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Original Article

The Impact of Extent of Resection and Histological Subtype on the Outcome of Adult Patients with High-grade Gliomas

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Objective: We reviewed the relationship between extent of resection and survival of patients with high-grade gliomas with special consideration of an oligodendroglial component.
Methods: A retrospective review was performed on 160 adult patients with histological diagnosis of high-grade gliomas since 2000. All histological slides were categorized as high-grade astrocytomas or oligodendroglial tumors. Extent of resection was assessed by early post-operative magnetic resonance imaging and classified as complete resection, incomplete resection and biopsy. Measured outcomes were overall survival and progression-free survival. The independent association of extent of resection and survival was analyzed by the multivariate proportional hazard model adjusting for prognostic factors.
Results: The lesions were classified as high-grade astrocytomas in 93 patients and high-grade oligodendroglial tumors in 67 patients. In high-grade astrocytomas, the median survival after complete resection ($n = 36$), incomplete resection ($n = 36$) and biopsy ($n = 21$) was 23.4, 15.3 and 12.6 months, respectively. Complete resection was independently associated with increased overall survival ($P < 0.001$) and progression-free survival ($P = 0.002$) compared with incomplete resection, while incomplete resection was not associated with survival benefit compared with biopsy by multivariate analysis. On the other hand, in high-grade oligodendroglial tumors, the majority of patients were still alive and there is no significant difference in the survival between complete resection ($n = 24$) and incomplete resection ($n = 33$), while even incomplete resection had a significantly longer overall survival ($P < 0.001$) and progression-free survival ($P = 0.006$) compared with biopsy ($n = 10$).
Conclusions: Maximal cytoreduction improves the survival of high-grade gliomas, although our data indicated that the impact of extent of resection in high-grade astrocytomas is different from that in high-grade oligodendroglial tumors.

Key words: astrocytoma malignant glioma multivariate analyses oligodendroglioma survival

INTRODUCTION

In recent years, surgery has drawn the most attention as a treatment of high-grade gliomas because surgical adjunctive methods including fluorescence visualization of the tumor by 5-aminolevulinic acid (1,2), navigation-guided fence-post-procedure (3), intraoperative neurophysiological monitoring (4) and intraoperative magnetic resonance (MR) imaging (5,6) have enabled extensive resection of high-grade gliomas. Extensive resection is associated with prolonged survival in high-grade astrocytomas, especially glioblastoma multiforme (GBM) (2,7 15). Stummer et al. (1,2) clearly demonstrated in retrospective analysis of randomized

prospective trials that complete resection of the enhancing tumor evaluated by early post-operative MR imaging is an independent and overwhelming prognostic factor in patients with newly diagnosed GBMs. Several retrospective volumetric analyses of the extent of resection (EOR) also indicated that the EOR improves survival in patients with GBMs (7,9,12) and anaplastic astrocytomas (AAs) (16). By evaluation of early post-operative MR imaging, the role of the EOR has gradually become evident in high-grade astrocytomas.

On the other hand, studies focused on the association between the EOR and prognosis of high-grade oligodendroglial tumors [anaplastic oligodendrogliomas (AOs) and anaplastic oligoastrocytomas (AOAs)] are limited to a few series (17–20), and the optimal role of surgery for oligodendroglial tumors remains a major controversy. Basically, in both World Health Organization (WHO) Grade II and III gliomas, several studies demonstrated that the presence of an oligodendroglial component (OC) constitute a favorable prognostic factor (21–29). It is apparent that the prognosis of high-grade oligodendroglial tumors is highly influenced by adjuvant therapies, because oligodendroglial tumors are generally chemosensitive and radiosensitive (30–33). In addition, in WHO Grade IV gliomas, some studies found that GBM with an OC tends to have better prognosis than ordinary GBM (12,34–37). Several studies have suggested that the incidence of chromosome 1p and 19q deletions, which have recently been demonstrated to be genetic markers predictive of good chemosensitivity and a better outcome in oligodendroglial tumors (32,33,38), is clearly higher in GBMs with OC than ordinary GBMs (34,36). We assume that GBM with OC belongs to the subgroup of oligodendroglial tumors by these biological characteristics.

In this study, we retrospectively reviewed the relationship between the EOR and survival of adult patients with high-grade glioma treated in our institutions with special consideration of the presence of the OC. The EOR was carefully assessed by early post-operative MR imaging. The aim of our study was to evaluate the hypothesis that the role of surgery for high-grade gliomas with OC is different from that for high-grade astrocytomas.

PATIENTS AND METHODS

Eligibility and Treatment

A retrospective review was performed at the Hokkaido University Hospital and our affiliated hospitals on patients aged over 20 years with a histological diagnosis of a high-grade glioma (WHO Grade III and IV) between January 2000 and February 2011. Eligible cases for this analysis included all patients who underwent initial biopsy or resection at our hospitals of a histologically confirmed GBM, AA, AOA and AO. In addition, all histological slides were re-evaluated by two neuropathologists (H.K. and H.N.) blinded to clinical background and outcome of patients and classified according to the 2007 WHO classification. GBMs with OC are defined based on histological specimens that identify tumor parts with features of oligodendroglial differentiation within typical histological findings of GBM. Pathological diagnosis did not refer to genetic information.

In this study, eligible cases included all patients who were treated with conventional external limited field irradiation (2 Gy/day, five days/week, total dose 54–60 Gy) in Hokkaido University Hospital within 6 weeks after surgery. Patients who had received previous radiotherapy for a low-grade glioma were excluded in this study. Patients lost to follow-up, defined as followed less than 6 months after diagnosis, with no progression or death during that interval, were also excluded. Patients with brain stem glioma and gliomatosis cerebri (defined as a diffuse glioma involving more than three cerebral lobes and without obvious tumor mass) were not included. Most patients received adjuvant chemotherapy. The standard chemotherapy regimen changed in 2006; the predominant regimen was nitrosourea (ACNU)-based or platinum [cisplatin (CDDP)]-based before 2006, and temozolomide (TMZ) chemotherapy thereafter.

EOR and Outcome Assessment

In tumor-debulking surgery, all patients underwent maximum possible resection of the tumor without developing new neurological deficits. The post-operative MR studies were obtained shortly after surgery in all patients (almost all cases were obtained within 24 h post-operatively). Pre- and post-operative T1-weighted MR imaging with contrast enhancement was used to determine the extent of tumor resection. Our patients were usually conducted conventional MR imaging with 5 mm slice thickness of the whole neuraxis, and the extent of tumor resection was estimated by these sequences. 'Complete resection' was defined as no evidence of residual pre-operative contrast enhancement as seen from axial, coronal and sagittal images (Fig. 1A), and 'incomplete resection' was defined as rim or nodule enhancement of the resection cavity (Fig. 1B and C). 'Biopsy' was defined as resection of a small part of the lesion for diagnostic purposes only (including stereotactic needle biopsy). For a small number of non-enhancing tumors, the range of tumor was defined as the area of increased signal intensity on FLAIR images (similar to the assessment of low-grade gliomas).

The following covariates were considered: age at diagnosis, pre-operative Karnofsky Performance Scale (KPS) score, preoperative maximum tumor diameter, tumor location (including whether the lesion had infiltrated eloquent brain areas), histological malignancy according to the WHO criteria and adjuvant post-operative TMZ therapy. The presumed eloquent brain areas consisted of motor strip (precentral gyrus), dominant hemisphere perisylvian language area, basal ganglia/internal capsule, thalamus and calcaline visual cortex (39).

The endpoints of this study were progression-free survival (PFS) and overall survival (OS), which were measured from

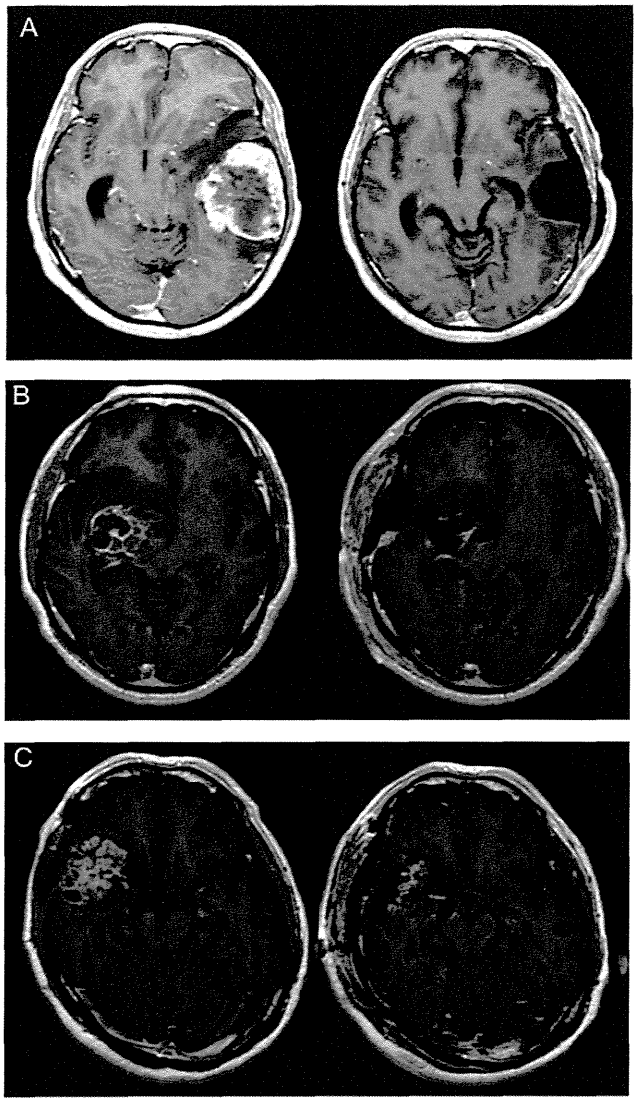

Figure 1. Pre- (left) and post-operative (right) axial T1-weighted magnetic resonance imaging with contrast enhancement in patients who underwent resection of high-grade gliomas. (A) 'Complete resection' without any residual pre-operative contrast enhancement lesion. (B and C) 'Incomplete resection' with residual small enhancement lesion around the resection cavity (B) or residual nodular contrast enhancement (C).

the time of initial surgical intervention that confirmed the diagnosis of high-grade glioma. All patients were followed in our institutions until death or last visit. Progression was defined as the development of radiographically evident progressive disease.

Statistical Analysis

Parametric data were expressed as mean ± standard deviations. In this study, two separate groups were established, 'high-grade astrocytomas', which included ordinary GBMs and AAs, and 'high-grade oligodendroglial tumors', which included GBM with OC, AOA and AO. A comparison of patient characteristics between high-grade astrocytomas and high-grade oligodendroglial tumors was performed by the Student *t*-test for continuous and ordered variables, and the χ^2 test for nominal variables. Age and maximum tumor diameter were analyzed as continuous variables, and pre-operative KPS score was analyzed as an ordinary variable.

Time to death or progression parameters were analyzed with the Kaplan Meyer method, and comparing them by log-rank tests. The Cox proportional hazards model was used to identify the univariate and multivariate predictors of survival and progression. Two separate Cox's analyses were performed with OS and PFS for the histological subgroups (high-grade astrocytomas and high-grade oligodendroglial tumors). Variables associated with OS in univariate analysis were included in the multivariate Cox model if $P \leq 0.20$. For all analyses, a P value <0.05 was accepted as significant. The statistical calculations were performed in StatView software version 5.0 (SAS Institute, Cary, NC, USA).

RESULTS

Patient Characteristics

The clinical characteristics of the 160 patients who met our inclusion criteria are summarized in Table 1. There were 87 males and 73 females with a mean age ± standard deviation of 55 ± 14 years (median: 57 years, range: 22 79). The histological diagnoses, which were re-evaluated by neuropathologists, were GBM in 73 patients (46%), AA in 20 patients (13%), GBM with OC in 14 patients (9%), AOA in 32 patients (20%) and AO in 21 patients (14%). Fourteen tumors (9%) had no contrast enhancement on MR imaging. Of these 14 cases, three patients were AA, seven were AOA, three were AO and one was GBM with OC. Complete resection, incomplete resection and biopsy were achieved in 60 cases (38%), 69 cases (43%) and 31 cases (19%), respectively. Seventy-two patients (45%) were given post-operative TMZ chemotherapy according to the Stupp regimen (40). Sixty-five patients (41%) received ACNU-based chemotherapy (ACNU by intravenous injection alone or combined with procarbazine and vincristine), and seven patients (four AO and three GBM patients) (4%) received CDDP-based chemotherapy (combined with ifosfamide and VP-16). The remaining 16 patients (10%) were not given any adjuvant chemotherapy.

As shown in Table 1, the patients with high-grade oligodendroglial tumors were statistically younger at diagnosis ($P < 0.001$) and had a better preoperative KPS score ($P = 0.03$) compared with patients with high-grade astrocytomas. In regards to the WHO criteria, high-grade astrocytomas were more advanced than high-grade oligodendroglial tumors ($P < 0.001$) because of the relatively small number of GBM with OC. No differences in gender, laterality of the tumor location, tumor maximum diameter, tumor involving eloquent area and post-operative adjuvant TMZ therapy were observed between high-grade astrocytomas and oligodendroglial tumors. Importantly, there were no statistically

Table 1. Descriptive statistics of study sample by histological subtypes

	All ($n = 160$)	Astrocytomas ($n = 93$)	Oligodendroglial tumors ($n = 67$)	P value[a]
Age (mean ± SD, years)	55 ± 14	59 ± 12	49 ± 14	<0.001
Sex				
Male	87	46	41	0.10
Female	73	47	26	
Side of tumor				
Right	91	51	40	0.33
Left	69	42	27	
Pre-operative KPS (mean ± SD, %)	79 ± 16	77 ± 17	83 ± 15	0.03
Tumor diameter (mean ± SD, cm)	4.6 ± 1.6	4.4 ± 1.5	4.7 ± 1.7	0.54
Eloquent area[b]				
Yes	72	47	25	0.07
No	88	46	42	
WHO grading				
Grade III	73	20	53	<0.001
Grade IV	87	73	14	
Post-operative TMZ				
Yes	72	41	31	0.67
No	88	52	36	
Extent of resection				
Biopsy	31	21	10	0.32
Incomplete	69	36	33	
Complete	60	36	24	
No. of deaths (%)	88 (55)	69 (74)	19 (28)	
No. of recurrences (%)	115 (72)	81 (87)	34 (51)	
Median follow-up (months)	21.1	16.0	38.7	

SD, standard deviation; KPS, Karnofsky performance scale; TMZ, temozolomide.
[a]Comparison between high-grade astrocytomas and high-grade oligodendroglial tumors.
[b]Tumor involved eloquent brain area (precentral gyrus, dominant hemisphere perisylvian language area, basal ganglia/internal capsule, thalamus and calcaline visual cortex).

significant differences in the EOR (complete resection, incomplete resection and biopsy alone) between these two groups ($P = 0.32$).

The median follow-up was 21.1 months. Eighty-eight (55%) patients died during the nearly 11-year follow-up period, with a median follow-up period for the remaining patients of 29.6 months. The cause of death in all cases was attributed to glioma. Progressions were identified in 115 (72%) cases. A total of 29 of the 115 cases with progression underwent repeat surgery.

Table 2. Univariate analysis of clinical and tumor parameters with overall survival (OS) and progression-free survival (PFS) in 93 patients with high-grade astrocytomas

	Overall survival			Progression-free survival		
	Hazard ratio	95% CI	P value	Hazard ratio	95% CI	P value
Age[a]	1.009	0.99–1.03	0.43	1.013	0.99–1.03	0.18
Pre-operative KPS						
<80	1.177	0.72–1.93	0.52	1.260	0.80–1.99	0.32
≥80	1.0			1.0		
Tumor diameter						
>4 cm	0.936	0.58–1.52	0.79	0.820	0.52–1.28	0.39
≤4 cm	1.0			1.0		
Eloquent area						
No	0.585	0.36–0.95	0.03	0.761	0.49–1.20	0.23
Yes	1.0			1.0		
WHO grading						
Grade III	0.674	0.37–1.22	0.19	0.657	0.38–1.31	0.13
Grade IV	1.0			1.0		
Post-operative TMZ						
No	1.211	0.74–1.99	0.45	1.278	0.81–2.01	0.29
Yes	1.0			1.0		

CI, confidence interval.
[a]Increasing variable.

Analysis of High-grade Astrocytomas

Predictors

Ninety-three patients underwent resection or biopsy of high-grade astrocytomas (73 GBMs and 20 AAs). Univariate analysis using the Cox proportional hazards model of high-grade astrocytomas is presented in Table 2. 'Tumor involving eloquent area' was the only significant predictor of shorter survival time in the univariate analysis ($P = 0.03$). Age at diagnosis and preoperative KPS score did not correlate to survival and progression in the patients with high-grade astrocytomas; therefore, these factors were not included in the multivariate analysis of the EOR. In addition, there was no significant difference in either time to death or progression for AAs versus GBMs ($P = 0.19$).

EOR and prognosis

Unadjusted OS and PFS curves for patients with high-grade astrocytomas by EOR are illustrated in Fig. 2. The Kaplan–Meier plots of OS revealed that the median survival after complete resection, incomplete resection and biopsy was 23.4, 15.3 and 12.6 months, respectively. The median time to tumor progression after complete resection, incomplete resection and biopsy was 12.9, 7.4 and 6.5 months,

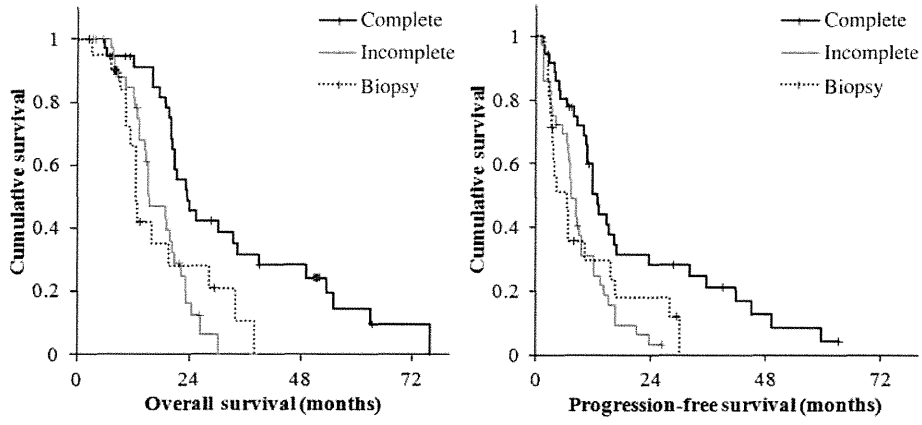

Figure 2. Overall (left) and progression-free (right) survival analysis for patients with high-grade astrocytomas demonstrated as the Kaplan Meier plots by the extent of surgical resection (complete resection, incomplete resection and biopsy alone).

Table 3. Multivariate analysis of extent of resection (EOR) affecting OS and PFS in 93 patients with high grade astrocytomas[a]

	Overall survival				Progression-free survival			
	Hazard ratio	95% CI		*P* value	Hazard ratio	95% CI		*P* value
Complete resection	0.356	0.19	0.66	<0.001	0.405	0.23	0.71	0.002
Incomplete resection	1.0				1.0			
Biopsy	1.085	0.53	2.24	0.82	1.158	0.63	2.14	0.64

[a]Adjusting for the effect of tumor location (involving eloquent area) and histological WHO grading.

respectively. Differences in both OS and PFS times based on the EOR were significant according to the log-rank test ($P < 0.01$).

The multivariate analysis using the Cox proportional hazard models of the EOR for OS and PFS is listed in Table 3. After adjusting for the effect of tumor location (involving eloquent area) and histological malignancy (WHO grading), complete resection was independently associated with increased OS and PFS compared with incomplete resection ($P < 0.001$ and 0.002, respectively). Incomplete tumor resection was not associated with a survival benefit compared with biopsy ($P - 0.82$).

Analysis of High-grade Oligodendroglial Tumors

Predictors

Sixty-seven patients were diagnosed as high-grade glioma with OC by a primary surgical specimen. The histological malignancy according to WHO grading was Grade III in 53 patients (32 AOAs and 21 AOs) and Grade IV (GBM with OC) in 14 patients.

As shown in Table 4, the significant predictors of shorter survival time in the univariate analysis included advanced age at onset ($P - 0.001$) and WHO Grade IV malignancy ($P - 0.02$). Older age and WHO Grade III malignancy were also associated with a worse rate of PFS ($P - 0.005$ and 0.04, respectively). There were a trend toward longer OS with larger tumor ($P - 0.08$) and lower preoperative KPS score ($P - 0.08$). Histological malignancy according to WHO grading was significantly correlated with survival in contrast to high-grade astrocytomas. Conversely, there was no significant difference in both OS and PFS for tumors that infiltrated the eloquent brain in high-grade oligodendroglial tumors.

EOR and prognosis

The Kaplan Meier plots of OS by the EOR are demonstrated in Fig. 3. The median survival had not been reached at the time of analysis in patients who underwent tumor-debulking surgery (complete resection or incomplete resection) because the majority of these patients were still alive, whereas the median survival was 19.3 months for patients who underwent biopsy alone. The median time to tumor progression after complete resection, incomplete resection and biopsy was 81.4, 61.3 and 6.5 months, respectively. Differences in both OS and PFS times were significant according to the log-rank test ($P < 0.01$).

Based on the multivariate analysis adjusted for the effect of patient age, pre-operative KPS score, tumor size and WHO grade, complete resection was not associated with survival benefit compared with incomplete resection ($P - 0.85$). There was a trend toward longer PFS with complete resection (hazard ratio: 0.517, compared with incomplete resection), but the difference between complete resection and incomplete resection did not reach statistical significance ($P - 0.16$). Both OS ($P < 0.001$) and PFS ($P - 0.006$) were significantly shorter in patients who underwent biopsy alone than in patients who underwent incomplete resection (Table 5).

DISCUSSION

In this study, we categorized high-grade gliomas into two groups, high-grade astrocytomas and high-grade oligodendroglial tumors, based on the presence of OC. Previous studies demonstrated that the survival of patients with AOA or AO is significantly longer than that of patients with AA (21,25,26,28,41), and some studies found that GBM with OC tends to have a better prognosis than ordinary GBM (12,34 37). In our series, 14 of 87 GBMs contained OC (16%). This result is similar to previous reports (34,35). Kraus et al. (36) mentioned that the physician ordering the patient's adjuvant treatment becomes altered to the better prognosis because of the high likelihood for a favorable response to chemotherapy in the presence of OC in a GBM. He et al. (34) found that the molecular profile associated with GBM with OC was different from that of ordinary GBM with frequent loss of heterozygosity on 1p and 19q. They suggested that GBM with OC represents a subgroup of tumors of oligodendroglial origin that is distinct from ordinary GBM in terms of the tumorigenesis pathway (34). By subanalysis of a clinical randomized trial of RTOG 83-02, Donahue et al. (25) suggested that high-grade gliomas with OC should be considered in the design and stratification of malignant glioma trials, because patients who have high-grade gliomas with OC have the potential for prolonged survival.

The primary aim of this retrospective analysis was to evaluate the impact of the extent of tumor resection in high-grade astrocytomas and high-grade oligodendroglial tumors. Previous studies demonstrated that complete resection of pre-operative contrast enhancing lesions improves survival in

Table 4. Univariate analysis of clinical and tumor parameters with OS and PFS in 67 patients with high-grade oligodendroglial tumors

	Overall survival				Progression-free survival			
	Hazard ratio	95% CI		*P* value	Hazard ratio	95% CI		*P* value
Age[a]	1.072	1.03	1.12	0.001	1.039	1.01	1.07	0.005
Pre-operative KPS								
<80	2.373	0.89	6.35	0.09	1.829	0.84	3.97	0.13
>80	1.0				1.0			
Tumor diameter								
>4 cm	2.640	0.88	7.97	0.08	1.985	0.95	4.12	0.07
<4 cm	1.0				1.0			
Eloquent area								
No	0.781	0.31	1.99	0.60	0.669	0.34	1.33	0.25
Yes	1.0				1.0			
WHO grading								
Grade III	0.321	0.12	0.83	0.02	0.453	0.21	0.96	0.04
Grade IV	1.0				1.0			
Post-operative TMZ								
No	0.640	0.22	1.84	0.41	0.811	0.38	1.75	0.59
Yes	1.0				1.0			

[a]Increasing variable.

Table 5. Multivariate analysis of EOR affecting OS and PFS in 67 patients with high-grade oligodendroglial tumors[a]

	Overall survival				Progression-free survival			
	Hazard ratio	95% CI		*P* value	Hazard ratio	95% CI		*P* value
Complete resection	0.878	0.24	3.25	0.85	0.517	0.21	1.30	0.16
Incomplete resection	1.0				1.0			
Biopsy	9.35	2.52	34.8	<0.001	3.718	1.45	9.54	0.006

[a]Adjusting for the effect of patient age, pre-operative Karnofsky performance scale, tumor size (maximum diameter) and histological WHO grading.

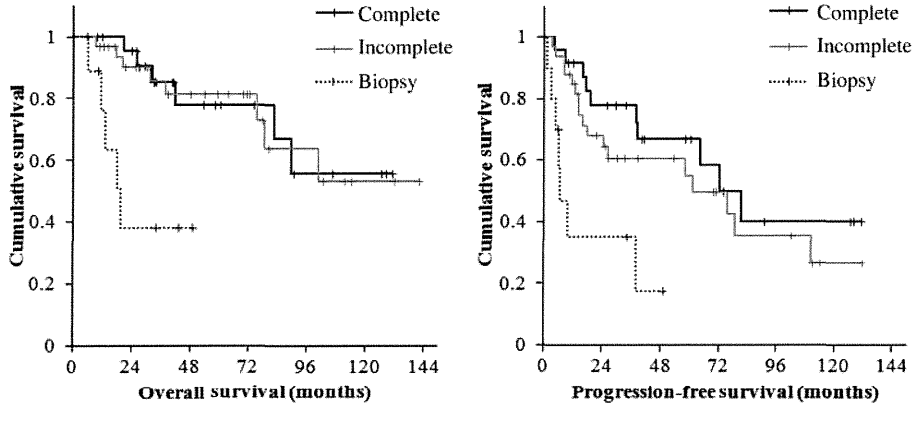

Figure 3. Overall (left) and progression-free (right) survival analysis for patients with high-grade oligodendroglial tumor demonstrated as the Kaplan Meier plots by the extent of surgical resection (complete resection, incomplete resection and biopsy alone).

GBMs and AAs (1,7–9,11,13–16). With volumetric analysis on AAs, Keles et al. (16) reported that post-operative residual contrast enhancement has a statistically significant unfavorable effect on survival. McGirt et al. (11) reported that gross total resection of contrast enhancement was independently associated with increased survival over subtotal resection in AA. Lacroix et al. (9) found that greater than 98% tumor resection was significantly associated with improved survival in newly diagnosed GBMs. In the present study, radiographically complete resection of enhancing lesions with early post-operative MR imaging was an independently good prognostic factor of both OS and PFS in high-grade astrocytomas in accordance with previous studies. Patients with residual enhancement on post-operative MR imaging did not have a survival benefit compared with patients who underwent biopsy alone. Our data confirmed that extensive surgery plays an important role in predicting the risk of progression and death in high-grade astrocytomas.

In this series of the patients with high-grade astrocytoma, the prognosis is not significantly different between AAs (WHO Grade III tumors) and GBMs (WHO Grade IV tumors). This result is intriguing. In reassessment of histopathology according to the WHO 2007 criteria, our neuropathologists classified high-grade oligodendroglial tumors regardless of the definite numeric value for the oligodendroglial tumor component portion. Patients who have AA with OC have the potential for prolonged (25); therefore, it is conceivable that the prognostic outcome of our patients with pure AA was relatively poor compared with previous reports. We suppose that the further investigation to increase the number of cases for AA which was rather less than that of GBM might be required. In addition, age and pre-operative KPS were also unrelated to the prognosis in the patients with high-grade astrocytomas. In this series, eligible patients were only able to undergo post-operative radiotherapy, so pessimistic patients with poor prognosis who could not undergo radiotherapy, i.e. very elderly or very poor preoperative KPS score, were excluded. Thus, prognosis might be less affected by age and pre-operative KPS.

There are a relatively small number of studies evaluating the relationship between the EOR and prognosis on high-grade gliomas with OC (17,18,20,42). In our patients with high-grade oligodendroglial tumors, including GBMs with OC, complete resection versus incomplete resection was not associated with survival in multivariate analysis. There was a trend toward longer PFS with complete resection, although the difference between complete resection and incomplete resection did not reach statistical significance ($P = 0.16$). Patients who underwent tumor resection (including both complete and incomplete resection) had significantly improved OS and PFS compared with patients who underwent biopsy alone (OS: $P < 0.001$ and PFS: $P = 0.006$, biopsy versus incomplete resection in multivariate analysis). In the subanalysis of Phase III trials for AOs and AOAs, tumor-debulking surgery was independently associated with longer OS time (18,42). The degree of resection was not distinct in these trials; therefore, our result is expected to be similar. Oligodendroglial tumors are well known to be generally chemosensitive tumor (30–33), leading to be better prognosis regardless of the extent of tumor resection compared with astrocytic tumor. In fact, in the present series, an objective response was obtained 24 cases (63%) among 38 high-grade oligodendroglial tumor patients with post-operative residual tumor (incomplete resection or biopsy), while an objective response was obtained 12 cases (24%) among 51 patients with high-grade astrocytoma patients with post-operative residual tumor [response to chemotherapy is assessed on the basis of criteria proposed by Macdonald et al. (43), and objective response defined as complete response or partial response]. Although the role of extensive surgery remains uncertain in high-grade oligodendroglial tumors, maximum safe resection should contribute to prolong survival even if the lesion involves eloquent areas.

CONCLUSION

Our data suggest that maximal cytoreduction should be attempted in high-grade gliomas regardless of histological subtype or tumor location. However, the impact of the EOR in high-grade astrocytomas might be different from that in high-grade oligodendroglial tumors. Certainly, this study has some limitations. This study is inherently limited by its retrospective design and the limited number of patients. In addition, there were relatively few deaths in patients with high-grade oligodendroglial tumors, which limited extensive multivariate analysis. However, when novel examinations enable us to confirm histological diagnosis pre-operatively, we anticipate that our present data may be important for the surgical strategy of high-grade gliomas.

Conflict of interest statement

None declared.

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Successful Treatment of Leptomeningeal Gliomatosis of Pilomyxoid Astrocytoma After Failed Frontline Chemotherapy

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Introduction: Pilomyxoid astrocytoma (PMA) is a rare variant of pilocytic astrocytoma. Compared with pilocytic astrocytoma, PMA is more aggressive, has a higher rate of local recurrence, and often disseminates to the leptomeninges. Leptomeningeal gliomatosis is another rare but often intractable neoplasm. PMA presenting as leptomeningeal gliomatosis can be a therapeutic challenge, particularly in young children for whom many pediatric oncologists consider radiation therapy only as a back-up treatment. However, chemotherapy, usually considered a frontline treatment for low-grade tumors such as PMA, has little impact on leptomeningeal gliomatosis.

Case Report: We report on a 5-year-old boy with an approximately 2-month history of progressively worsening loss of vision. Radiographic studies with contrast revealed an enhanced mass within the optic nerve, an enhanced lesion in the leptomeninges, and diffusely scattered nonenhanced white matter lesions in the craniospinal axis. The patient was treated with a 10-week carboplatin and vincristine regimen without a biopsy. After completing induction and 1 maintenance cycle, however, the patient developed coma caused by hydrocephalus. External ventricular drainage was performed and a biopsy was taken through ventriculoscopy, revealing PMA. The patient was then treated with craniospinal irradiation and concomitant temozolomide, a regimen to which he had a complete response. Two years after initial presentation the patient was free of disease.

Conclusions: This report documents a rare, intractable tumor and provides evidence that radiation therapy, given as craniospinal irradiation, can be effective for leptomeningeal gliomatosis.

Key Words: gliomatosis, leptomeningeal, pilomyxoid astrocytoma

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Pilomyxoid astrocytoma (PMA) is a rare glioma, histologically composed of compact, piloid cells, and a predominantly myxoid background.[1 3] The disease shares histopathologic similarities with pilocytic astrocytoma (PA), and early studies describe PMA as a manifestation of PA.[3] More recent reports consider PMA a separate entity, because it differs from PA in histology (eg, PMA lacks Rosenthal fibers), demonstrates more aggressive behavior (higher mortality and shorter disease-free survival), and tends to present in younger patients.[1,2] Some evidence suggests that the relationship between PMA and PA is closer, however, with the latter disease being, from a morphologic perspective, a rare "maturation" phenomenon of the former.[4] Although no standard of care has been established for PMA, the disease is often treated as a low-grade tumor with frontline therapy being based on morphology.[2]

PMA tends to disseminate to the leptomeninges more frequently than PA does.[5] However, a literature search revealed only 1 report that discussed leptomeningeal seeding from PMA in an adult.[5] That patient was initially treated with a combined regimen of radiotherapy and temozolomide (TMZ); however, disease recurred in the spinal area outside the radiation field. This case suggests that PMA can spread as leptomeningeal gliomatosis.

We report on a child with PMA presenting as leptomeningeal gliomatosis who failed to respond to frontline chemotherapy but had a good outcome on our treatment regimen of combined craniospinal irradiation (CSI) and TMZ.

CASE STUDY

A 5-year-old boy complained of progressive visual loss lasting nearly 2 months. Physical examination revealed no manifestations of neurofibromatosis type 1. Cranial magnetic resonance (MR) imaging showed a thick mass within the optic nerve and chiasm; the lesion was isointense on T1-weighted images and hyperintense on T2-weighted images. After contrast administration the lesion enhanced in association with diffuse leptomeningeal enhancement (Fig. 1A). Spinal MR imaging revealed diffuse enhancement of the spinal leptomeninx at all levels (Fig. 1B). Because these MR imaging findings were consistent with optic nerve and leptomeningeal dissemination of the tumor, we decided to proceed with frontline chemotherapy of carboplatin (CBDCA) and vincristine (VCR) without biopsy. The child accordingly received a 10-week induction regimen of CBDCA and VCR according to the schedule previously described by Packer et al.[6] CBDCA was administered at a dose of 175 mg/m^2 as an intravenous infusion on days 0, 7, 14, 21, 42, 49, 56, and 63. VCR was administered at a dose of 1.5 mg/m^2 as an intravenous bolus infusion on days 0, 7, 14, 21, 28, 35, 42, 49, 56, and 63.

Because MR images taken after induction chemotherapy indicated stable disease (defined as a decrease of <25% or an increase of <25% in measurable tumor area), the patient proceeded to maintenance chemotherapy consisting of CBDCA at a dose of 175 mg/m^2 as an intravenous infusion on days 0, 7, 14, and 21 and VCR at a dose of 1.5 mg/m^2 as an intravenous bolus infusion on days 0, 7, and 14 of each cycle, followed by a 2-week rest period. However, after the first maintenance cycle, the boy developed deep coma caused by hydrocephalus. An external ventricular drain was inserted to relieve pressure, and endoscopic biopsy was performed. After cerebrospinal fluid (CSF) drainage, the patient's orientation improved and he became more alert. Pathologic examination of the biopsy specimen and cytologic analysis of the collected CSF sample were consistent with a diagnosis of PMA (Figs. 2A, B). CSF showed pleocytosis and a high protein concentration of 70 mg/dL (normal 9 to 42 mg/dL). Monoclonal antibody staining to determine proliferating capacity of the biopsied sample, as indicated by the frequency of Ki-67-positive cells, was high at 20%.

After the fifth maintenance cycle, MR imaging showed a mixed response with shrinkage of the optic nerve lesion contrasting with

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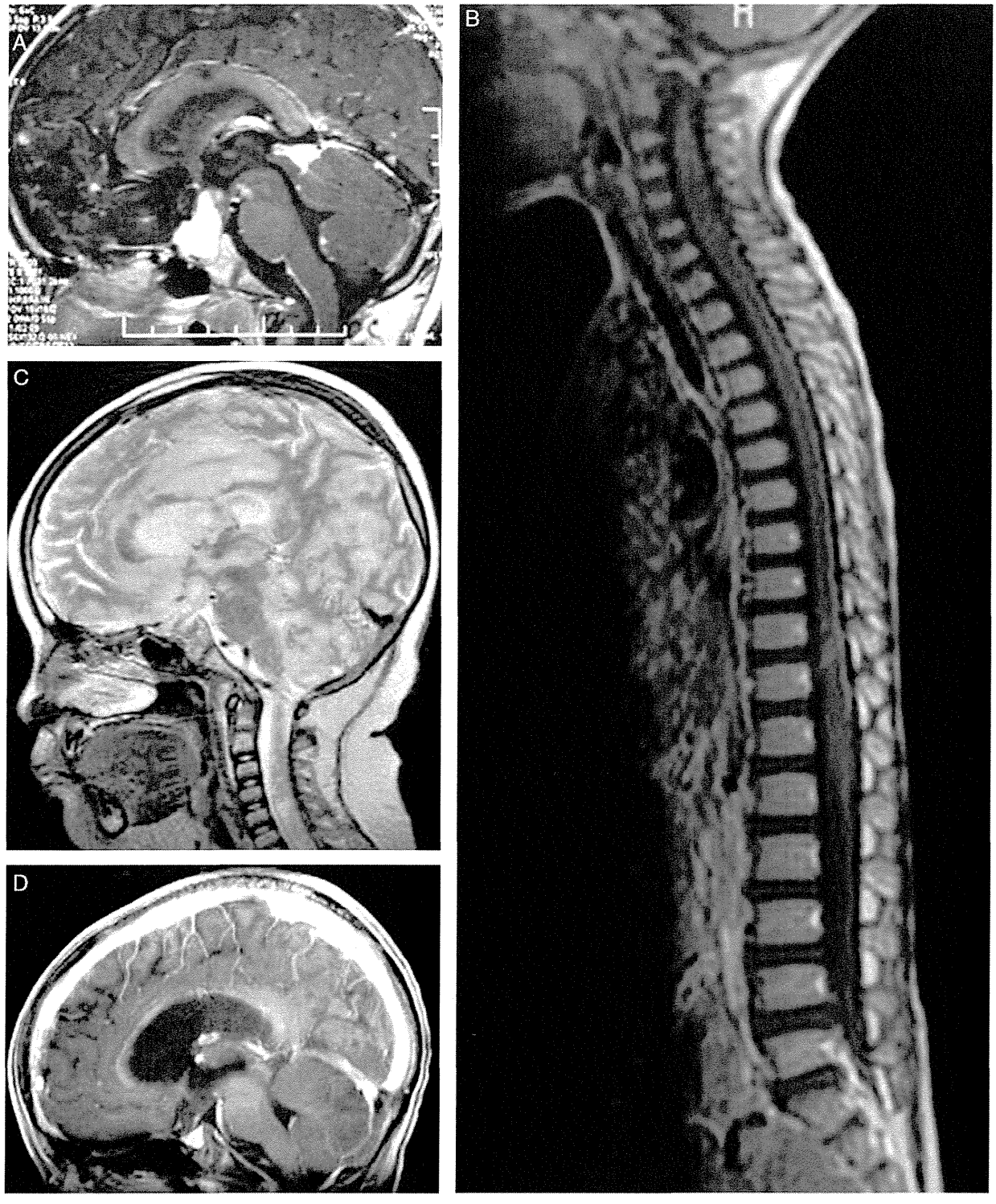

FIGURE 1. Radiographic findings: (A) Sagittal, T1-weighted, contrast-enhanced magnetic resonance imaging (MRI) taken at initial presentation of the 5-year-old patient. The optic nerve is seen to enter the enhanced portion of the tumor, and patchy, linear enhancement of the leptomeninges is visible. B, Sagittal, T1-weighted, contrast-enhanced MRI of the spine showing diffuse extramedullary gadolinium enhancement. C, Sagittal T2-weighted image after 5 cycles of maintenance chemotherapy. No enhanced lesion of the optic nerve is visible, but global growth of the T2-prolonged lesions is evident. D, Sagittal, T1-weighted, contrast-enhanced image of the patient at 7 years of age, after 3 months of maintenance temozolomide treatment. The T1-weighted contrast-enhanced lesion and T2-prolonged lesions show a complete response.

expansive growth of the gliomatosis lesions (Fig. 1C). Because his neurological status worsened with decreasing speech production, loss of vision, and gait ataxia, the patient was then treated with craniospinal radiation at a dose of 24 Gy (1.8 Gy/fraction, 5 fractions/wk) with concomitant TMZ at a dose of 75 mg/m^2/d, given orally 7 days per week from the first day of radiotherapy until the last day of radiotherapy. MR scans at 3 weeks after completion of radiotherapy showed disappearance of the leptomeningeal gliomatosis lesions. After a 4-week break, we initiated adjuvant therapy with TMZ at a dose of 150 to 200 mg/m^2 orally on days 1 to 5, every 28 days. After the third course of adjuvant TMZ, we saw no evidence of disease on MR images or CSF samples, in which protein level had normalized (16 mg/dL) (Fig. 1D). TMZ treatment was discontinued after 4 courses. The patient is blind but alive with no evidence of disease 2 years after the start of treatment. Neuropsychological testing revealed a verbal intelligence quotient of 53, hence the patient is taught in a special education setting.

The patient's parents gave informed consent before all treatments and testing. All the protocols we used were approved by our hospital's institutional review board.

DISCUSSION

We describe a child with optic nerve and leptomeningeal dissemination of PMA presenting as leptomeningeal gliomatosis. PMA was originally described by Jänisch et al[3] in 1985 as "diencephalic pilocytic astrocytoma with clinical onset in infancy," with the term "pilomyxoid astrocytoma" first introduced in 1999 by Tihan et al.[1] PMA is a newly defined distinct glioma listed as grade II in the 2007 World Health Organization classification.[7] PMA is found typically in the hypothalamic/chiasmatic regions, sites that are also affected by classical PA. Predominantly affecting infants and children (median age, 10 mo), PMA seems to have a less favorable prognosis than PA. Local recurrences and cerebrospinal spread are more likely to occur in PMA than in PA, despite multimodal chemotherapy. Although distinguishable on clinical and histologic grounds, a closer relationship between the 2 diseases may exist based on the cellular origins of PMA and PA.[4] The present case highlights the propensity of this tumor to disseminate through the CSF and neuraxis.

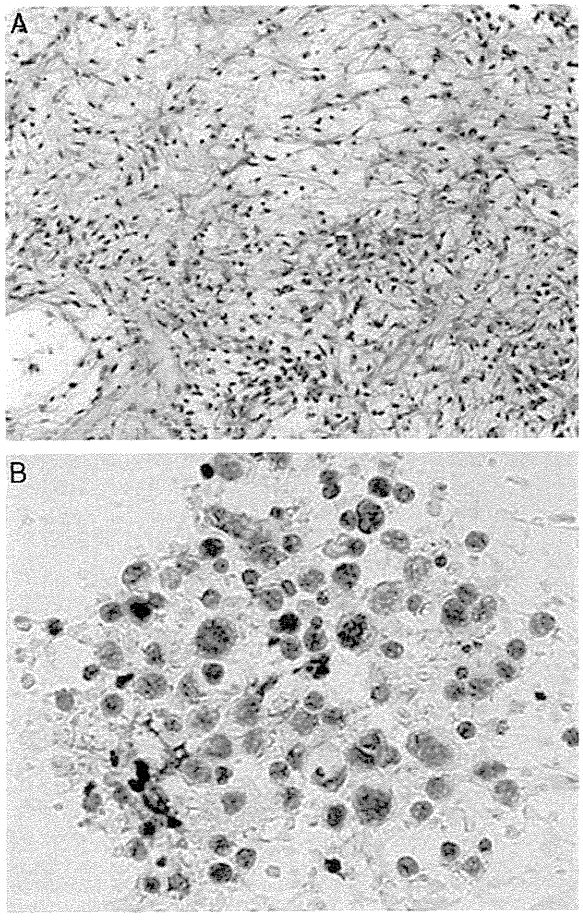

FIGURE 2. A, Biopsy sample stained with hematoxylin and eosin showing monomorphous piloid astrocytes embedded in a predominantly myxoid background (original magnification ×100). B, The cells in the cerebrospinal fluid displayed high-grade features, including round-to-oval hyperchromatic, pleomorphic nuclei. Variable amounts of cytoplasm staining with glial fibrillary acidic protein were observed (original magnification ×400).

There is no standard treatment for leptomeningeal gliomatosis; indeed, treatment of this condition has largely been unsuccessful in previous studies.[8] The most frequent approach is to use CSI as the main treatment with adjuvant systemic and/or intrathecal chemotherapy. In a series of 18 patients with leptomeningeal gliomatosis who underwent multimodal treatment, the median survival from the initiation of treatment was only 3.5 months.[9] For the present patient, we initially used frontline chemotherapy consisting of CBDCA and VCR, a regimen described by Packer et al.[6] They reported that 2 of 3 cases with diffuse leptomeningeal lesions responded to this regimen.[6] The primary rationale for using frontline chemotherapy for children with progressive or unresectable gliomas has been to delay the need for radiotherapy. None of the patients described by Packer and colleagues, however, had leptomeningeal gliomatosis arising from PMA. Because our initial frontline regimen failed to stop the growth of leptomeningeal lesions (8 mo after the initiation of treatment), we decided to switch to radiotherapy, given as CSI, combined with TMZ according to the Stupp regimen for glioblastoma multiforme.[10] Clinical and radiographic improvements were considerable, and the first cerebral MR imaging showed a complete response. Our patient represents the first report of a child with optic nerve and leptomeningeal dissemination of PMA and CSF seeding who was treated with low-dose CSI and concurrent TMZ.

We successfully treated the present patient with low-dose CSI (24 Gy) and concurrent TMZ. To date, no consensus exists on the recommended dose of CSI for the treatment of PMA with leptomeningeal gliomatosis. Moreover, although 35 Gy is most commonly used when CSI can be delivered alone, no studies have reported the impact of treatment with CSI and concurrent TMZ for this condition. Enting et al[5] reported on a patient with leptomeningeal PMA who was treated with a combination of whole-brain radiotherapy and TMZ. Distant spinal recurrence was noted after whole-brain radiotherapy. Even in leptomeningeal gliomatosis arising from PA, both the activity of chemotherapy and prognosis are highly variable.[11,12] Given that TMZ may produce the biological effect of radiosensitization, has shown some activity with only mild toxicity in this disease, and is easy to administer,[13,14] we opted for systemic treatment with TMZ combined with low-dose CSI in the present patient. This low dose of CSI combined with chemotherapy was well tolerated in other central nervous system malignancies,[15,16] and dose reduction of CSI seems to significantly reduce the severity of cognitive loss, particularly in younger patients who receive CSI to eradicate disease involving the leptomeninges.[17]

The present report contributes to our understanding of the diagnostic profile of PMA and describes the combination of

CSI and TMZ as an alternative for leptomeningeal dissemination of PMA. Leptomeningeal dissemination is a globally aggressive neoplasm with different management requirements from intraparenchymal glioma that develops from PA or PMA. Although leptomeningeal gliomatosis arising from PMA is a rare phenomenon, its histopathologic and clinical characteristics can be distinguished, and we suggest aggressive treatment with low-dose CSI as an effective option. More work is needed to address the issue of optimal therapy and the relative value of more intensive chemotherapy, as compared with CSI or radiotherapy, for this enigmatic pediatric neoplasm. This report is the first to show that leptomeningeal gliomatosis arising from PMA can be successfully treated with a combination of CSI and TMZ after failure of frontline chemotherapy.

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Original Article

Phase II Study of Single-agent Bevacizumab in Japanese Patients with Recurrent Malignant Glioma†

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Objective: This single-arm, open-label, Phase II study evaluated the efficacy and safety of single-agent bevacizumab, a monoclonal antibody against vascular endothelial growth factor, in Japanese patients with recurrent malignant glioma.

Methods: Patients with histologically confirmed, measurable glioblastoma or World Health Organization Grade III glioma, previously treated with temozolomide plus radiotherapy, received 10 mg/kg bevacizumab intravenous infusion every 2 weeks. The primary endpoint was 6-month progression-free survival in the patients with recurrent glioblastoma.

Results: Of the 31 patients enrolled, 29 (93.5%) had glioblastoma and 2 (6.5%) had Grade III glioma. Eleven (35.5%) patients were receiving corticosteroids at baseline; 17 (54.8%) and 14 (45.2%) patients had experienced one or two relapses, respectively. The 6-month progression-free survival rate in the 29 patients with recurrent glioblastoma was 33.9% (90% confidence interval, 19.2–48.5) and the median progression-free survival was 3.3 months. The 1-year survival rate was 34.5% with a median overall survival of 10.5 months. There were eight responders (all partial responses) giving an objective response rate of 27.6%. The disease control rate was 79.3%. Eight of the 11 patients taking corticosteroids at baseline reduced their dose or discontinued corticosteroids during the study. Bevacizumab was well-tolerated and Grade $\geq$3 adverse events of special interest to bevacizumab were as follows: hypertension [3 (9.7%) patients], congestive heart failure [1 (3.2%) patient] and venous thromboembolism [1 (3.2%) patient]. One asymptomatic Grade 1 cerebral hemorrhage was observed, which resolved without treatment.

Conclusion: Single-agent bevacizumab provides clinical benefit for Japanese patients with recurrent glioblastoma.

Key words: bevacizumab – glioblastoma – Asian continental ancestry group – Phase II – glioma

INTRODUCTION

Glioblastoma (GBM) is the most aggressive form of primary malignant brain tumor and the prognosis for patients with GBM is poor (1,2); the majority will relapse following initial treatment and <10% are alive at 5 years (3). The standard treatment for patients with newly diagnosed GBM is surgical resection followed by temozolomide (TMZ) and radiotherapy (RT), and then adjuvant TMZ alone (Stupp regimen) (4). Treatment options for patients with recurrent GBM, however, are limited and include repeat resection, RT and systemic chemotherapy, such as TMZ, nitrosoureas, platinum-based regimens (carboplatin, cisplatin), cyclophosphamide, irinotecan and etoposide, and appropriate treatment will depend on the patient and tumor characteristics (5). Currently there is no standard therapy for recurrent GBM and the estimated 6-month progression-free survival (PFS) rate for patients with recurrent disease is 9–28% (6–11) with a 1-year survival rate of 14–32% (6–8,10,11). Therefore, new treatment strategies for recurrent GBM are needed.

An alternative therapeutic approach is the inhibition of angiogenesis through the vascular endothelial growth factor (VEGF), a key regulator of angiogenesis. High levels of VEGF are expressed in GBM cells (12,13), and hypoxia and acidosis, conditions commonly seen in solid tumors, upregulate VEGF expression in glioma cells *in vivo* (14). In a mouse model, monoclonal antibodies to VEGF have been shown to inhibit the growth of the C6 glioma (15). Bevacizumab (Avastin®) is a monoclonal antibody that inhibits VEGF and is currently approved for a range of metastatic cancers (colorectal, non-small-cell lung, breast, ovarian cancer and renal cancers) (16–19) as well as for use in adults with recurrent GBM in many countries including the USA (20,21). Early Phase II studies in patients with recurrent GBM showed the efficacy of bevacizumab in combination with irinotecan (22,23). Subsequently, two Phase II studies (24–26) showed the efficacy of single-agent bevacizumab with regard to response rates and 6-month PFS in patients with recurrent GBM who had previously received RT and TMZ. These two studies formed the basis of bevacizumab's approval by the Food and Drug Administration (FDA) in 2009. Moreover, other studies have shown the efficacy of bevacizumab in recurrent GBM whether given as a single agent (27) or combined with irinotecan (28,29) and other chemotherapies, such as etoposide, carboplatin and fotemustine (30–33). Given the current evidence for bevacizumab in recurrent GBM in Western patient populations, we investigated the efficacy and safety of single-agent bevacizumab in a Phase II, single-arm, open-label study (JO22506) in Japanese patients with recurrent malignant glioma.

PATIENTS AND METHODS

The trial was carried out in accordance with the principles of Good Clinical Practice and the Declaration of Helsinki; all patients provided written informed consent prior to any study-related procedure. The protocol was approved by the institutional review boards of all participating centers. The study was registered with the Japan Pharmaceutical Information Center-Clinical Trials Information (JapicCTI), trial number: JapicCTI-090841.

Eligibility

Eligible patients were aged ≥20 years with histologically confirmed GBM or World Health Organization (WHO) Grade III glioma, the latter being reconfirmed at the time of surgery for recurrent glioma. Patients had magnetic resonance imaging (MRI)-confirmed disease recurrence or progression with measurable lesions within 2 weeks prior to the first study treatment and no evidence of acute or subacute cerebral hemorrhage and had received prior TMZ and RT for malignant glioma. Other key inclusion criteria were a Karnofsky performance status (KPS) ≥70%, a life expectancy of ≥3 months and adequate hematologic, renal and hepatic function (i.e. absolute neutrophil count ≥1500/mm^3, platelet count ≥100 000/mm^3, hemoglobin ≥10 g/dl, bilirubin ≤ 1.5 × the upper limit of normal (ULN), aspartate aminotransferase and alanine aminotransferase ≤ 2.5 × ULN, serum creatinine ≤ 1.25 × ULN). The following minimum intervals of time must have elapsed between the termination of therapies and the start of bevacizumab treatment: RT 8 weeks; surgical therapy and incisional biopsy 4 weeks; endocrine therapy and immunotherapy 3 weeks; post-traumatic intervention (except for patients with non-healing wounds) 2 weeks; transfusion and the use of hematopoietic growth factors 2 weeks; aspiration cytology and needle biopsy 1 week; nitrosoureas 6 weeks, procarbazine 3 weeks, vincristine 2 weeks and other chemotherapies 4 weeks and other investigational new drugs and unapproved drugs 4 weeks. Patients were excluded if they had: prior treatment with bevacizumab; a history of treatment with carmustine wafers, stereotactic radiotherapy, proton therapy or neutron capture therapy; ≥3 prior regimens for malignant glioma and inadequately controlled hypertension, heart disease, symptomatic cerebrovascular disorder, gastrointestinal (GI) perforation, fistula or abdominal abscess within 6 months prior to enrollment.

Study Design

This single-arm, open-label, Phase II study was conducted at 10 sites in Japan. One cycle of treatment was defined as one

bevacizumab infusion administered on Day 1 every 2 weeks. Eligible patients received 10 mg/kg bevacizumab as an intravenous infusion administered over 90 ($\pm$ 15) min on Day 1 of each cycle, which could be reduced to 30 min by Cycle 3 if no infusion reactions occurred. Treatment continued until disease progression (PD) or unacceptable toxicity. Bevacizumab doses were adjusted only for changes of $\geq$10% in body weight during the study. In the event of unacceptable toxicity, bevacizumab treatment was delayed or discontinued according to pre-specified criteria. Bevacizumab was discontinued if multiple adverse events (AEs) fulfilling the pre-specified delay or discontinuation criteria occurred in the same cycle, if cerebral hemorrhage occurred and if delayed treatment could not be restarted within 6 weeks of the last bevacizumab infusion. Patients who discontinued bevacizumab were followed for survival. Bevacizumab was provided by Chugai Pharmaceutical Co. Ltd (Tokyo, Japan).

Assessment of Efficacy

The primary endpoint was 6-month PFS in patients with recurrent GBM only. Six-month PFS was defined as the percentage of patients who remained alive and progression free at 24 weeks and was chosen based on published evidence demonstrating its extrapolation to the overall survival (OS) (6,7). Secondary efficacy endpoints included the 1-year survival, PFS, objective response rate (ORR), duration of response (DOR), OS and disease control rate (DCR).

Efficacy was assessed every third cycle (i.e. Cycles 3, 6, 9 etc.). Progression and objective response were determined by comprehensive evaluation of the results from MRI scans, corticosteroid dose assessment and neurocognitive function assessment. They were assessed by an independent radiology facility (IRF) by reference to Macdonald's Criteria (34). Response was classified according to the following categories: complete response (CR), partial response (PR), no change (NC) and PD. Confirmation of the response was determined on two consecutive assessments $\geq$4 weeks apart: patients who were determined as having CR or PR were defined as responders; patients who were determined as having NC or PD were defined as non-responders.

Percentage tumor shrinkage was also assessed and was calculated from the sum of the products of the diameters (SPD) at baseline and the smallest SPD after baseline.

Assessment of Safety

AEs were assessed throughout the study and were graded according to the Common Terminology Criteria for AEs version 3.0 (35). Body weight, vital signs and laboratory tests were assessed prior to the start of each cycle.

Statistical Methods

The efficacy analysis population comprised all patients with recurrent GBM. Patients with Grade III glioma were also evaluated for efficacy, but were not included in the primary analysis. All patients were evaluated for safety.

Statistical analysis to detect a 6-month PFS of 35% was established based on data from previous studies [BRAIN study [24] (42.6% with bevacizumab monotherapy) and the NCI-06-C-0064E study [26] (29% with bevacizumab monotherapy)], in which a 15% threshold for 6-month PFS was defined. Under these conditions, 28 patients with recurrent GBM would provide at least 80% power to detect a 20% increase in 6-month PFS from 15 to 35% at the 5% one-sided significance level. Assuming that other WHO Grade III glioma patients would be enrolled, the overall target sample size was 32 patients.

The 6-month PFS, median PFS, OS and DOR were calculated by the Kaplan–Meier method and confidence intervals (CIs) calculated by Greenwood's formula (36). Exact binomial CIs were used for estimated intervals for response rates.

RESULTS

Patients

Between August 2009 and July 2010, 31 patients were enrolled, 29 of whom were included in the efficacy analysis population. All enrolled patients received a median of 6 bevacizumab doses. Treatment was discontinued in a total of 25 patients: 23 (74.2%) due to PD; 2 (6.5%) due to AEs. Efficacy and safety analyses, except for OS, were performed after an observation period of $\geq$6 months (data cut-off 7 January 2011); the OS analyses, which included data collected through to 22 August 2011, were performed after all enrolled patients had been observed for $\geq$1 year.

Demographic Data

The majority of patients (29; 93.5%) had GBM; 2 (6.5%) had Grade III glioma (Table 1). The median age was 54.0 years (range: 23–72); 10 (32.3%) patients were aged $\geq$65 years. The percentage of males to females was well balanced. Patients were in relatively good health with 61.3% having a KPS of 90–100, and 64.5% of patients not receiving corticosteroids at the start of the study. Similar numbers of patients had experienced 1 [17 (54.8%)] or 2 [14 (45.2%)] relapses.

Efficacy Outcomes

At the time the PFS and OS analyses were performed, 22 PD events and 21 death events had been reported in the 29 patients with recurrent GBM. The 6-month PFS rate in the 29 patients with recurrent GBM (primary endpoint) was 33.9% (90% CI, 19.2–48.5), and this exceeded the 15% threshold ($P = 0.0170$). Kaplan–Meier estimates of PFS showed a steady decline over the initial 6 months with a median PFS of 3.3 months (95% CI 2.8–6.0) (Fig. 1). The 1-year survival rate for these patients was 34.5% (90%

Table 1. Demographic and baseline disease characteristics

Parameter	All patients ($n = 31$)	GBM ($n = 29$)	WHO Grade III ($n = 2$)[a]
Median age, years (range)	54.0 (23 72)	57.0 (23 72)	32.5 (30 35)
Age groups in years, *n* (%)			
<40	6 (19.4)	4 (13.8)	2 (100)
41 64	15 (48.4)	15 (51.7)	0 (0.0)
>65	10 (32.3)	10 (34.5)	0 (0.0)
Gender, *n* (%)			
Male	16 (51.6)	14 (48.3)	2 (100)
Female	15 (48.4)	15 (51.7)	0 (0.0)
KPS, *n* (%)			
70 80	12 (38.7)	12 (41.4)	0 (0.0)
90 100	19 (61.3)	17 (58.6)	2 (100)
Relapse/progression status, *n* (%)			
First	17 (54.8)	17 (58.6)	0 (0.0)
Second	14 (45.2)	12 (41.4)	2 (100)
Duration of malignant glioma[b]			
Median, months (range)	15.2 (5.6 213.3)	15.0 (5.6 213.3)	46.8 (27.8 65.8)
Time from RT to bevacizumab[c]			
Median, months (range)	13.2 (3.8 209.6)	13.1 (3.8 209.6)	44.8 (25.5 64.1)
Corticosteroid use at baseline, *n* (%)			
Yes	11 (35.5)	10 (34.5)	1 (50.0)
No	20 (64.5)	19 (65.5)	1 (50.0)

GBM, glioblastoma; WHO, World Health Organization; KPS, Karnofsky performance status; RT, radiotherapy; q2w, every 2 weeks.
[a]One patient had anaplastic astrocytoma and one patient had anaplastic oligoastrocytoma.
[b]Time since the initial diagnosis of malignant glioma.
[c]Time from the last RT to the first dose of bevacizumab.

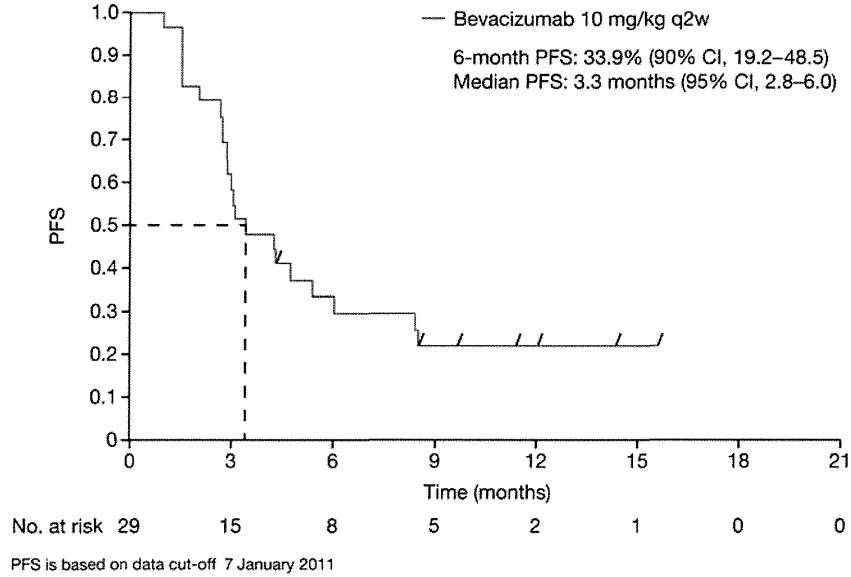

Figure 1. Progression-free survival determined by independent radiology facility in patients with recurrent glioblastoma (GBM).

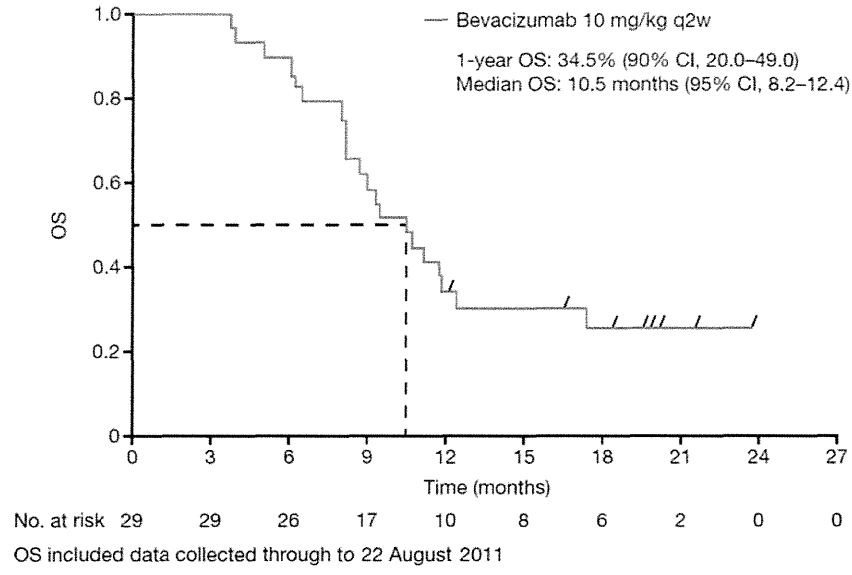

Figure 2. Overall survival in patients with recurrent GBM.

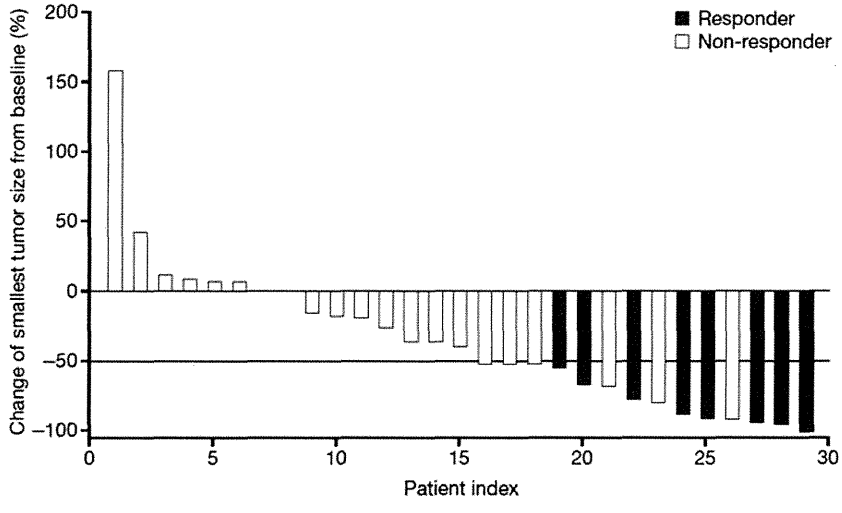

Figure 3. Waterfall plot showing the change in tumor size from baseline.

CI 20.0–49.0) with a median OS of 10.5 months (95% CI 8.2–12.4) (Fig. 2).

There were eight responders (all PR) with an ORR of 27.6% (95% CI 12.7–47.2). The DCR (0 CR + 8 PR + 15 NC) was 79.3% (95% CI 60.3–92.0). The two patients with WHO Grade III glioma completed one and two cycles of treatment, respectively; both experienced PD. Twenty-one patients (72.4%) with recurrent GBM experienced tumor shrinkage during the treatment period (Fig. 3), including 13 patients who were classified as non-responders. Of the 11 patients who were taking corticosteroids at baseline, dose reductions or discontinuation of corticosteroids occurred in 8 patients.

Efficacy endpoints were investigated in different patient subgroups (Table 2). Patients who were aged <50 years or <65 years, male, with a high KPS (90–100), on their first treatment relapse, not receiving corticosteroid therapy at baseline, or having been diagnosed with GBM at the initial diagnosis of malignant glioma, appeared to have a better response to bevacizumab treatment than other patients.

Safety Outcomes

All 31 patients experienced AEs with a total of 220 AEs reported during the study (Table 3). Serious AEs occurred in 11 (35.5%) patients, the most common being convulsion [2 (6.5%) patients]. Two (6.5%) patients discontinued the study due to AEs: one patient experienced a Grade 1 cerebral hemorrhage, and one patient had Grade 2 neutropenia that meant re-treatment within 6 weeks was not possible. A total of 13 (41.9%) patients experienced an AE of Grade ≥3, the most common being hypertension [3 (9.7%) patients]. No

Table 2. Six-month PFS and ORR by subgroup in patients with recurrent GBM

Variable	Bevacizumab 10 mg/kg, q2w ($n = 29$)	
	Six-month PFS, % (95% CI)	ORR, %
Age, years		
<65 ($n = 19$)	42.1 (19.9–64.3)	36.8
≥65 ($n = 10$)	15.0 (0.0–40.2)	10.0
Age, years		
<50 ($n = 11$)	45.5 (16.0–74.9)	45.5
≥50 ($n = 18$)	26.7 (5.7–47.6)	16.7
Gender		
Female ($n = 15$)	24.0 (1.3–46.7)	20.0
Male ($n = 14$)	42.9 (16.9–68.8)	35.7
KPS		
70–80 ($n = 12$)	16.7 (0.0–37.8)	8.3
90–100 ($n = 17$)	47.1 (23.3–70.8)	41.2
Relapse/progression status		
First ($n = 17$)	46.3 (22.3–70.4)	35.3
Second ($n = 12$)	16.7 (0.0–37.8)	16.7
Corticosteroid use at baseline		
Yes ($n = 10$)	20.0 (0.0–44.8)	10.0
No ($n = 19$)	42.1 (19.9–64.3)	36.8
Initial diagnosis of malignant glioma by site		
GBM ($n = 23$)	43.0 (22.6–63.5)	34.8
Other ($n = 6$)	0.0 (0.0–0.0)	0.0

PFS, progression-free survival; ORR, objective response rate; CI, confidence interval.

Table 3. Adverse events ≥Grade 3 and adverse events of special interest to bevacizumab

Patients, n (%)	Bevacizumab 10 mg/kg, q2w ($n = 31$)	
	All grade	Grade ≥3
Total patients with at least one AE	31 (100.0)	13 (41.9)
Irregular menstruation	3 (9.7)	2 (6.5)
Pyrexia	7 (22.6)	1 (3.2)
Convulsion	3 (9.7)	1 (3.2)
Depressed level of consciousness	1 (3.2)	1 (3.2)
Hydrocephalus	1 (3.2)	1 (3.2)
Increased intracranial pressure	1 (3.2)	1 (3.2)
Brain edema	1 (3.2)	1 (3.2)
Hemiplegia	1 (3.2)	1 (3.2)
Appendicitis	1 (3.2)	1 (3.2)
Urinary tract infection	1 (3.2)	1 (3.2)
Delirium	1 (3.2)	1 (3.2)
Neutropenia	5 (16.1)	1 (3.2)
Leukopenia	5 (16.1)	1 (3.2)
AEs of special interest to bevacizumab	22 (71.0)	5 (16.1)
Proteinuria	13 (41.9)	—
Hemorrhage[a,b]	10 (32.3)	—
Hypertension	10 (32.3)	3 (9.7)
Congestive heart failure	1 (3.2)	1 (3.2)
Venous thromboembolism	1 (3.2)	1 (3.2)

AE, adverse event.
[a]All events were Grade 1.
[b]Includes: epistaxis, gingival bleeding, conjunctival hemorrhage, infusion site hemorrhage, blood urine present, cerebral hemorrhage, hemorrhage subcutaneous, metrorrhagia.

incidence of Grade 4 or 5 hypertension was observed. One patient died of brain edema (Grade 5 AE), which was considered by the investigator to be related to PD with no causal relationship with bevacizumab treatment.

A total of 22 (71.0%) patients experienced AEs of special interest to bevacizumab, comprising proteinuria, hemorrhage, hypertension, congestive heart failure and venous thromboembolism (Table 3). One Grade 1 cerebral hemorrhage was observed on MRI; this was asymptomatic and resolved without treatment. Five (16.1%) patients had Grade 3 AEs of special interest to bevacizumab, comprising congestive heart failure [1 (3.2%) patient], venous thromboembolism [1 (3.2%) patient] and hypertension [3 (9.7%) patients]. No patients reported the other AEs of special interest to bevacizumab, i.e. reversible posterior leukoencephalopathy syndrome, wound-healing complications, GI perforation or fistulae.

Abnormal laboratory results were reported in 74.2% of patients. The most common abnormal laboratory result was proteinuria, which was reported in 41.9% of patients. Abnormal laboratory results classed as ≥Grade 3 were observed in two patients, reported as neutropenia and leukopenia.

DISCUSSION

This is the first clinical trial to investigate the safety and efficacy of single-agent bevacizumab in Japanese patients with recurrent GBM. Our data demonstrated that single-agent bevacizumab 10 mg/kg was effective in terms of the 6-month PFS, ORR, OS and 1-year survival, and was well tolerated in this Japanese population. In addition, the majority [21 (72.4%)] of patients with recurrent GBM experienced some tumor shrinkage during the treatment period.

The observed 6-month PFS of 33.9% and ORR of 27.6% seen in our study were more favorable than previous published data. These data are numerically higher than those reported for other studies with other chemotherapy and/or RT regimens (6-month PFS 9–21% and ORR 4–9%)

(6,7,10,11,37), and comparable with those reported for single-agent bevacizumab (42.6 and 28.2% for 6-month PFS and ORR, respectively) (24).

The use of Macdonald's Criteria was standard when this study was initiated; however, subsequently the Response Assessment in Neuro-Oncology (RANO) Working Group has recommended assessing MRI T2-weighted or fluid-attenuated inversion recovery (FLAIR) of non-enhancing lesions in addition to enhancing lesions (38). As the Macdonald's Criteria only assess contrast-enhancing lesions, there are risks that pseudoprogression and pseudoresponses may be considered real treatment effects. In our study an IRF assessed the changes in the T2/FLAIR signal, which was not included in the primary response evaluation based on Macdonald's Criteria. No significant increase in the T2/FLAIR signal was confirmed in the eight responders for the DOR, and seven out of eight responders exhibited $\geq$6 months' DOR. Based on these results, we are convinced that the objective response seen in our study is not a pseudoresponse.

Of the 29 GBM patients treated, 21 exhibited tumor shrinkage, including 8 patients who had a PR and 13 'non-responders' who were determined as NC or PD but exhibited some benefit with bevacizumab that was not captured by the response criteria; the maximum percentage of tumor shrinkage in 6 patients was >50%. The apparent discrepancy between the number of responders and the number of patients with tumor shrinkage is likely to be due to the ways in which the endpoints are calculated. The percentage of tumor shrinkage is calculated from the SPD at baseline and the smallest SPD after baseline, whereas for a patient to be classed as a responder, there had to be a decrease in tumor volume by $\geq$50% in the product of two diameters according to confirmation MRI performed $\geq$4 weeks after an observed response, as well as no increase in corticosteroid dosage and no neurologic deterioration. This leads to the difference between the number of patients with tumor shrinkage and the number of responders.

The 6-month PFS and ORR results were better for patients who had experienced one relapse than for those who had experienced two relapses, which is the same as a previously published observation (24). In addition, in our study bevacizumab improved the 6-month PFS and the ORR in the subgroups of patients who were aged <50 or <60 years compared with older patients. Although neither our study nor the previously published study (24) was powered to detect a statistical difference in these subgroups, the results could suggest that earlier administration of bevacizumab, or treatment with bevacizumab in younger patients, may lead to better tumor response and is something that requires investigation in further clinical trials.

Regarding the survival endpoints, our study showed results that were better than previously published data. The median OS of 10.5 months in GBM patients and 9.4 months in all patients was longer than that reported in other GBM trials (5.0–7.3 months) (6–8,10,11) and comparable with data with single-agent bevacizumab (9.3 months) (24,25). In addition, the 1-year survival rate for GBM patients (34.5%) was as good as the published data (14–32%) (6–8,10,11).

In addition to the favorable efficacy measures, a trend was also observed where 8 of the 11 patients who were taking corticosteroids at baseline were able to reduce their dose or discontinue corticosteroids altogether during the course of the study. This is consistent with other findings that suggest that bevacizumab may have corticosteroid-sparing effects in patients with recurrent GBM (39). Corticosteroid reduction may reduce infection rates and other related toxicities and therefore is expected to improve the health-related quality of life for patients.

Bevacizumab was well tolerated in our study and the incidence of AEs of special interest to bevacizumab was similar to that seen in other published studies with single-agent bevacizumab (24–26,40). No new bevacizumab safety signals were seen in this Japanese population.

In our study, and in the other single-agent bevacizumab studies (24–26,40), bevacizumab was administered after prior treatment with TMZ and RT. We observed an apparently greater benefit with bevacizumab in those patients with one relapse compared with those who have had two relapses following treatment with TMZ and RT. It is expected that bevacizumab may also provide benefit when administered concurrently with TMZ and RT rather than after TMZ/RT therapy. Currently, two randomized, double blind, Phase III studies are ongoing (AVAglio (41) and RTOG 0825 (42)) in which the addition of bevacizumab to standard of care (concurrent RT plus TMZ followed by adjuvant TMZ) is being evaluated in patients with newly diagnosed GBM.

There are many novel targeted agents under investigation for the treatment of gliomas (43); however, results with these new agents have been disappointing to date. Single-target agents alone may not be able to prevent tumor growth given the multiple pathways involved in many intracellular processes of tumor development. A key to future improvements in the treatment of gliomas will be the combination of other chemotherapeutic agents or molecular targeted therapies with bevacizumab to block these multiple pathways. This potential approach needs to be explored in future clinical trials.

In conclusion, the results of this study show that single-agent bevacizumab could provide significant clinical benefit for Japanese patients with recurrent GBM.

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Conflict of interest statement

Dr Masao Matsutani is a coordinating investigator of this study, a member of the advisory committee on MSD KK and a member of the independent safety review board for Nobelpharma Co. Ltd; consulting fees as a coordinating investigator of this study have been received by him from Chugai Pharmaceutical Co. Ltd. Dr Ryo Nishikawa is a member of the Avaglio study steering committee (funded by F. Hoffmann-La Roche, Ltd) and has received research funding and speaking fees from MSD KK, and honoraria from Nobelpharma Co. Ltd. No other conflicts of interest were declared.

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