Introduction

The incidence of brain tumors among those with epilepsy is about 4%.9,22 Conversely, the frequency of epilepsy is 30% or more among patients with brain tumors, though this depends on tumor type.8 In 30–50% of patients with a brain tumor, epileptic seizure is the presenting symptom, and an additional 10–30% will develop seizures later during the disease course.7,9,25,29 Furthermore, epilepsy has been reported in >80% of low-grade gliomas (WHO grade 2),27 in 30 to 60% of high-grade gliomas,24 in up to 40% of meningiomas,14 and in approximately 20% of primary CNS lymphomas.11 In particular, patients with chronic brain tumor associated epilepsy (BTAE) often have low-grade glioma and experience complex partial seizures.1

Seizures, especially in brain tumor patients, have a signifi-
Brain Tumor Associated Epilepsy

cant impact on quality of life. They interfere with driving and working, reduce independence, increase anxiety, and generate depression.5,10 Furthermore, they are often drug resistant.23 The resistances shown by brain tumor patients to anti-epileptic

156

drugs (AEDs) probably reflect different pathophysiological mechanisms, such as, those affecting peritumoral brain tissue morphology, pH, ion level, and amino acid changes, and different pharmacological interactions.23 Although seizure frequencies in patients with BTAE can be effectively reduced by administering AEDs, these agents can create a host of new problems, for example, they can interact with corticosteroid metabolism,19,29 reduce the efficacies of a variety of chemotherapeutic agents,18 and cause side effects more frequently than in epileptic patients without a brain tumor.7

During brain tumor 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 BTAE. Furthermore, chemotherapeutics can also accelerate AED metabolism, and prevent seizure control during chemotherapy.

However, some of the newer AEDs are not metabolized by cytochrome P 450 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 brain tumor patients or concerning potential interactions between these agents and many chemotherapeutics. Topiramate, is one of these recently developed AEDs, and is interesting from a pharmacokinetic standpoint, because it induces cytochrome P 450 isoenzyme only at low levels, and this is associated with lower pharmacological interactions.23

In the present study, we examined the efficacy of topiramate in patients with brain tumor associated epilepsy during adjuvant chemotherapy and the risk factors for development of BTAE.

**Material and Methods**

1. Study population

This prospective observational study involved 81 patients who were recruited from March 2006 to February 2009. All patients underwent adjuvant systemic chemotherapy for a brain tumor with concomitant topiramate as an anti-epileptic drug (AED) at our institute, and all met the following inclusion criteria: 1) an age of >20 years; 2) a pathological diagnosis confirmed after surgical intervention; 3) abnormal electroencephalographic findings; and 4) a brain tumor located in the supratentorial area. Patients with a prolonged seizure history before brain tumor diagnosis, a history of medically intractable seizure, a contraindication regarding topiramate administration, such as, a renal stone or dementia, or regarding systemic chemotherapy, or a normal finding on electroencephalogram (EEG) without seizure before chemotherapy were excluded. The purpose of the study was explained to patients and their families prior to enrollment. When a patient or family member requested a specific treatment protocol, the patient concerned was excluded. The local ethical committee at our institute approved the study protocol.

2. Evaluation before chemotherapy

Adequate hematologic, renal, and hepatic functions were determined using blood samples and were defined as follows: absolute granulocyte count $>$15,000/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 $\geq$ 60 mL/m$^2$.

Patients scheduled to undergo systemic chemotherapy for a brain tumor 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, FP2-A2, channels 1 and 2), left and right frontal-CZ (FP1-CZ, 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, USA). 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.21 The higher level of significance of abnormality EEG shows, the more frequent seizures can 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.89

Functional statuses were determined using the Karnofsky