring with ondansetron treatment. Gastrointestinal disturbance was generally transient, lasting an average

of 1-2 days. In all patients, the toxicity was manageable without the necessity for dose reduction or delays.

Therapeutic efficacy

The median follow-up period was 12 months (range 6–18 months). In the nine GBM patients (Table 3), we observed no CR (0%), no PR (0%), six SD (67%), and three PD (33%); the overall response rate (CR + PR) was 0%. In the seven AA patients (Table 3), there was one CR (14%; Fig. 1), one PR (14%; Fig. 2), five SD (71%), and none with PD (0%): the overall response rate (CR + PR) was 29%.

In GBM patients (Fig. 3), the median time to progression (TTP) was 3.5 months, and the rates of progression-free survival (PFS) at 6 and 12 months were 40% and 0%, respectively. In the AA patients (Fig. 4), the median TTP was 9 months, and rates of PFS at 6 and 12 months were 80% and 30%, respectively.

Discussion

Temozolomide is a well-tolerated, orally bioavailable alkylator with activity in glioma patients.[6] It has already been approved for use in patients with recurrent AA in the United States, and the European Union. Approval in Japan is warranted.

Table 3. Response rates

	Anaplastic astrocytoma; *n* (%)	Glioblastoma; *n* (%)
Complete response (CR)	1	0
Partial response (PR)	1	0
Stable disease (SD)	5	6
Progressive disease (PD)	0	3
Overall response (CR + PR)	2 (29)	0 (0)

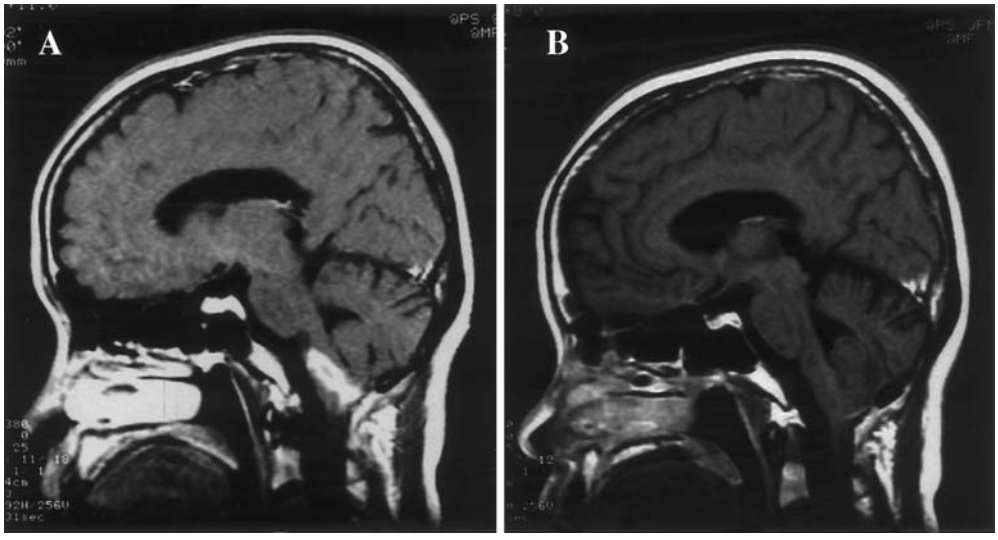

Fig. 1A,B. Recurrent anaplastic astrocytoma in the medulla lesion, before (**A**) and after (**B**) three cycles of temozolomide. Gadolinium-enhanced magnetic resonance imaging reveals a complete response

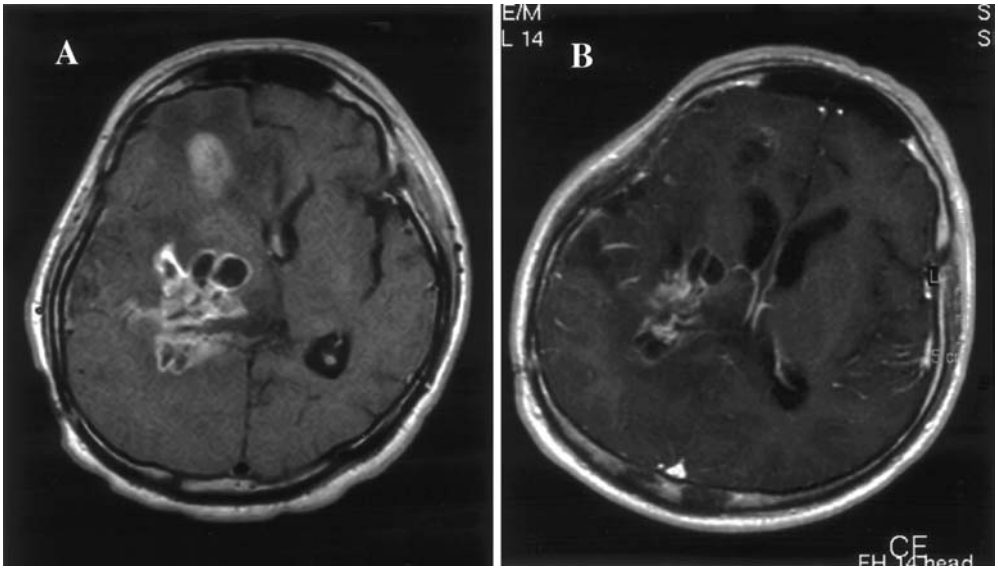

Fig. 2A,B. Recurrent anaplastic astrocytoma in right thalamic lesion, before (**A**) and after (**B**) one cycle of temozolomide. Gadolinium-enhanced magnetic resonance imaging reveals a partial response

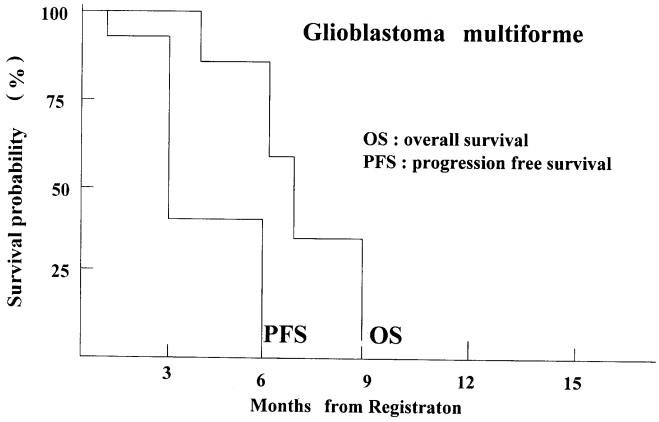

Fig. 3. Kaplan-Meier curve of progression-free and overall survival for patients with recurrent glioblastoma multiforme ($n = 9$)

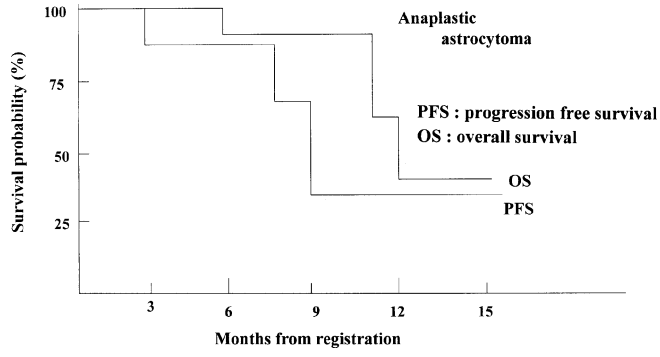

Fig. 4. Kaplan-Meier curve of progression-free and overall survival for patients with recurrent anaplastic astrocytoma ($n = 7$)

The MTD for patients with prior exposure to nitrosourea was 150 mg/m^2, and the MTD for patients without prior exposure was 250 mg/m^2.[10] All patients in our study had been pretreated with at least two chemotherapy regimens after receiving conventional radiation (Table 1). One patient with a CR with the MTD at 150 mg/m^2 was not treated at the next-higher dosage. All but 1 of the 16 patients were treated at doses of 200 mg/m^2 without CTC grade 3 or 4 toxicities. Temozolomide has a favorable toxicity profile and is well tolerated. By contrast, nitrosoureas cause delayed and prolonged myelosuppression, which is cumulative.

The most common nonhematological toxicities associated with temozolomide were gastrointestinal toxicity, with a rapid onset and short duration. In all subjects, it was mild to moderate and clinically manageable with standard antiemetics. This profile is comsistent with toxicities observed in other phase I clinical trials.[2,6,7]

In patients with AA, the objective response rate according to MRI data was 29%, and 71% had SD. In patients with GBM, the objective response rate was 0%, and 67% had SD. Although recurrent AA was associated with higher response rates, response rates in patients with recurrent GBM were low and the response was of short duration, with most patients achieving temporary disease stabilization. Similar results were reported in previous studies.[4,8,9]

In conclusion, the favorable safety profile and the efficacy of temozolomide in Japanese patients is not incompatible with the results seen in patients in the United States and the European Union. After approval is gained in Japan, the next aim should be to develop an effective regimen that could be tested in an adjuvant setting.

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