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Safety of Gliadel Implant for Malignant Glioma: Report of Postmarketing Surveillance in Japan

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Abstract

Clinical trial data of Carmustine implant (Gliadel Wafer) in Japanese patients with malignant glioma are limited; thus, we conducted a postmarketing surveillance study to evaluate the safety of Gliadel in real-world clinical practice in Japan. In this postmarketing surveillance study, all patients who received Gliadel placement for malignant glioma surgeries from its market launch (January 9, 2013) to July 10, 2013 were enrolled from 229 institutions using a central registration system. Up to eight wafers of Gliadel (containing 61.6 mg of carmustine) were used to cover the site of brain tumor resection intraoperatively according to the size and shape of the tumor resection cavity. The observation period lasted 3 months after Gliadel placement. Patients were followed up for 1 year postoperatively. Safety was assessed by the incidence of adverse events (AEs) and adverse drug reactions (ADRs). In total, 558 patients were included. Most patients (66.7%) received eight Gliadel wafers. The percentage of patients with ADRs was 35.7% (365 ADR episodes in 199 patients). Of the AEs of special interest, the most common were cerebral edema (22.2%, 124/558 patients), convulsion (9.9%, 55/558 patients), impaired healing (4.8%, 27/558 patients), and infection (3.4%, 19/558 patients). This first all-case postmarketing surveillance report of the safety of Gliadel in real-world clinical practice in Japan suggests that the risk of toxicity with Gliadel placement is relatively tolerable. The survival benefits of Gliadel placement should be evaluated and considered carefully by the clinician taking into account possible toxicities.

Keywords: Gliadel implant, malignant glioma, postmarketing surveillance

Introduction

Brain tumors are classified by the World Health Organization (WHO) into four grades (i.e., Grades I–IV) according to their prognosis and life expectancy.[1)] Malignant gliomas are WHO Grades III and IV gliomas[1)] and are the second most common brain tumor types next to meningioma.[2)]

Carmustine implant (Gliadel Wafer, Eisai Inc., Woodcliff Lake, NJ, USA), referred to hereafter as Gliadel, is a nitrosourea formulated as an extended-release polyanhydride biodegradable polymer wafer used for intracerebral implantation. It is indicated for the treatment of malignant gliomas as an adjunct to surgery.[3)] The range of tissue permeation of Gliadel extends to several millimeters.[4)] Once the wafer is implanted in the brain at the site of tumor excision, carmustine is released slowly over a period of approximately 5 days, and the wafer degrades over a period of 6–8 weeks.[4)] This local adjuvant chemotherapy method allows the controlled delivery of a high concentration of carmustine to the residual tumor, while lowering systemic toxicities.[5–7)]

In Japan, a multicenter phase I/II study of Gliadel was performed to evaluate its efficacy and safety in patients with newly diagnosed malignant glioma. In that study, the overall survival rates at 12 and 24 months were 100.0% and 68.8%, respectively.[8)] Based on those results, the Gliadel 7.7 mg implant

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was approved in Japan in September 2012 and was marketed from January 2013.

Clinical trial data of Japanese patients at the time of Gliadel approval and launch are limited as it is challenging to conduct large-scale clinical studies. Additionally, several previous studies reported cases of cerebral edema likely caused by high exposure to the anti-tumor drug and cases of infection probably associated with foreign body reaction after implant placement.[9–13] Given that postmarketing surveillance studies allow the collection of large amounts of real-world clinical data, and it was necessary to evaluate thoroughly the onset and causality of these conditions in Japanese patients, we conducted a postmarketing surveillance study of all patients who received Gliadel since its launch in real-world clinical practice in Japan. Additionally, we aimed to comprehensively collect the background information of the 250 patients registered by May 2013 (the time at which the target number of patients was reached).

Materials and Methods

Study design and eligibility

This postmarketing surveillance study was conducted by Eisai Co., Ltd., Tokyo, Japan, in accordance with the principles of Good Post-Marketing Study Practice in Japan.

Patients were enrolled using a central registration system. A total of 229 institutions participated in this study. All patients who received Gliadel for the indication of malignant glioma from the market launch of Gliadel on January 9, 2013 to July 10, 2013 were enrolled in this study. Even though the target sample size was reached in May 2013, the Pharmaceuticals and Medical Devices Agency suggested the continued registration of patients using Gliadel from July 2013 until the date approval conditions were to be lifted.

Regarding the dosage and administration of Gliadel, in general, up to eight wafers of Gliadel (containing 61.6 mg of carmustine) were used to cover the site of brain tumor resection intraoperatively according to the size and shape of the tumor resection cavity.

The observation period lasted 3 months after the placement of Gliadel. Patients were then followed up for 1 year after the placement of Gliadel, except for 151 patients in which the study was discontinued due to the patients' death. Data were collected through case report forms (submission of case report forms at 3 months and 1 year after Gliadel placement) recorded by the attending physicians.

The major items investigated included patient characteristics; disease characteristics, including pathological diagnosis and WHO classification; Karnofsky performance status (KPS) score before and after Gliadel placement; details of Gliadel placement, including number of wafers placed; treatment, including adjuvant chemotherapy and radiotherapy after Gliadel placement; and incidence of adverse events (AEs) and adverse drug reactions (ADRs).

Safety

AEs were classified according to system organ class and preferred terms (MedDRA/J version 17.1), and the relationship to Gliadel, seriousness, and severity (according to common terminology criteria for AEs [CTCAE] v4.0, JCOG version in Japanese) were evaluated. ADRs were defined as AEs for which the causal relationship with Gliadel could not be ruled out. The AEs of special interest were cerebral edema, convulsion, hydrocephalus, impaired healing (including abnormal wound healing), and infection (including intracranial infection, meningitis, and brain abscess). The incidences of AEs and ADRs during the 3 months after Gliadel placement were determined and analyzed according to patient, tumor, and treatment factors. In addition, AEs falling under at least one of the following criteria were evaluated as serious, and AEs falling under none of these criteria were evaluated as non-serious: 1) Death; 2) Persistent or significant disability/incapacity; 3) Life-threatening, which refers to an event in which the patient was at risk of death at the time of the event, but does not refer to an event which hypothetically might have caused death if it was more severe; 4) Hospitalization or extension of hospitalization; 5) Congenital anomaly/birth defect; and 6) Other medically important conditions, which are serious events requiring treatment to avoid 1)–5) listed above, such as immediate life-threatening or endangering patients even if not death or hospitalization.

Statistical analysis

The target sample size was set at 250 subjects, which was expected to enable the detection of at least one episode of an unknown ADR occurring at an incidence of 1.0% with a probability of 90%. Judging from the ADR incidences in a previous phase I/II clinical study,[8] and the international double-blind comparative studies,[9,11,13] the sample size of 250 patients was expected to enable the collection of sufficient information on the occurrence of AEs of special interest.

Frequency distribution by category (number and percentage of patients) was obtained for qualitative data, and summary statistics (mean, standard

deviation [SD], median, minimum value, maximum value) were calculated for quantitative data. Factors influencing the incidence of ADRs were identified and analyzed using logistic regression analyses.

Results

A total of 561 patients were registered. Among them, three patients were overlapping as they had transferred to other hospitals and, thus, were excluded from the present analysis. A total of 558 patients were included.

Patient and tumor characteristics

The background characteristics of 558 patients are shown in Table 1. Of the 558 patients, 320 (57.3%) patients were male and 236 (42.3%) patients were female. The median age was 62.0 (range, 16–92) years, and the percentage of elderly patients aged 65 years or older was 41.8% (233/558 patients).

The percentages of newly diagnosed patients and those with recurrence were 61.6% (344/558 patients) and 38.4% (214/558 patients), respectively. The percentages of patients with first, second, third, and fourth or subsequent recurrences were 26.7% (149/558 patients), 6.6% (37/558 patients), 2.7% (15/558 patients), and 2.3% (13/558 patients), respectively. The percentages of patients with solitary and multiple tumors were 85.5% (477/558 patients) and 14.2% (79/558 patients), respectively. The site of the tumor was above the tentorium in 539 (96.6%) and below the tentorium in 21 (3.8%) of the 558 patients. The pathological tissue type was glioblastoma in 422 (75.6%), anaplastic astrocytoma in 42 (7.5%), anaplastic oligodendroglioma in 33 (5.9%), anaplastic oligoastrocytoma in 16 (2.9%), anaplastic ependymoma in 7 (1.3%), other malignant glioma in 16 (2.9%), and tumor other than malignant glioma in 22 (3.9%) patients. These 22 patients consisted of 7 patients of glioma which were classified as Grade II and therefore was regarded as off-label use, 7 patients of primary brain tumor which were not classified as gliomas, and 8 patients which were other than primary brain tumors or which were unclassifiable.

The median and mean tumor excision rates were 95.0% (range, 5%–100%) and 86.9%, respectively. The excision rate was 100% in 149 (26.7%) patients and 95% or higher in 324 (58.1%) patients. Complications were present in 418 (74.9%) patients. The nature of the complications was cerebral edema in 346 (62.0%) patients, hepatic function disorder in 9 (1.6%), renal impairment in 5 (0.9%), and other complications in 212 (38.0%) patients. The median and mean KPS scores immediately before the placement of Gliadel were 80.0 (range, 10–100) and 72.1, respectively. The KPS score was 80–100 in 291 (52.2%) patients and 10–70 in 267 (47.8%) patients.

Gliadel placement

The details of Gliadel placement in patients are shown in Table 2. The majority of patients received eight Gliadel wafers (66.7% [372/558 patients]). The median and mean number of wafers placed was 8 (range, 1–8) and 6.9 (wafers placed in the second operation were not included), respectively. The percentage of patients who underwent a second placement of Gliadel was 0.5% (3/558 patients).

Chemotherapy and radiotherapy after Gliadel placement

Among the newly diagnosed patients, chemotherapy was administered in 86.9% (298/343) of the patients. Among patients with recurrence, chemotherapy was administered in 74.4% (160/215) of the patients. In newly diagnosed patients, the most frequently used antineoplastic drugs were temozolomide (86.3% [296/343 patients]), bevacizumab (3.2% [11/343 patients]), and interferon β (6.1% [21/343]). In patients with recurrence, temozolomide (64.2% [138/215 patients]), bevacizumab (14.4% [31/215 patients]), and interferon β (8.4% [18/215 patients]) were used.

AEs and ADRs

Among the 558 patients, 640 episodes of AEs in 305 (54.7%) patients were reported. A total of 443 episodes of serious AEs were seen in 242 (43.4%) patients. The most common AEs according to system organ class were nervous system disorders (333 episodes in 217 [38.9%] patients), followed by general disorders and administration site conditions (51 episodes in 50 [9.0%] patients), and infections and infestations (55 episodes in 48 [8.6%] patients). According to preferred terms, AEs that occurred with an incidence of 2% or higher were as follows: cerebral edema (143 episodes in 143 [25.6%] patients), convulsion (55 episodes in 55 [9.9%] patients), pyrexia (30 episodes in 30 [5.4%] patients), paralysis of one side of body (26 episodes in 26 [4.7%] patients), impaired healing (16 episodes in 16 [2.9%] patients), hydrocephalus (16 episodes in 16 [2.7%] patients), cerebrospinal fluid leakage (14 episodes in 14 [2.5%] patients), white blood cell count decreased (12 episodes in 12 [2.2%] patients), epilepsy (11 episodes in 11 [2.0%] patients), and headache (11 episodes in 11 [2.0%] patients).

A total of 365 episodes of ADRs in 199 patients were documented, and the percentage of patients with ADRs was 35.7%. A total of 303 episodes of serious ADRs were observed in 177 patients, and the percentage of patients with serious ADRs was

Table 1 Background characteristics

Item	Category	Safety analysis set n	%
Total		558	100.0
Sex	Male	320	57.3
	Female	236	42.3
	Unknown/not recorded	2	0.4
Age (years)	Mean ± SD	59.3 ± 15.3	
	Median (range)	62.0 (16–92)	
	<65	325	58.2
	≥65	233	41.8
Body weight (kg)	Mean ± SD	57.79 ± 12.00	
	Median (range)	56.80 (28.7–98.6)	
First episode/recurrence	First episode	344	61.6
	Recurrence	214	38.4
	1st recurrence	149	26.7
	2nd recurrence	37	6.6
	3rd recurrence	15	2.7
	4th recurrence or more	13	2.3
Tumor excision rate (%)	Mean ± SD	86.9 ± 18.6	
	Median (range)	95.0 (5–100)	
Pathological tissue type	Glioblastoma	422	75.6
	Anaplastic astrocytoma	42	7.5
	Anaplastic oligodendroglioma	33	5.9
	Anaplastic oligoastrocytoma	16	2.9
	Anaplastic ependymoma	7	1.3
	Other malignant glioma	16	2.9
	Other than malignant glioma	22	3.9
WHO classification of central nervous tumor (malignancy classification)	Grade IV	428	76.7
	Grade III	112	20.1
	Grade II	7	1.3
	Not applicable	11	2.0
Type of tumor lesions	Solitary	477	85.5
	Multiple	79	14.2
	Unknown/not recorded	2	0.4
Tumor lesion site	Above the tentorium	539	96.6
	Below the tentorium	21	3.8
	Unknown/not recorded	1	0.2
Complications	Absent	139	24.9
	Present	418	74.9
	Unknown/not recorded	1	0.2
Complication, cerebral edema	Absent	211	37.8
	Present	346	62.0
	Unknown/not recorded	1	0.2

Table 1 (Continued)

Item	Category	Safety analysis set n	%
Complication, renal impairment	Absent	552	98.9
	Present	5	0.9
	Unknown/not recorded	1	0.2
Complication, hepatic function disorder	Absent	548	98.2
	Present	9	1.6
	Unknown/not recorded	1	0.2
Complication, others	Absent	345	61.8
	Present	212	38.0
	Unknown/not recorded	1	0.2
KPS immediately before Gliadel placement	Mean ± SD	72.1 ± 21.2	
	Median (range)	80.0 (10–100)	
	80–100	291	52.2
	10–70	267	47.8

KPS: Karnofsky performance status, SD: standard deviation, WHO: World Health Organization.

Table 2 Status of Gliadel placement

Item	Category	n	%
Total		558	100.0
Number of Gliadel wafers placed	1	4	0.7
	2	15	2.7
	3	24	4.3
	4	33	5.9
	5*	31	5.6
	6	47	8.4
	7	32	5.7
	8	372	66.7
	Mean ± SD	6.9 ± 1.8	
	Median (range)	8.0 (1–8)	
Second placement of Gliadel	Absent	555	99.5
	Present	3	0.5

*The number of Gliadel wafers placed was 4.5 in one patient, but it was counted as 5 in the analysis.
SD: standard deviation.

31.7% (Table 3). The most common ADRs according to System Organ Class were nervous system disorders (253 episodes in 166 [29.7%] patients), followed by general disorders and administration site conditions (36 episodes in 36 [6.5%] patients), and infections and infestations (20 episodes in 19 [3.4%] patients). According to preferred terms, cerebral edema was the most common (124 episodes in 124 [22.2%] patients), followed by convulsion (43 episodes in 43 [7.7%] patients), pyrexia (21 episodes in 21 [3.8%] patients), paralysis of one side of body (17 episodes in 17 [3.0%] patients,), impaired healing (14 episodes in 14 [2.5%] patients), and epilepsy (11 episodes in 11 [2.0%] patients).

Factors influencing the incidence of ADRs

Logistic regression analyses (univariate analysis, multivariate analysis [full model], and multivariate analysis [model selected by backward elimination method, standard for variable reduction $p = 0.2$]) were conducted to examine the influence of the following factors on the incidence of ADRs: sex, age (≥65 and <65 years), body weight, history of allergy, disease history, complication (cerebral edema, renal impairment, hepatic function disorder, and others), classification of disease by first episode/recurrence, excision rate (≥95% and <95%), type of tumor lesions, number of Gliadel wafers placed (continuous volume), KPS score immediately before Gliadel placement (10–70 and 80–100), administration of antineoplastic drugs (temozolomide, bevacizumab, and interferon), and radiotherapy (Table 4). The standard for variable reduction for the backward elimination method in multivariate analysis was set at $p = 0.2$. With the aim of improving sensitivity in detecting the factors influencing the incidence of ADRs, the effects of the variables that remained in the model with this standard were evaluated.

Multivariate analysis (model selected by backward elimination method) revealed that age (odds ratio, 0.743; 95% confidence interval [CI], 0.502–1.101; $p = 0.138$), body weight (odds ratio, 0.988; 95% CI, 0.972–1.003; $p = 0.126$), presence or absence of

Table 3 Adverse drug reactions (ADRs)

	Overall	Serious	Nonserious
Total number of patients surveyed		558	
Number of patients exhibiting ADRs	199	177	44
Number of episodes of ADRs	365	303	62
Percentage of patients exhibiting ADRs	35.7%	31.7%	7.9%
Type of ADRs*	Percentage of patients exhibiting ADRs (number of episodes) according to the type of ADR (%)		
Infections and infestations	19 (3.4)	18 (3.2)	1 (0.2)
Abscess	1 (0.2)	1 (0.2)	–
Brain abscess	2 (0.4)	2 (0.4)	–
Central nervous system ventriculitis	1 (0.2)	1 (0.2)	–
Meningitis	6 (1.1)	6 (1.1)	–
Meningitis bacterial	2 (0.4)	2 (0.4)	–
Wound infection	5 (0.9)	4 (0.7)	1 (0.2)
Serratia infection	1 (0.2)	1 (0.2)	–
Extradural abscess	1 (0.2)	1 (0.2)	–
Pneumocystis jirovecii pneumonia†	1 (0.2)	1 (0.2)	–
Neoplasms benign, malignant, and unspecified (including cysts and polyps)	2 (0.4)	2 (0.4)	–
Tumor hemorrhage	2 (0.4)	2 (0.4)	–
Blood and lymphatic system disorders	2 (0.4)	2 (0.4)	–
Lymphopenia	1 (0.2)	1 (0.2)	–
Neutropenia	1 (0.2)	1 (0.2)	–
Metabolism and nutrition disorders	3 (0.5)	1 (0.2)	2 (0.4)
Hypokalemia†	1 (0.2)	–	1 (0.2)
Hyponatremia	1 (0.2)	–	1 (0.2)
Decreased appetite	1 (0.2)	1 (0.2)	–
Psychiatric disorders	6 (1.1)	2 (0.4)	4 (0.7)
Apathy†	1 (0.2)	1 (0.2)	–
Delirium†	1 (0.2)	1 (0.2)	–
Insomnia	4 (0.7)	–	4 (0.7)
Nervous system disorders	166 (29.7)	159 (28.5)	12 (2.2)
Altered state of consciousness	3 (0.5)	3 (0.5)	–
Aphasia	8 (1.4)	7 (1.3)	1 (0.2)
Cerebral infarction	4 (0.7)	4 (0.7)	–
Cerebrospinal fluid leakage	9 (1.6)	6 (1.1)	3 (0.5)
Convulsion	43 (7.7)	42 (7.5)	1 (0.2)
Depressed level of consciousness	1 (0.2)	1 (0.2)	–
Disturbance in attention†	1 (0.2)	1 (0.2)	–
Dyslalia	1 (0.2)	1 (0.2)	–
Epilepsy	11 (2.0)	10 (1.8)	1 (0.2)
Hemorrhage intracranial	1 (0.2)	1 (0.2)	–
Headache	5 (0.9)	2 (0.4)	3 (0.5)
Paralysis of one side of body	17 (3.0)	17 (3.0)	–

Table 3 (Continued)

	Overall	Serious	Nonserious
Hydrocephalus	7 (1.3)	7 (1.3)	–
Intracranial pressure increased	1 (0.2)	1 (0.2)	–
Paresis	1 (0.2)	1 (0.2)	–
Somnolence	2 (0.4)	2 (0.4)	–
Status epilepticus	1 (0.2)	1 (0.2)	–
Subdural hygroma†	1 (0.2)	1 (0.2)	–
Pneumocephalus†	7 (1.3)	6 (1.1)	1 (0.2)
Cerebral edema	124 (22.2)	124 (22.2)	–
Sixth nerve disorder	1 (0.2)	1 (0.2)	–
Third nerve paresis	1 (0.2)	–	1 (0.2)
Cerebral vasoconstriction†	1 (0.2)	1 (0.2)	–
Cerebral cyst	1 (0.2)	1 (0.2)	–
Cerebrospinal fluid retention	1 (0.2)	–	1 (0.2)
Eye disorders	2 (0.4)	1 (0.2)	1 (0.2)
Eyelid edema	1 (0.2)	–	1 (0.2)
Papilledema	1 (0.2)	1 (0.2)	–
Visual acuity reduced	1 (0.2)	1 (0.2)	–
Vascular disorders	5 (0.9)	4 (0.7)	1 (0.2)
Hypertension	2 (0.4)	1 (0.2)	1 (0.2)
Deep vein thrombosis	3 (0.5)	3 (0.5)	–
Respiratory, thoracic, and mediastinal disorders	2 (0.4)	2 (0.4)	–
Pulmonary embolism	2 (0.4)	2 (0.4)	–
Gastrointestinal disorders	4 (0.7)	1 (0.2)	3 (0.5)
Nausea	3 (0.5)	–	3 (0.5)
Vomiting	1 (0.2)	1 (0.2)	–
Hepatobiliary disorders	1 (0.2)	1 (0.2)	–
Hepatic function abnormal	1 (0.2)	1 (0.2)	–
Skin and subcutaneous tissue disorders	6 (1.1)	1 (0.2)	5 (0.9)
Alopecia†	2 (0.4)	–	2 (0.4)
Rash	1 (0.2)	–	1 (0.2)
Swelling face	1 (0.2)	–	1 (0.2)
Skin edema	1 (0.2)	–	1 (0.2)
Drug reaction with eosinophilia and systemic symptoms†	1 (0.2)	1 (0.2)	–
Renal and urinary disorders	1 (0.2)	–	1 (0.2)
Urinary incontinence	1 (0.2)	–	1 (0.2)
General disorders and administration site conditions	36 (6.5)	20 (3.6)	16 (2.9)
Impaired healing	14 (2.5)	12 (2.2)	2 (0.4)
Pyrexia	21 (3.8)	7 (1.3)	14 (2.5)
Disuse syndrome†	1 (0.2)	1 (0.2)	–
Investigations	7 (1.3)	2 (0.4)	5 (0.9)
Alanine aminotransferase abnormal	1 (0.2)	–	1 (0.2)
Alanine aminotransferase increased	1 (0.2)	–	1 (0.2)

Table 3 (Continued)

	Overall	Serious	Nonserious
Aspartate aminotransferase abnormal	1 (0.2)	–	1 (0.2)
Aspartate aminotransferase increased	1 (0.2)	–	1 (0.2)
Fibrin D dimer increased†	1 (0.2)	–	1 (0.2)
Gamma-glutamyltransferase abnormal	1 (0.2)	–	1 (0.2)
Lymphocyte count decreased	2 (0.4)	–	2 (0.4)
Neutrophil count decreased	2 (0.4)	–	2 (0.4)
Nuclear MRI brain abnormal	1 (0.2)	–	1 (0.2)
White blood cell count decreased	4 (0.7)	2 (0.4)	2 (0.4)
White blood cell count increased	1 (0.2)	–	1 (0.2)
Injury, poisoning, and procedural complications	5 (0.9)	3 (0.5)	2 (0.4)
Wound dehiscence	2 (0.4)	2 (0.4)	–
Wound secretion	1 (0.2)	–	1 (0.2)
Wound complication	1 (0.2)	–	1 (0.2)
Postoperative wound complication	1 (0.2)	1 (0.2)	–

*MedDRA/J version 17.1.
†ADRs that were not expected based on the precautions noted in the current package insert of Gliadel.

history of allergy (odds ratio, 1.645; 95% CI, 0.952–2.845; $p = 0.075$), complication of cerebral edema (odds ratio, 1.707; 95% CI, 1.164–2.503; $p = 0.006$), and complications (others) (odds ratio, 1.716; 95% CI, 1.179–2.498; $p = 0.005$) were factors associated with the incidence of ADRs.

AEs of special interest

After collecting case report forms, it was evaluated whether each AE truly corresponded to the category for AEs of special interest or not.

Cerebral edema

In total, 124 episodes of cerebral edema in 124 (22.2%) patients were considered ADRs (Table 5). The CTCAE Grade was Grade 1 in 26 patients, Grade 2 in 61 patients, Grade 3 in 27 patients, and Grade 4 in 11 patients. There was no occurrence of Grade 5 cerebral edema.

Multivariate analysis of various complications showed that cerebral edema was a significant complication in 536 (odds ratio 3.016, 95% CI 1.828–4.976; $p < 0.0001$) of the 558 patients (Table 6). Factors associated with the incidence of cerebral edema were paralysis of one side of body, epilepsy, cerebral edema, and liver dysfunction before treatment.

Convulsion

Fifty-five episodes of convulsion (including epilepsy and status epilepticus) in 55 (9.9%, 55/558) patients were considered ADRs (Table 3). The CTCAE Grade was Grade 1 in 17 patients, Grade 2 in 23 patients, Grade 3 in 14 patients, and Grade 4 in 1 patient. There was no occurrence of Grade 5 convulsion.

Impaired healing

Twenty-nine episodes of impaired healing (including cerebrospinal fluid leakage, cerebrospinal fluid retention, wound dehiscence, wound secretion, wound complication, and postoperative wound complication) in 27 (4.8%, 27/558) patients were considered ADRs (Table 3). The CTCAE Grade was Grade 1 in 5 episodes in 5 patients, Grade 2 in 5 episodes in 5 patients, Grade 3 in 16 episodes in 14 patients, and Grade 4 in 3 episodes in 3 patients. There was no occurrence of Grade 5 impaired healing.

Infection

Twenty episodes of infection in 19 (3.4%, 19/558) patients were considered ADRs. The CTCAE Grade was Grade 2 in 2 episodes in 2 patients, Grade 3 in 14 episodes in 14 patients, and Grade 4 in 4 episodes in 3 patients. There was no occurrence of Grade 1 or Grade 5 infections.

Hydrocephalus

Seven episodes of hydrocephalus in seven (1.3%, 7/558) patients were considered ADRs. The CTCAE Grade was Grade 3 in six patients and Grade 4 in

Table 4 Logistic regression analyses of factors that influenced the incidence of ADRs

Background factor	Category	Number of cases examined	Number of cases with onset	Percentage of cases with onset (%)	Univariate model			Multivariate (full model)			Multivariate (final model) (backward elimination method: p <0.2)		
					OR	95% CI	p-value	OR	95% CI	p-value	OR	95% CI	p-value
Sex	Female	236	88	37.3	–	–	–						
	Male	320	111	34.7	0.893	0.629–1.268	0.527	1.135	0.724–1.777	0.581			
Age (years)	<65	325	119	36.6	–	–	–						
	≥65	233	80	34.3	0.905	0.636–1.287	0.579	0.714	0.462–1.103	0.129	0.743	0.502–1.101	0.138
Body weight*					0.990	0.976–1.005	0.191	0.984	0.965–1.004	0.108	0.988	0.972–1.003	0.126
History of allergy	Absent	485	166	34.2	–	–	–						
	Present	64	31	48.4	1.805	1.068–3.051	0.027	1.586	0.901–2.791	0.110	1.645	0.952–2.845	0.075
Disease history	Absent	375	130	34.7	–	–	–						
	Present	176	67	38.1	1.158	0.799–1.679	0.437	1.097	0.731–1.645	0.656			
Complication, cerebral edema	Absent	211	60	28.4	–	–	–						
	Present	346	139	40.2	1.690	1.169–2.442	0.005	1.732	1.165–2.575	0.007	1.707	1.164–2.503	0.006
Complication, renal impairment	Absent	552	198	35.9	–	–	–						
	Present	5	1	20.0	0.447	0.050–4.027	0.473	0.395	0.043–3.624	0.411			
Complication, hepatic function disorder	Absent	548	193	35.2	–								
	Present	9	6	66.7	3.676	0.909–14.858	0.068	2.777	0.641–12.028	0.172			
Complication, others	Absent	345	108	31.3	–	–	–						
	Present	212	91	42.9	1.650	1.158–2.353	0.006	1.729	1.178–2.539	0.005	1.716	1.179–2.498	0.005
First episode/ recurrence classification	First episode	343	120	35.0	–	–	–						
	Recurrence	215	79	36.7	1.079	0.757–1.540	0.673	0.855	0.487–1.501	0.586			
Excision rate	≥95%	324	111	34.3	–	–	–						
	<95%	233	88	37.8	1.165	0.820–1.653	0.394	1.242	0.846–1.821	0.268			
Type of tumor lesions	Solitary	477	169	35.4	–	–	–						
	Multiple	79	29	36.7	1.057	0.645–1.734	0.825	0.895	0.525–1.525	0.682			
Number of Gliadel wafers placed†					0.968	0.878–1.066	0.507	0.954	0.857–1.061	0.386			
KPS immediately before Gliadel placement	80–100	291	105	36.1	–	–	–						
	10–70	267	94	35.2	0.963	0.680–1.362	0.829	0.858	0.574–1.282	0.455			
Concomitant administration of temozolomide for malignant glioma	Absent	123	46	37.4	–	–	–						
	Present	434	153	35.3	0.911	0.602–1.380	0.661	0.983	0.603–1.601	0.944			

Table 4 (Continued)

Background factor	Category	Number of cases examined	Number of cases with onset	Percentage of cases with onset (%)	Univariate model			Multivariate (full model)			Multivariate (final model) (backward elimination method: $p<0.2$)		
					OR	95% CI	*p*-value	OR	95% CI	*p*-value	OR	95% CI	*p*-value
Concomitant administration of bevacizumab for malignant glioma	Absent	515	180	35.0	–	–	–						
	Present	42	19	45.2	1.537	0.816–2.898	0.184	1.430	0.717–2.852	0.309			
Concomitant administration of IFN for malignant glioma	Absent	518	187	36.1	–	–	–						
	Present	39	12	30.8	0.787	0.389–1.589	0.504	0.775	0.354–1.696	0.524			
Concomitant radiotherapy for malignant glioma	Absent	221	81	36.7	–	–	–						
	Present	336	118	35.1	0.935	0.657–1.332	0.711	0.872	0.506–1.504	0.623			

*Body weight is expressed as the value estimated for increases by 1 kg.
†The number of Gliadel wafers placed is expressed as the value estimated for increases by one wafer each.
ADRs: adverse drug reactions, CI: confidence interval, IFN: interferon, KPS: Karnofsky performance status, OR: odds ratio.

one patient. There was no occurrence of Grade 1, Grade 2, or Grade 5 hydrocephalus.

Discussion

This is the first all-case postmarketing surveillance report of the safety of Gliadel for malignant glioma in a large number of patients in real-world clinical practice in Japan. In this postmarketing surveillance study, we collected a wide variety of patients who were not included in the local phase I/II study in Japan, such as the elderly aged 65 years or older, patients with a low tumor resection rate, and patients with a lower KPS. Cerebral edema was the most common AE (25.6%; 143/558 patients) and ADR (22.2%, 124/558 patients). A similar incidence of cerebral edema was reported in the phase I/II study in Japan (25%, 6/24 patients).[8]

The integrated analysis of the international double-blind comparative studies (Gliadel arm, respectively[9,11,13]) indicated the incidence of cerebral edema as ADR was 4.9% (12/246 patients).[14] Compared with the result of this analysis, cerebral edema as ADR was more frequently observed in this study and the local phase I/II study. As possible reasons, we infer that clinical practice differs among countries and the timing of each study was different as well. In multiple therapeutic environments, it was likely that the frequency of diagnostic imaging performed after the placement of Gliadel became diverse. Therefore, capability to detect cerebral edema was possibly different.

We found patients with duplicated occurrence of the following major AEs: out of patients with impaired healing, approximately 30% developed infection; out of patients with cerebral edema, approximately 20% developed convulsion, and 3% developed epilepsy (data on file, respectively). A causal relationship among those AEs could be suggested to some extent; however, further investigation will be needed to make a judgment with reference to such as results of ongoing prospective studies.

Regarding serious ADRs of special interest in our study, each serious ADR other than cerebral edema was not relatively high (cerebral edema [22.2%, 124/558], convulsion [9.5%, 53/558], impaired healing [3.8%, 21/558], infection [3.2%, 18/558], and hydrocephalus [1.3%, 7/558]), and the CTCAE Grade was predominantly less than Grade 3 (data not shown).

In multivariate analysis, cerebral edema was a significant complication in 536 of the 558 patients included. Further, paralysis of one side of body, epilepsy, cerebral edema, and liver dysfunction

Table 5 Occurrence of cerebral edema as an adverse event of special interest

	Overall	CTCAE grade*				
		Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Number of patients surveyed				558		
Number of patients exhibiting cerebral edema	124	25	61	27	11	0
Number of episodes of cerebral edema	124	26	61	27	11	0
Percentage of patients exhibiting cerebral edema	22.2%	4.7%	10.9%	4.8%	2.0%	0.0%
Type of cerebral edema†	Percentage (%) of patients exhibiting cerebral edema (ADR) as an adverse event of special interest (number of episodes) according to the type					
Nervous system disorders	124 (22.2)	26 (4.7)	61 (10.9)	27 (4.8)	11 (2.0)	-
Cerebral edema	124 (22.2)	26 (4.7)	61 (10.9)	27 (4.8)	11 (2.0)	-

*CTCAE v4.0-JCOG, numbers of patients were counted for each grade.
†MedDRA/J version 17.1.
ADR: adverse drug reaction, CTCAE: common terminology criteria for adverse events.

Table 6 Multivariate analysis of various complications (n = 536)

Explanatory variables (comparison group vs reference group) (yes vs no)	Parameter estimated value (b)	Standard error of (b)	Chi-square test	*p*-value	OR	95% CI
Intercept	−1.7020	0.2778	37.5342	<0.0001	–	–
Cerebral edema	1.1038	0.2555	18.6576	<0.0001	3.016	1.828–4.976
Liver dysfunction	1.6093	0.7784	4.2738	0.0387	4.999	1.087–22.988
Epilepsy	0.7707	0.3505	4.8357	0.0279	2.161	1.087–4.296
Paralysis of one side of body	1.4847	0.6541	5.1517	0.0232	4.414	1.225–15.907
Combination with temozolomide for malignant glioma	−0.4961	0.2559	3.7563	0.0526	0.609	0.369–1.006
Combination with interferon for malignant glioma	−0.8891	0.5816	2.3375	0.1263	0.411	0.131–1.285

CI: confidence interval, OR: odds ratio.

before treatment were identified as factors influencing the postoperative development of cerebral edema. Large brain tumors could cause paralysis of one side of body as well as cerebral edema. Liver failure/disease can induce hepatic encephalopathy. Hepatic encephalopathy is characterized by swelling of the astrocytes, which consequently leads to cerebral edema. Thus, cerebral edema is also a common feature of patients with acute liver failure.[15,16] Although Gliadel wafers may be the main trigger of cerebral edema in the cases reported herein, it is possible that cerebral edema is a direct effect of tumor resection surgery or a result of underlying patient conditions and comorbidities.

The international phase III study,[9] to which we referred in planning our study, reported that the profile of AEs was similar for Gliadel arm and placebo arm. Cerebral edema as AE in Gliadel arm was 22.5% (27/120). That was numerically comparable with that of our study (25.6%), but might be never lower than our result. Subjects of the international study were the primary malignant glioma who underwent primary surgical resection. All of them had a KPS score of 60 or higher, mean age in Gliadel arm was 52.6 years, and patients with prior cytoreductive therapy were excluded from the eligibility criteria. It suggests that those patients are probably in relatively good general conditions. On the other hand, approximately 40% patients of the baseline in this study were recurrences. Additionally, 62% (346/558) had a history of cerebral edema complication. Considering patient background and

possible treatment or complication history comprehensively, it may be difficult to infer that AEs after Gliadel placement are particularly high in Japanese patients.

The findings of the present study indicate that the occurrence of cerebral edema was the most frequent among Japanese patients. Although the causes for this difference are unclear, Japanese patients undergoing Gliadel implantation should be monitored carefully to detect the onset of edema and administer prompt treatment. This finding is important for managing Gliadel implantations in Japanese patients with malignant glioma. Still, the overall safety profile of Gliadel was consistent with that reported previously for Japanese patients[8] as well as those in the US and Europe.[9,13]

The main limitation of this study was the heterogeneity of treatment, particularly of patients with recurrent disease. Other limitations of this study were the limited generalizability to other ethnic populations, lack of a comparator group, and other limitations inherent to postmarketing surveillance studies. The main strength of this study was the evaluation of the safety of Gliadel in a real-world clinical setting in a large sample of patients with heterogeneous baseline characteristics, regardless of age and presence of complications.

Conclusions

The results of this postmarketing study suggest that the risk of toxicity during Gliadel treatment is mostly manageable for Japanese patients with malignant glioma. Cerebral edema was the most common AE; however, no new safety concerns were detected. Paralysis of one side of body, epilepsy, cerebral edema, and liver dysfunction before treatment were identified as factors influencing the incidence of postoperative cerebral edema.

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Conflicts of Interest Disclosure

Dr. Ryo Nishikawa has received a manuscript fee from Eisai Co., Ltd. All authors, except Dr. Ryo Nishikawa, are employees of Eisai Co., Ltd. The study sponsor, Eisai Co., Ltd, was involved in the study design; in the collection, analysis, and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication.

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