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Clinical Analysis for Brain Tumor-Related Epilepsy during Chemotherapy for Systemic Cancer with Single Brain Metastasis

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Purpose
The purpose of this prospective observational study was to determine the incidence, patterns, and predisposing factors for brain tumor-related epilepsy (BTRE) during chemotherapy for systemic cancer with single brain metastasis (BM).

Materials and Methods
Between February 2006 and June 2010, 103 patients who underwent chemotherapy for systemic cancer with single BM were enrolled. We compared the clinical factors of patients and BM between patients with and without BTRE. We determined the number of patients with BTRE attacks, and seizure-free survival according to the following comparative groups: presence vs. absence of a history of BTRE; high-risk vs. low-risk groups; and presence vs. absence of disease-progression of BM.

Results
Ninety-three of 103 patients (90.3%) remained seizure-free during chemotherapy. The seizure-free rates were 88.9% and 91.0% among patients with or without a history of BTRE, respectively (p=0.694), 87.8% and 92.6% among high- and low-risk patients (p=0.427), respectively, and 62.5% and 98.7% among patients with or without disease-progression of BM (p=0.001), retrospectively. Based on multivariate analysis, the significance of abnormal findings on electroencephalogram (EEG) (p=0.017), and the absence of disease-progression of BM (p=0.001) had an association with seizure-free survival.

Conclusion
The significance of abnormal findings on EEG, and disease-progression of BM play important roles in the development of BTRE during chemotherapy for systemic cancer with BM.

Key words
Brain neoplasms, Metastasis, Epilepsy, Chemotherapy, Pharmacology

Introduction

The incidence of brain tumors among those with epilepsy is approximately 4% [1]. Conversely, the frequency of epilepsy is ≥30% among patients with brain tumors, although this depends on the tumor type [2]. In 30-50% of patients with brain tumors, epileptic seizures are the presenting symptom, and an additional 10-30% of patients will develop seizures later during the course of the disease [1,3,4]. Furthermore, epilepsy has been reported in > 80% of patients with low-grade gliomas (World Health Organization grade 2) [5], 30-60% of patients with high-grade gliomas [6], up to 40% of patients with meningiomas [7], and approximately 20% of patients with primary central nervous system lymphomas [8]. In fact, approximately 25% of patients with brain metastases (BMs) have seizures and 10% of those patients complain of seizures as the presenting symptom [3,9].

Brain tumor-related epilepsy (BTRE), especially in systemic cancer patients, has a significant impact on the quality of life. BTRE interferes with driving and working, reduces independence, increases anxiety, and generates depression [10]. Furthermore, BTRE are often drug-resistant [11]. The resistance of patients with BTRE to anti-epileptic drugs (AEDs) probably reflects different pathophysiologic mechanisms, such as those affecting peritumoral brain

tissue morphology, pH, ion levels, and amino acid changes, and different pharmacologic interactions [11]. Although the frequencies of seizures can be effectively reduced by administrating AEDs, these agents can create a host of new problems. For example, AEDs can interact with corticosteroid metabolism [4,12], reduce the efficacies of a variety of chemotherapeutic agents [13], and cause side effects more frequently than epileptic patients without brain tumors [3].

During systemic chemotherapy, drug interactions are a primary concern because the majority of chemotherapeutics have a narrow therapeutic index. Therefore, careful and proactive planning is required to achieve adequate chemotherapeutic dosing without inducing toxicity in patients with BTRE. Furthermore, chemotherapeutics can also accelerate AED metabolism, and prevent seizure control during chemotherapy.

However, some of the newer AEDs are not metabolized or metabolized to a lesser degree by the cytochrome P450 isoenzyme, which may substantially reduce the risks of drug interactions. However, despite the more favorable pharmacokinetic profiles of recently introduced AEDs, little clinical information is available regarding the effects of these drugs in patients with brain tumors or concerning potential interactions between these agents and many chemotherapeutics. Topiramate, one of the recently developed AEDs, is interesting from a pharmacokinetic standpoint because topiramate induces the cytochrome P450 isoenzyme only at low levels, and this is associated with lower pharmacologic interactions [14].

In the present study during systemic chemotherapy of BM we examined the incidence and patterns of BTRE, and compared the clinical characteristics of patients and features of BM between patients who did and did not have a BTRE. Additionally, we investigated the predisposing factors for development of a BTRE in BM patients, and analyzed the factors influencing seizure-free survivals during systemic chemotherapy of BM.

Materials and Methods

1 Study population

This prospective observational study involved 103 patients who were recruited between February 2006 and June 2010. All patients underwent chemotherapy for systemic cancer with single BM and concomitant topiramate as an AED at our institute, and met the following inclusion criteria: 1) age > 20 years; 2) diagnosis made by surgical intervention or magnetic resonance imaging (MRI) of the brain; 3) abnormal electroencephalographic findings; 4) BM located in the supratentorial area; and 5) single BM. Patients with a history of prolonged seizures before the diagnosis of BM, a history of medically-intractable seizures, contraindication to topiramate administration (such as, a renal stone or dementia, or systemic chemotherapy), or a normal finding on electroencephalogram (EEG) without seizures before chemotherapy were excluded. A radiologic review was undertaken to diagnose a single BM by two neuroradiologists (S.Y.G. and L.H.Y.). Single BM was defined as one metastatic lesion to the brain without considering extracranial metastases. A MRI was performed using a 1.5 T clinical scanner (Signa Horizon, GE Healthcare, Milwaukee, WI).

The purpose of the study was explained to patients and their families prior to enrollment. The local ethical committee at our institute approved the study protocol (MSH-2006-010).

2 Initial treatment of brain metastasis

Surgical resection was considered in the following conditions: 1) new onset of neurological deficits; 2) large mass with mass effect or severe peritumoral edema; 3) presence of tumor bleeding; 4) presence of increased intracranial pressure; and 5) surgically accessible location. Radiotherapy was considered in patients with deeply-located BM which led to the new onset of neurologic symptoms. In patients with a BM of small size and no neurologic symptoms, we started systemic chemotherapy for primary cancer.

3 Evaluation before chemotherapy

Adequate hematologic, renal, and hepatic functions were determined using blood samples and defined as follows: absolute granulocyte count, > 1,500/dL; white blood cell count, > 4,000/dL; platelet count, > 100,000/dL; total bilirubin level, < 1.8 mg/dL; transaminase level, < 2.5 times the upper limit of normal; and creatinine concentration, ≥ 60 mL/m^2/1.73.

Patients scheduled to undergo chemotherapy for systemic cancer with single BM underwent EEG. EEG was performed using gold cup electrodes directly applied to the scalp, and located according to the international 10-20 system. Skin impedance was maintained at < 5 KΩ. Outputs were recorded from the following locations: left and right frontal-mastoid (FP1-A1 and FP2-A2 [channels 1 and 2]), left and right frontal-CZ (FP1-CZ and FP2-CZ [channels 3 and 4]), plus a ground electrode placed at the center of the forehead. EEGs were recorded using a portable Aspect A-1000 EEG monitor (Aspect Medical System, Inc., Natick, MA). The importance of EEG abnormalities was categorized according to severity and specificity: significance I abnormality, intermittent generalized slowing; significance II abnormality, intermittent regional slowing; and significance III abnormality, spike waves or continuous generalized or regional slowing [15]. The higher the level of significance of the EEG abnormality, the more frequent seizures occur.

The presence of cognitive impairment was determined before every cycle using the Mini-Mental State Examination (MMSE), which involves repeating lists of words, arithmetic, language use and comprehension, and basic motor skills [16].

Functional status was determined using the Karnofsky Performance Scale (KPS) according to which patients with a score ≥ 70

are deemed to be capable of self-care, and patients with a score < 70 are considered to require assistance to conduct the activities of daily life [17].

4 Evaluation during systemic chemotherapy

Blood samples, MMSE, and KPS were checked before every cycle in patients who underwent cyclic chemotherapy, whereas examinations were performed monthly in patients on continuous chemotherapy.

When a seizure occurred, we attempted to perform brain computed tomography scans and obtained blood samples in order to determine the metabolic origin of the seizure. Seizure type, frequency, time of the attack, and the total number of seizures were documented. Seizure types were defined according to the scheme proposed by the International League against Epilepsy in 1981 [18]. Data concerning seizures, such as auras, ictal patterns, ictal duration, postictal amnesia, and postictal neurologic sequelae, were gathered from the clinical notes which were recorded by the patients or family members. The frequency of seizures during chemotherapy was calculated by summing seizures from the start of chemotherapy to the completion of chemotherapy.

The severity of side effects produced by topiramate was evaluated using the "Common Terminology Criteria for Adverse Events (CTCAE)" [19]. Topiramate was switched to another AED at grade 4 toxicity.

5 AED application and titration

If an abnormal signal was observed by EEG, even in patients who did not have a history of BTRE, topiramate was started at 50 mg/day 2 weeks before chemotherapy. In patients who were already taking another AED, AEDs were switched to topiramate at an initial dose of 50 mg/day 2 weeks before chemotherapy. Topiramate was increased to 100 mg/day at the start of chemotherapy. Thereafter, topiramate was adjusted according to response using weekly increments of 25 mg/day to a maximum allowable dose of 400 mg/day. When seizures occurred, add-on AEDs, such as levetiracetam, were considered. During follow-up, blood samples were collected monthly for hematotoxicity evaluation. All patients enrolled in this study underwent chemotherapy for systemic cancer with single BM and concomitant topiramate for ≥ 3 months.

6 Analyses of BTRE

We analyzed the total number of seizures, seizure-free rates, and seizure-free survival during chemotherapy. One hundred three patients were examined for BTRE patterns. In additionally, we compared BTRE patterns in the following subgroups: 1) patients who did and did not have a history of seizures before chemotherapy; 2) patients with or without a BTRE risk factor; and 3) patients with or without disease-progression of BM.

Risk factors of BTRE were taken from the review by Beaumont and Whittle [20]. The following locations have the lowest BTRE thresholds: limbic and temporal lobe; the perirolandic primary motor and primary somatic sensory cortices; the frontal parasagittal region of the supplementary motor area; and the opercula and insula regions of the secondary somatic sensory areas. Therefore, we classified patients with BM which was located in an area of the lowest BTRE threshold as "high risk;" all other patients were categorized as "low risk."

Disease-progression of BM was defined as follows: 1) in the case of surgical resection for BM, the appearance of a new enhancing lesion at a remote or original site from the brain tumor bed, or at least a 25% increase in the product of the two largest perpendicular diameters of the residual BM; 2) in the case of radiotherapy or front systemic chemotherapy for BM, the appearance of a new enhancing lesion at a remote site from the original BM, or at least a 25% increase in the product of the two largest perpendicular diameters of the original BM.

7 Statistical analysis

Discrete variables were compared using a chi-square test or Fisher's exact test and continuous variables were compared using a Student's t-test. Seizure-free survival was determined using the Kaplan-Meier method. The log-rank test and Cox regression analysis was used to examine the association between the variables and seizure-free survival. Univariate analysis was used to determine the effects of age, gender, KPS score, significance of abnormal EEG findings, previous history of seizures, histopathology of primary cancer, location of brain tumor, therapeutic modality for primary cancer, and disease-progression of BM. Variables that were significantly associated with seizure-free survival based on univariate analysis were subjected to multivariate analysis. Differences were regarded significant when the probability values were < 0.05. Statistical analyses were performed using SPSS ver. 12.0 (SPSS Inc., Chicago, IL).

Results

Table 1 shows patient clinical characteristics before systemic chemotherapy with concomitant topiramate and Table 2 illustrates the characteristics of single brain metastasis. Between February 2006 and June 2010, 103 patients that met the inclusion criteria constituted the study cohort. There were 64 men and 39 women with an overall mean age of 60.8 years (range, 22 to 79 years). With a median follow-up of 8.7 months (range, 3.2 to 15.8 months), 10 patients (9.7%) had BTRE attacks.

Table 1. Clinical characteristics of the patients (n=103)

	Total (n=103)	Patients with BTRE (n=10)	Patients without BTRE (n=93)	p-value
Mean age (range, yr)	60.8 (22-79)	64.4 (37-79)	60.4 (22-76)	0.043[a]
Gender				0.137[b]
Male	64 (62.1)	7 (70.0)	57 (61.3)	
Female	39 (37.9)	3 (30.0)	36 (38.7)	
History of seizure				0.337[b]
Presence	36 (35.0)	4 (40.0)	32 (34.4)	
Absence	67 (65.0)	6 (60.0)	61 (65.6)	
KPS score				0.318[b]
100-90	68 (66.0)	6 (60.0)	62 (66.7)	
80-70	27 (26.2)	2 (20.0)	25 (26.9)	
≤60	8 (7.8)	2 (20.0)	6 (6.4)	
Abnormality of EEG				0.019[b]
Significance I	53 (51.4)	3 (30.0)	50 (53.8)	
Significance II	29 (28.2)	1 (10.0)	28 (30.1)	
Significance III	21 (20.4)	6 (60.0)	15 (16.1)	
Mean MMSE (range)	24.4 (12-30)	22.7 (12-30)	24.6 (17-30)	0.227[a]
Extracranial metastasis				0.108[b]
0	38 (36.9)	2 (20.0)	36 (38.7)	
1	43 (41.7)	5 (50.0)	38 (36.9)	
≥2	22 (21.4)	3 (30.0)	19 (18.4)	

Values are presented as number (%). BTRE, brain tumor related epilepsy; KPS, Karnofsky Performance Scale; EEG, electroencephalogram; MMSE, Mini-Mental State Examination. [a]Student's t-test, [b]Fisher's exact test.

Table 2. Characteristics of single brain metastases (n=103)

	Total (n=103)	Patients with BTRE (n=10)	Patients without BTRE (n=93)	p-value[a]
Histology of primary cancer				<0.05
Non-small cell lung cancer	67 (65.1)	7 (70.0)	60 (64.5)	
Small cell lung cancer	6 (5.8)	1 (10.0)	5 (5.4)	
Renal cell carcinoma	9 (8.7)	1 (10.0)	8 (8.6)	
Hepatocellular carcinoma	7 (6.8)	0 (0.0)	7 (7.5)	
Colorectal cancer	5 (4.9)	0 (0.0)	5 (5.4)	
Breast cancer	3 (2.9)	0 (0.0)	3 (3.2)	
Others	6 (5.8)	1 (10.0)	5 (5.4)	
Main location of tumors				<0.05
Frontal lobe	24 (23.3)	2 (20.0)	22 (23.7)	
Non-motor cortex	15 (14.6)	1 (10.0)	14 (15.1)	
Motor cortex	9 (8.7)	1 (10.0)	8 (8.6)	
Temporal and limbic lobe	31 (30.1)	4 (40.0)	27 (29.0)	
Parietal lobe	16 (15.5)	2 (20.0)	14 (15.1)	
Non-sensory cortex	7 (6.8)	1 (10.0)	6 (6.5)	
Sensory cortex	9 (8.7)	1 (10.0)	8 (8.6)	
Occipital lobe	3 (2.9)	0 (0.0)	3 (3.2)	
Deep locations	29 (28.2)	2 (20.0)	27 (29.0)	
Therapeutic modality				<0.05
Radiosurgery	33 (32.0)	3 (30.0)	30 (32.3)	
Fractionated stereotactic radiotherapy	4 (3.9)	0 (0.0)	4 (4.3)	
Whole brain radiotherapy	5 (4.9)	1 (10.0)	4 (4.3)	
Surgical resection	51 (49.5)	5 (50.0)	46 (49.5)	
None	10 (9.7)	1 (10.0)	9 (9.6)	

Values are presented as number (%). BTRE, brain tumor related epilepsy. [a]Fisher's exact test.

Table 3. Clinical characteristics of patients before systemic chemotherapy according to each comparative group (n=103)

	Previous seizure history		Risk group		Disease-progression of BM	
	Absence	Presence	Low risk	High risk	Presence	Absence
No. of patients	67 (65.0)	36 (35.0)	54 (52.4)	49 (47.6)	24 (23.3)	79 (76.7)
Mean age (range, yr)	62.1 (22-79)	58.4 (25-76)	60.4 (22-75)	61.2 (25-79)	64.8[a] (25-79)	59.6[a] (22-76)
Gender						
Male	40 (59.7)	24 (66.7)	33 (61.1)	32 (65.3)	16 (66.7)	48 (60.8)
Female	27 (40.3)	12 (33.3)	21 (38.9)	17 (34.7)	8 (33.3)	31 (39.2)
KPS						
100-90	44 (65.7)	24 (66.7)	31 (57.4)	31 (63.3)	15 (62.5)	53 (67.1)
80-70	18 (26.9)	9 (25.0)	13 (24.1)	13 (26.5)	5 (20.8)	22 (27.8)
≤60	5 (7.5)	3 (8.3)	5 (9.3)	4 (8.2)	4 (16.7)[a]	4 (5.1)[a]
Abnormality of EEG						
Significance I	48 (71.6)[a]	5 (13.8)[a]	41 (75.9)[a]	12 (22.4)[a]	11 (45.8)	42 (53.2)
Significance II	12 (18.0)[a]	17 (47.2)[a]	12 (22.2)[a]	19 (38.8)[a]	8 (33.3)	21 (26.6)
Significance III	7 (10.4)[a]	14 (38.9)[a]	1 (1.9)[a]	18 (36.7)[a]	5 (20.8)	16 (20.3)
Mean MMSE (range)	24.9 (15-30)	23.4 (12-30)	24.6 (15-30)	23.9 (12-30)	22.3 (12-30)	24.8 (17-30)
Extracranial metastasis						
0	23 (34.3)	15 (41.7)	20 (37.0)	18 (36.7)	8 (33.3)	30 (40.0)
1	29 (43.3)	14 (38.9)	21 (38.9)	22 (44.9)	9 (37.5)	34 (43.0)
≥2	15 (22.4)	7 (19.4)	13 (24.1)	9 (18.4)	7 (29.2)	15 (19.0)

Values are presented as number (%). BM, brain metastasis; KPS, Karnofsky performance scale; EEG, electroencephalogram; MMSE, Mini-Mental State Examination. [a]Those variables have statistically significant difference ($p < 0.05$).

The overall seizure-free rate was 90.3%. Thirty-six patients (35.0%) had brain tumors associated with a history of seizures, while 67 patients (65.0%) did not have brain tumors associated with a history of seizures.

1 Previous history of BTRE: presence vs. absence

Thirty-six patients (35.0%) had a history of BTRE. No statistical difference was observed between the two subgroups with respect to age, gender, KPS score, and MMSE. However, by EEG those without a history of BTRE had more significance I abnormalities (71.6% vs. 13.8%, $p < 0.05$). In contrast, patients with a history of BTRE had more significance II or III abnormalities (86.2% vs. 28.4%, $p < 0.05$). Table 3 details clinical characteristics before systemic chemotherapy according to a history of BTRE.

Patients with a BTRE history had more BMs located in the motor cortex of the frontal lobe (19.4% vs. 3.0%, $p < 0.05$) and in the temporal limbic lobe (41.7% vs. 23.9%, $p < 0.05$) than those without a BTRE history. In contrast, patients without a BTRE history had more BMs located in the non-motor cortex of the frontal lobe and deep brain (17.9% vs. 8.3%, $p < 0.05$). Table 4 summaries BM features according to BTRE history.

In the log-rank test and Kaplan-Meier method, because the seizure-free survival period in patients with or without a history of BTRE did not reach the median value, we could not calculate the median time to seizure attack, and no statistical difference was detected (p=0.694).

The median duration of follow-up duration was 9.2 months (range, 3.2 to 15.1 months) in patients with a history of BTRE and 8.6 months (range, 3.4 to 15.8 months) in patients without a history of BTRE ($p > 0.05$). Fig. 1 shows the seizure-free survival curve in the two groups of patients.

2 Risk of BTRE: high- vs. low-risk

Forty-nine patients (47.6%) were included in the high-risk group and 54 patients (52.4%) were in the low-risk group. These two groups were similar in with respect to a BTRE history, and non-significantly different in terms of age, gender, KPS score, and MMSE. However, on EEG patients in the low-risk group had more significance I abnormalities than patients in the high-risk group (75.9% vs. 22.4%, $p < 0.05$). In contrast, patients in the high-risk group had more significance II and III abnormalities (75.5% vs. 24.1%, $p < 0.05$). Table 3 details the clinical characteristics of patients before systemic chemotherapy according to BTRE risk.

Differences were expected between these two risk groups in terms of BM features because the group allocations were made using BM features. With respect to therapeutic modality for BM, there was no significant difference between the two groups ($p > 0.05$). Table 4 summarizes brain tumor features according to BTRE risk.

Also, the seizure-free survival period in the two groups did not reach a median value in the log-rank test. There was no statistical

Table 4. Features of single brain metastases according to each comparative group (n=103)

	Seizure history		Risk group		Disease-progression of BM	
	Absence	Presence	Low risk	High risk	Presence	Absence
No. of patients	67 (65.0)	36 (35.0)	54 (52.4)	49 (47.6)	24 (23.3)	79 (76.7)
Histology of primary cancer						
Non-small cell lung cancer	42 (62.7)	25 (69.4)	36 (66.7)	31 (63.3)	17 (70.8)	50 (63.3)
Other cancer	25 (37.3)	11 (30.6)	18 (33.3)	18 (36.7)	7 (29.2)	29 (36.7)
Main location of tumors						
Frontal lobe	14 (20.9)	10 (27.8)	15 (27.8)	9 (18.4)	5 (20.8)	19 (24.1)
Non-motor cortex	12 (17.9)[a]	3 (8.3)[a]	15 (27.8)[a]	0 (0.0)[a]	3 (12.5)	12 (15.2)
Motor cortex	2 (3.0)[a]	7 (19.4)[a]	0 (0.0)[a]	9 (18.4)[a]	2 (8.3)	7 (8.9)
Temporal and Limbic lobe	16 (23.9)[a]	15 (41.7)[a]	0 (0.0)[a]	31 (63.3)[a]	8 (33.3)	23 (29.1)
Parietal lobe	10 (15.0)	6 (16.7)	7 (13.0)	9 (18.4)	4 (16.7)	12 (15.2)
Non-sensory cortex	4 (6.0)	3 (8.3)	7 (13.0)[a]	0 (0.0)[a]	2 (8.3)	5 (6.3)
Sensory cortex	6 (9.0)	3 (8.3)	0 (0.0)[a]	9 (18.4)[a]	2 (8.3)	7 (8.9)
Occipital lobe	3 (4.5)	0 (0.0)	3 (5.6)[a]	0 (0.0)[a]	1 (4.2)	2 (2.5)
Deep locations	24 (35.8)[a]	5 (13.9)[a]	29 (53.7)[a]	0 (0.0)[a]	6 (25.0)	23 (29.1)
Surgical intervention						
Radiosurgery	23 (34.3)	10 (27.8)	17 (29.8)	16 (32.7)	7 (29.2)	26 (32.9)
Fractionated stereotactic radiotherapy	3 (4.5)	1 (2.8)	2 (3.7)	2 (4.1)	0 (0.0)	4 (5.1)
Whole brain radiotherapy	3 (4.5)	2 (5.6)	2 (3.7)	3 (6.1)	1 (4.2)	4 (5.1)
Surgical resection	31 (46.3)	20 (55.5)	27 (50.0)	24 (49.0)	13 (54.2)	38 (48.1)
None	7 (10.4)	3 (8.3)	6 (11.1)	4 (8.2)	3 (12.5)	7 (8.9)

Values are presented as number (%). BM, brain metastasis. [a]Those variables have statistically significant difference ($p < 0.05$).

difference in seizure-free survival between the two groups (p=0.427), and Fig. 2 shows the Kaplan-Meier survival curve. The median duration of follow-up was 8.8 months (range, 3.5 to 15.8 months) in the high-risk group and 8.6 months (range, 3.2 to 14.7 months) in the low-risk group ($p > 0.05$).

3 Disease-progression of BM: presence vs. absence

Disease-progression occurred in 24 BMs (23.3%) and was not detected in 79 BMs (76.7%). Patients with disease-progression were older (64.8 years vs. 59.6 years, $p < 0.05$), and had a KPS score of ≤ 60 (16.7% vs. 5.1%, $p < 0.05$). Table 3 shows the clinical characteristics of patients during systemic chemotherapy according to disease-progression of BM.

Concerning an origin of BM, there was no statistical difference between non-small cell lung cancer and other cancers ($p > 0.05$). Also, there was no significant difference in disease-progression of BM after surgical resection or radiotherapy for BM ($p > 0.05$). Table 4 summarizes the BM features with respect to disease-progression of BM.

Although the seizure-free survival period did not reach a median value in the log-rank test, there was a significant statistical difference between patients with and without disease-progression (p=0.001) based on Kaplan-Meier analysis. In Fig. 3, the Kaplan-Meier survival curve presents the difference. The median duration of follow-up was 8.4 months (range, 3.2 to 14.4 months) in patients with disease-progression of BM and 8.9 months (range, 3.4 to 15.8 months) in patients without disease-progression ($p > 0.05$).

4 Results of Cox regression analysis for seizure-free survival

Table 5 shows the results of regression analysis of each factor. Three variables, including the significance of the EEG abnormality, the risk for epileptogenesis according to the location of the BM, and the disease-progression of BM, had a positive association with seizure-free survival. Based on univariate analysis, the odds ratio of significance of abnormality in EEG was 3.42 (95% confidence interval [CI], 1.21 to 5.92; p=0.024) in I vs. III, and 2.63 (95% CI, 1.77 to 3.56; p=0.050) in II vs. III. After multivariate adjustment, the odds ratio of the significance of the EEG abnormality was 3.46 (95% CI, 1.5 to 5.93; p=0.017) in I vs. III, and 2.71 (95% CI, 1.85 to 4.18, p=0.048) in II vs. III. The odds ratio of risk for epileptogenesis was 2.46 (95% CI, 1.61 to 3.47, p=0.046) based on univariate analysis. However, after multi-factor adjustment, the variable of risk for epileptogensis did not have an association with seizure-free survival. In terms of disease-progression of BM, the odds ratio was 4.41 (95% CI, 1.52 to 6.80; p=0.003) based on univariate analysis, and 4.63 (95% CI, 2.23 to 7.04; p=0.001) after multi-factor adjustment.

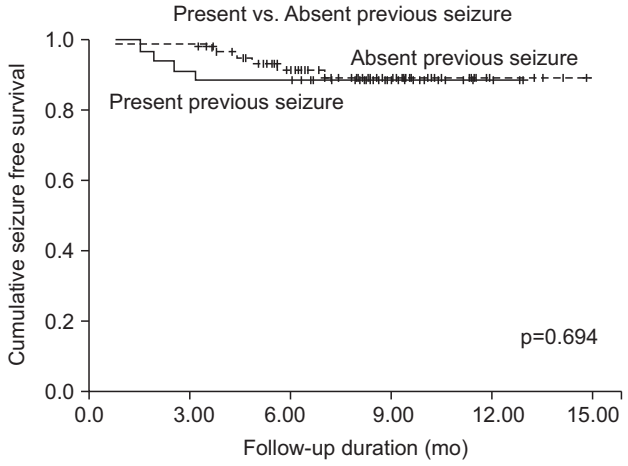

Fig. 1. Seizure-free survival curve in patients with previous history of seizure and in those without previous history of seizure.

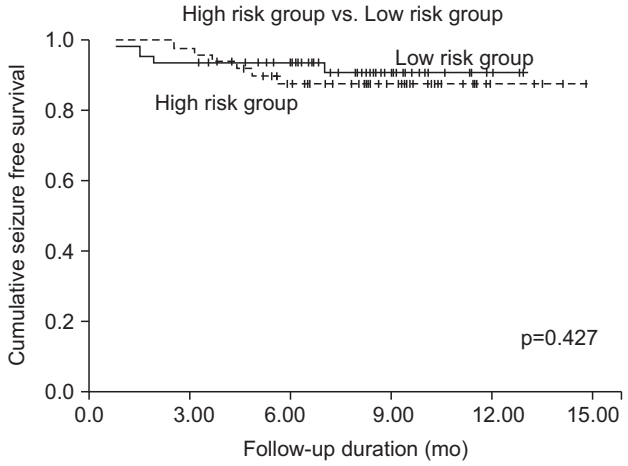

Fig. 2. Seizure-free survival curve in high risk group and low risk group.

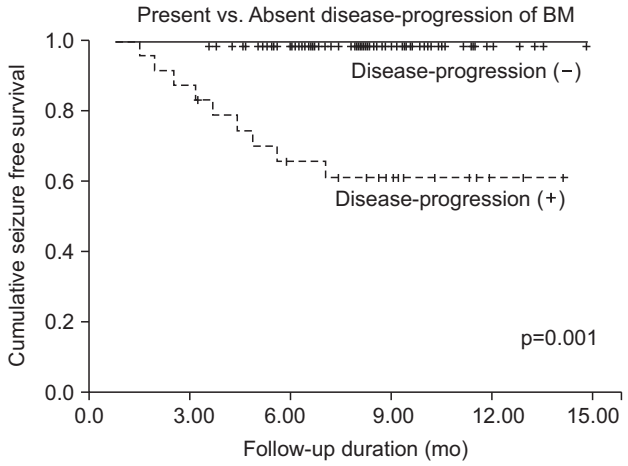

Fig. 3. Seizure-free survival curve in patients according to the disease-progression of single brain metastasis (BM) during chemotherapy for systemic cancer.

5 Patterns of BTRE during systemic chemotherapy for BM

Table 6 shows the patterns of BTRE during systemic chemotherapy for BM. The mean dose of topiramate was 183.4 mg/day (range, 100 to 400 mg/day). Ten patients (9.7%) suffered from BTRE during systemic chemotherapy. Specifically, 2 patients experienced one seizure, 4 patients had 2 seizures, and 4 patients had ≥3 seizures. The first seizure occurred in 1 patient within 1 month of chemotherapy, in 2 patients between 1 and 2 months, in 3 patients between 2 and 4 months, and in 4 patients after 4 months. A total of 24 seizures occurred (3 partial seizures, 12 partial seizures with evolving secondary generation, and 9 generalized tonic-clonic seizures).

Six of 67 patients (9.0%) without a history of BTRE and four of 36 patients (11.1%) with a history of BTRE experienced seizure attack while on topiramate, which was not statistically significant. However, the number of seizures per patient in patients with or without a BTRE history were 0.19 and 0.31, respectively, and this difference was significant (p=0.024).

Although new onset seizures occurred in six patients without a BTRE history, 88.9% (32 of 36) of those with a previous BTRE history achieved a seizure-free state on topiramate. Seizure-free rates were similar in the low- and high-risk groups (92.6% and 87.8%, respectively). Although seizures occurred in 7.4% (4 patients) in the low-risk group and in 12.2% (6 patients) in the high-risk group, this difference was not significant (p=0.283). Furthermore, no statistical difference was observed between the two groups in terms of seizure number per patient (0.20 vs. 0.26, p=0.202).

In terms of disease-progression of BM, 9 (37.5%) patients with disease-progression of BM experienced seizures and only 1 (1.3%) patient without disease-progression of BM experienced a seizure (p=0.000); the average number of seizures per patient was 0.96 for patients with disease-progression of BM and only 0.01 in patients without disease progression of BM (p=0.000). Furthermore, these two differences were highly significant.

Discussion

BTRE is difficult to control with AEDs, perhaps because of the underlying pathophysiologic mechanisms and interactions with other drugs [11]. These seizures may be extremely distressing for patients, and are a major source of morbidity and diminished quality of life in patients with brain tumors and other cancers [21]. For these reasons, AEDs are administered for prophylaxis to brain tumor patients during chemotherapy. In fact, a meta-analysis of 4 randomized trials involving ≥1 AED and 318 patients with a variety of intracranial neoplasms showed that prophylaxis with phenytoin, phenobarbital, or valproate is ineffective [10]. Furthermore, after

Table 5. Cox regression analysis for factors affecting seizure-free survival during chemotherapy for systemic cancer with single brain metastasis

	Univariate analysis (p-value)	Odd ratio (95% CI)	Multivariate analysis (p-value)	Odd ratio (95% CI)
Gender (male vs. female)	0.891	1.21 (0.88-1.50)	NA	
Age (≥ 60 yr vs. < 60 yr)	0.743	1.08 (0.77-1.30)	NA	
KPS score (≥ 70 vs. < 70)	0.127	1.89 (0.95-2.24)	NA	
Significance of abnormality in EEG				
I vs. II	0.285	1.65 (0.84-1.98)	NA	
I vs. III	0.024	3.42 (1.21-5.92)	0.017	3.46 (1.35-5.93)
II vs. III	0.050	2.63 (1.77-3.56)	0.048	2.71 (1.85-4.18)
Histopathology of primary cancer (Non-small cell lung cancers vs. other cancers)	0.341	1.57 (0.88-1.88)	NA	
Therapeutic modality (radiotherapy vs. surgery)	0.524	1.24 (0.74-1.62)	NA	
Previous history of seizure (presence vs. absence)	0.328	1.48 (0.82-2.10)	NA	
Risk for epileptogenesis (high risk vs. low risk)	0.046	2.46 (1.61-3.47)	0.055	2.25 (1.27-3.24)
Disease-progression of brain metastasis (presence vs. absence)	0.003	4.41 (1.52-6.8)	0.001	4.63 (2.23-7.04)

CI, confidence interval; NA, not assessed; KPS, Karnofsky Performance Scale; EEG, electroencephalogram.

Table 6. Patterns of brain tumor related epilepsy according to each comparative group during chemotherapy for systemic cancer with single BM

	Total (n=103)	Seizure history		Risk group		Disease-progression of BM	
		Absence (n=67)	Presence (n=36)	Low risk (n=54)	High risk (n=49)	Presence (n=24)	Absence (n=79)
No. of patients	10 (9.7)	6 (9.0)	4 (11.1)	4 (7.4)	6 (12.2)	9 (37.5)[a]	1 (1.3)[a]
One seizure	2	1	1	1	1	1	1
Two seizures	4	3	1	1	3	4	0
≥ Three seizures	4	1	2	2	2	4	0
Total No. of seizure	24	13	11	10	14	23	1
No. of seizure per patient	0.23	0.19[a]	0.31[a]	0.20	0.26	0.96[a]	0.01[a]
Timing of first seizure attack (mo)							
< 1	1	1	0	1	0	0	1
1-2	2	0	2	2	0	2	0
2-4	3	1	2	0	3	3	0
> 4	4	4	0	1	3	4	0
Type of seizure							
Partial seizure	3	2	1	1	2	3	0
Partial seizure with evolving 2ndary generalization	12	7	5	6	6	11	1
Generalized seizure	9	4	5	3	6	9	0

BM, brain metastasis. [a]Those variables have statistically significant difference ($p < 0.05$).

adding patients from 8 non-randomized studies to the meta-analysis, which raised the total to 1,100 patients; 24% were shown to have side effects (mainly cognitive difficulties and rashes), which led to treatment discontinuation. As a result, the American Academy of Neurology recommends that prophylactic AEDs not be routinely administered to patients with a newly diagnosed brain tumor, or alternatively treatment be tapered off after the first post-operative week [3]. Nevertheless, it is possible that certain subgroups of patients could benefit from prophylaxis with newer AEDs, which are purported to have fewer side effects. However, relatively few studies have been performed on the use of these newer AEDs in BTRE patients.

The present study showed that the most important factor to control BTRE during systemic chemotherapy is disease-progression of BM. To increase the efficacy of chemotherapy for systemic cancer with BM, we have to choose drugs with less drug-interaction and less side effects, which were administered concomitantly during systemic chemotherapy. Topiramate is a new generation AED that is uniquely not subject to drug interactions because it is metabolized less by cytochrome P450, and is less likely to produce side effects than traditional AEDs [14]. In this study, we gave a prophylactic AED to the patients who had no previous history of BTRE if they had abnormal EEG findings. Among 67 patients without a previous seizure attack, a new BTRE occurred in 6 patients (9.0%). According to the literature, an epileptic seizure is the clinical presenting sign of a brain tumor in 30-50% of patients, and an additional 10-30% of brain tumors patients develop seizures later during the disease course [1,3,4]. In particular, patients with BM experience seizure in approximately 25% of patients and 10% of patients complain of seizures as the initial presenting symptom [3,9]. Despite topiramate prophylaxis, our study showed that 6 (9.7%) patients developed new onset BTRE. Furthermore, despite systemic chemotherapy, 5 of 6 patients experienced disease-progression of BM and all had abnormal EEG signals. In fact, it was thought that because this study was performed in patients with abnormal findings of EEG, the results might not show complete prophylaxis for BTRE in patients without previous BTRE.

Although many studies have been undertaken to determine the risk of developing BTRE, no comprehensive study has previously reported that brain tumor progression is a risk factor of BTRE development, whereas several studies have found that tumor type and location are strongly related to BTRE development [11,20]. The present study presented that BMs with a low threshold of epileptogenesis in location have a tendency to develop BTRE more frequently than those with a high threshold of epileptogensis based on univariate analysis. However, adjustment for multiple factors presented that BM located in low threshold of epileptogenesis did not have a tendency to develop BTRE.

Additionally, our study suggested that the significance of EEG abnormalities and response to chemotherapy should have an association with seizure-free survival. There have been no comprehensive studies to use EEG during administrating AED in patients with BMs. Especially, although patients have no history of BTRE, if they have abnormal finding on EEG, we can consider use of prophylactic AED in BM patients.

Several studies have been undertaken on new AEDs for BTRE. Wagner et al. [22] presented preliminary experience for levetiracetam in patients with a primary brain tumor, after surgery and reported a seizure-free rate of 20% for 20 patients. However, Wagner et al. [22] exclusively enrolled patients with primary brain tumors, which probably accounts for differences from our results because of different types of brain tumors. In a retrospective analysis conducted by Newton et al. [23], seizure frequency was reduced in 90% of patients with brain tumors by adding levetiracetam. Newton et al. [23] studied 34 patients with primary brain tumors and 7 metastatic brain tumors, and concluded that levetiracetam should be considered as add-on therapy with traditional AEDs or as a substitute anti-convulsant monotherapy.

Our prospective observational study has many limitations of defining the incidence and the patterns of BTRE, and a predisposing factor for BTRE during systemic chemotherapy. First, the histologic origins of primary tumors were too heterogeneous, thus many factors in each primary tumor, such as the biology and the chemotherapeutic agents of each primary tumor, varied. The clinical courses of BM, as well as the primary tumor, differed. Therefore, our results did not individualize all of the different conditions in different tumors. Second, we confined the study period during chemotherapy. We overlooked the effects of initial treatment of BM, such as radiotherapy or surgery. Even after chemotherapy for systemic cancer with a single BM, these therapeutic modalities can influence the development of BTRE. Third, we could not standardize our results in all BTRE during chemotherapy for systemic cancer with BM because the involved chemotherapeutic agents and many other drugs influenced the development of BTRE. Many medications can cause drug interactions, and thus we cannot account for all possible interactions between the medications used to treat systemic cancer. Fourth, as our study showed results in patients with single BM only, we cannot apply our results to all types of brain tumors. Therefore, a more comprehensive study is required to resolve this issue.

Conclusion

This prospective observational study suggested that disease progression of BM and the significance of EEG abnormalities should have an association with development of BTRE and seizure-free survival during chemotherapy for systemic cancer with BM. Many hurdles must be overcome before we are able to control BTRE during treatment of brain tumors. During concomitant chemotherapy, drug interactions between AEDs and chemotherapeutics administered concomitantly are important considerations when choosing AEDs, as are the intrinsic side effects of AEDs. Further studies are warranted to confirm our results and determine the nature of the interactions between many drugs which are administered concomitantly and chemotherapeutics.

Conflicts of Interest

Conflict of interest relevant to this article was not reported.

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