ORIGINAL ARTICLE

# Prophylactic Anticonvulsants in Patients with Brain Tumour

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**ABSTRACT:** ***Objective:*** We conducted a clinical trial to determine if prophylactic anticonvulsants in brain tumour patients (without prior seizures) reduced seizure frequency. We stopped accrual at 100 patients on the basis of the interim analysis. ***Methods:*** One hundred newly diagnosed brain tumour patients received anticonvulsants (AC Group) or not (No AC Group) in this prospective randomized unblinded study. Sixty patients had metastatic, and 40 had primary brain tumours. Forty-six (46%) patients were randomized to the AC Group and 54 (54%) to the No AC Group. Median follow-up was 5.44 months (range 0.13 -30.1 months). ***Results:*** Seizures occurred in 26 (26%) patients, eleven in the AC Group and 15 in the No AC Group. Seizure-free survivals were not different; at three months 87% of the AC Group and 90% of the No AC Group were seizure-free (log rank test, p=0.98). Seventy patients died (unrelated to seizures) and survival rates were equivalent in both groups (median survival = 6.8 months versus 5.6 months, respectively; log rank test, p=0.50). We then terminated accrual at 100 patients because seizure and survival rates were much lower than expected; we would need ≥ 900 patients to have a suitably powered study. ***Conclusions:*** These data should be used by individuals contemplating a clinical trial to determine if prophylactic anticonvulsants are effective in subsets of brain tumour patients (e.g. only anaplastic astrocytomas). When taken together with the results of a similar randomized trial, prophylactic anticonvulsants are unlikely to be effective or useful in brain tumour patients who have not had a seizure.

**RÉSUMÉ: Une question importante en neuro-oncologie à la quelle il est difficile de répondre**: **l'utilité des anticonvulsivants prophylactique chez les patients porteurs d'une tumeur cérébrale.** ***Objectif***: Nous avons procédé à un essai thérapeutique pour déterminer si les anticonvulsivants administrés de façon préventive chez les patients porteurs d'une tumeur cérébrale, sans épisode convulsif antérieur, réduisent la fréquence des crises épileptiques. Nous avons limité le recrutement à 100 patients suite à une analyse intérimaire. ***Méthodes***: Cent patients, atteints de tumeurs cérébrales dont le diagnostic était récent, ont reçu des anticonvulsivants (groupe AC) ou n'en ont pas reçu (groupe sans AC) dans le cadre d'une étude prospective, ouverte, randomisée. Soixante patients avaient une maladie métastatique et quarante avaient une tumeur cérébrale primitive. Quarante-six (46%) des patients ont été randomisés au groupe AC et 54 (54%) au groupe sans AC. Le suivi médian a été de 5,44 mois (écart de 0,13 à 30,1 mois). ***Résultats***: Vingt-six patients ont présenté des crises (26%), onze dans le groupe AC et 15 dans le groupe sans AC. La survie sans crise n'était pas différente: à trois mois, 87% des patients du groupe AC et 90% de ceux du groupe sans AC n'avaient pas présenté de crise (test du log-rang, p=0,98). Soixante-dix patients sont décédés (décès non reliés à une crise convulsive) et les taux de survie étaient équivalents dans les deux groupes (survie médiane de 6,8 mois versus 5,6 mois respectivement; test du log-rang p=0,50). Nous avons limité le recrutement à 100 patients parce que le taux de crise et de survie étaient beaucoup plus bas que prévu: nous aurions eu besoin de plus de 900 patients pour que l'étude ait une puissance statistique suffisante. ***Conclusions***: Ces données devraient être utilisées par ceux qui se proposent de faire un essai thérapeutique pour déterminer si les anticonvulsivants prophylactiques sont efficaces dans des sous-groupes de patients atteints de tumeurs cérébrales (e.g. seulement des astrocytomes anaplasiques). Quand ces résultats sont considérés conjointement avec ceux d'un essai thérapeutique similaire, il est peu probable que les anticonvulsivants prophylactiques soient efficaces ou utiles chez les patients porteurs de tumeurs cérébrales qui n'ont pas eu de crise.

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Seizures are reported to occur in at least 20% of patients with metastatic or primary brain tumour.[1-17] Brain tumour patients who present with seizures are treated with anticonvulsants but these drugs are frequently used prophylactically. A generalized seizure may be lethal if it is prolonged or if the patient does not recover consciousness.[18-22] Seizures may cause unacceptable toxicity or interact with other drugs, such as corticosteroids[23-25] or chemotherapeutic agents which may compromise the patient's overall treatment. Retrospective studies of prophylactic anticonvulsants in patients with metastases have been conflicting

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and show increased[8] or reduced[2,9] seizure frequency with seizure prophylaxis.

In primary brain tumour, seizures are reported to occur in 20% - 90% of patients. Seizure risk is related to tumour location, particularly frontal and parietal lobes[11,26-30] and their rate of growth. Seizures are more common in slowly growing tumours[31-36] but less so in more malignant ones.[17,27] A complicating issue is the risk of postoperative seizures because all patients undergo craniotomies or biopsies for diagnosis. Retrospective studies[26,27] of patients with malignant supratentorial gliomas found no significant reduction of postoperative seizures with prophylactic anticonvulsants. The only other prospective randomized trial of prophylactic anticonvulsants in patients with brain tumour (published after we began our trial) found seizure prophylaxis ineffective.[7] This study used divalproex sodium as an anticonvulsant and randomized a smaller number of patients. The data we present here, and those from Glantz et al[7] were used to construct a practice parameter by the American Academy of Neurology (AAN) that recommends that prophylactic anticonvulsants not be used in patients with brain tumour.[37] We think it is important that the details of our data be examined so that the basis and limitations of these recommendations be understood.

To determine if anticonvulsants are useful in preventing seizures in patients with brain tumour, we conducted a multicentre unblinded randomized prospective clinical trial of a prophylactic phenytoin in patients without prior seizures. The objectives were to determine: 1) if anticonvulsants would reduce the incidence of first seizures, and 2) the toxicity of anticonvulsants in these patients. Although we terminated accrual at 100 patients, because of the results of an interim analysis, our data are useful since they are prospective, randomized and based on a significant number of patients.

## Methods

### Subjects

Subjects were recruited from three institutions (Memorial Sloan-Kettering Cancer Center, Tom Baker Cancer Centre, Cross Cancer Institute) over 2.9 years (Table 1). All patients had a pathologically documented primary brain tumour or systemic cancer with a typical radiographic appearance of brain metastases. Patients were recruited within one month of brain tumour diagnosis. Adequate hepatic, bone marrow and renal function were required. Patients were ineligible if their life expectancy was less than four weeks, they had any prior seizures, a known allergy to anticonvulsants, were pregnant, lactating or not using effective contraception, or abused ethanol or drugs. This study received approval from each participating centre's Institutional Review Board; informed, signed consent was obtained from all patients.

### Procedures

Patients were identified from neurology in- and outpatient services, the radiation therapy outpatient department or by regular review of neuroradiologic studies. All patients were evaluated by one of the investigators (PAF, SW, DF, PB). Baseline physical and neurologic examinations were performed and informed consent obtained. Each patient was then randomly assigned to the *Anticonvulsant Group* (AC Group) or the *No Anticonvulsant Group* (No AC Group). Patients were stratified according to primary versus metastatic brain tumour, and within metastatic tumour, melanoma versus nonmelanoma primaries because of the particularly high incidence of seizures associated with melanoma brain metastases. Prior to the beginning of enrolment, opaque envelopes containing the treatment assignment were provided to the study centres by a biostatistician. Permuted block randomisation with varying block sizes was employed within strata. Upon entry into the study the next sequential envelope in the relevant strata was opened to determine treatment assignment. Neither subjects nor investigators were blinded to the patients' treatment group.

### Treatment plan and compliance

If assigned to the AC Group patients received an oral loading dose of 15 mg/kg phenytoin in three divided doses with a standard daily dose of approximately 5 mg/kg p.o. each night. If the patient could not tolerate phenytoin, phenobarbital (60 mg p.o. for one week then 90 mg daily) was used; 45 (98%) patients in the AC Group received phenytoin and one (2%) received phenobarbital. Where possible serum anticonvulsant levels were measured monthly for three months then once every three months to measure compliance; doses were adjusted for subtherapeutic levels. Patients randomized to the No AC Group who were already taking anticonvulsants had them tapered over one to two weeks. This included any patient who had undergone a neurosurgical procedure and received peri-operative anticonvulsants. Thirteen (24%) patients in the No AC Group were on anticonvulsants at the time of randomization.

### Follow-up

Patients were evaluated monthly for the first three months and then at three month intervals. Follow-up was done at the time of their regularly scheduled appointments or by telephone. All patients were reviewed either when a seizure or significant toxicity occurred. Seizures (observed or reported) of any type (e.g. generalized, partial, etc.) were included as endpoints.

### Statistical analysis

Seizure occurrence by three months postrandomization was the primary end point of this study. A total of 300 eligible patients was planned. This ensured that the trial would have a power of at least 0.80 to detect an absolute reduction in seizure incidence in the AC Group of 15% (i.e. a reduction of seizure rate from 20% to 5%). This assumed a one-sided test with one interim analysis. The overall Type 1 error was set at 0.05 with the interim and final analysis Type 1 error 0.01 and 0.045, respectively. Allowances were made for noncompliance (20%) and losses due to early deaths (15%). A three-month seizure rate of 20% was assumed in the control group. Statistical analyses were done with SAS and Splus. Seizure-free survival curves were generated by the Kaplan-Meier method and the distributions compared via the log-rank statistic. The Cox proportional hazards model was used for all multivariate analyses.

Potential prognostic factors evaluated included age, sex, Karnofsky Performance Status (KPS), location of tumour (infratentorial versus supratentorial and for supratentorial tumour frontal location versus other), craniotomy versus no

craniotomy and hemorrhagic versus nonhemorrhagic tumour. For patients in the AC Group, compliant versus noncompliant patients were compared. The incidence of toxicities (systematic and neurologic) were compared using Fisher's exact test.

### Decision to terminate the trial

After 2.9 years when 100 patients had been enrolled, the study was closed to further accrual because: 1) The observed seizure rate at three months in the No AC Group was 10% which put the anticipated rate of 20% outside the confidence intervals (95% CI, 0.6%-19.8%). This indicated that it was extremely unlikely that the anticipated difference in seizure rates (from 20% vs 5%) would be realized. 2) The mortality prior to three months of follow-up, projected to be 15% was about 30%. The combination of these two factors indicated that the power of the trial (based on an accrual of 300 patients) to detect a clinically important difference was reduced to <20%. Over 900 patients would have to be accrued to maintain a power of 80% given these circumstances. This was not considered to be feasible. Because our data were gathered prospectively and therefore reflect what actually happened with these patients, we present the results of the 100 patients studied. Furthermore, our cohort is larger than the only other prospective study performed to address this issue.[36]

### At study completion

Fifty-four (54%) patients died, 26 (26%) had a seizure, eight (8%) were lost to follow-up or withdrew for other reasons, and

**Table 1:** Baseline Characteristics

| Characteristic | ALL PATIENTS | | METASTATIC BT | | PRIMARY BT | |
|---|---|---|---|---|---|---|
| | AC Grp N=46 | No AC Grp N=54 | AC Grp N=26 | No AC Grp N=34 | AC Grp N=20 | No AC Grp N=20 |
| Mean Age (yrs) | 56 | 56 | 60.9 | 57.5 | 51.2 | 53.6 |
| Male (%) | 71 | 52 | 69 | 41 | 75 | 70 |
| **Karnofsky Performance Status (mean)** | 79.6 | 76.6 | 78 | 73.8 | 82 | 81 |
| Brain | 26 | 34 | | | | |
| Metastases | | | | | | |
| breast | 1 | 8 | 1 | 8 | | |
| lung | 18 | 14 | 18 | 14 | | |
| melanoma | 1 | 3 | 1 | 3 | | |
| other | 6 | 9 | 6 | 9 | | |
| **Primary Brain Tumours** | 20 | 20 | | | | |
| Glioblastoma multiforme | 17 | 11 | | | 17 | 11 |
| anaplastic astrocytoma | 2 | 4 | | | 2 | 4 |
| anaplastic oligodendrocytes | 1 | 2 | | | 1 | 2 |
| low grade glioma | 0 | 3 | | | 0 | 3 |
| **Tumours characteristics** | | | | | | |
| Total number of tumours | 90 | 120 | 52 | 81 | 38 | 39 |
| supratentorial | 79 | 103 | 41 | 67 | 38 | 36 |
| infratentorial | 11 | 17 | 11 | 14 | 0 | 3 |
| both | 6 | 10 | 6 | 8 | 0 | 2 |
| frontal | 22 | 25 | 12 | 18 | 10 | 7 |
| meningeal | 1 | 2 | 1 | 2 | 0 | 0 |
| presence of hemorrhage | 7 | 7 | 4 | 4 | 3 | 3 |
| **Method of Diagnosis** | | | | | | |
| Typical x-ray | 23 | 29 | 23 | 29 | 0 | 0 |
| Craniotomy | 19 | 20 | 2 | 4 | 17 | 16 |
| Biopsy | 4 | 5 | 1 | 1 | 3 | 4 |
| **Time from diagnosis until randomization** | | | | | | |
| (median, mos) | 0.77 | 0.87 | 0.66 | 0.61 | 1.07 | 0.95 |

BT = brain tumours; AC = anticonvulsant; AC Grp = patients randomized to take prophylactic anticonvulsants; No AC Grp = patients randomized not to take prophylactic anticonvulsants.



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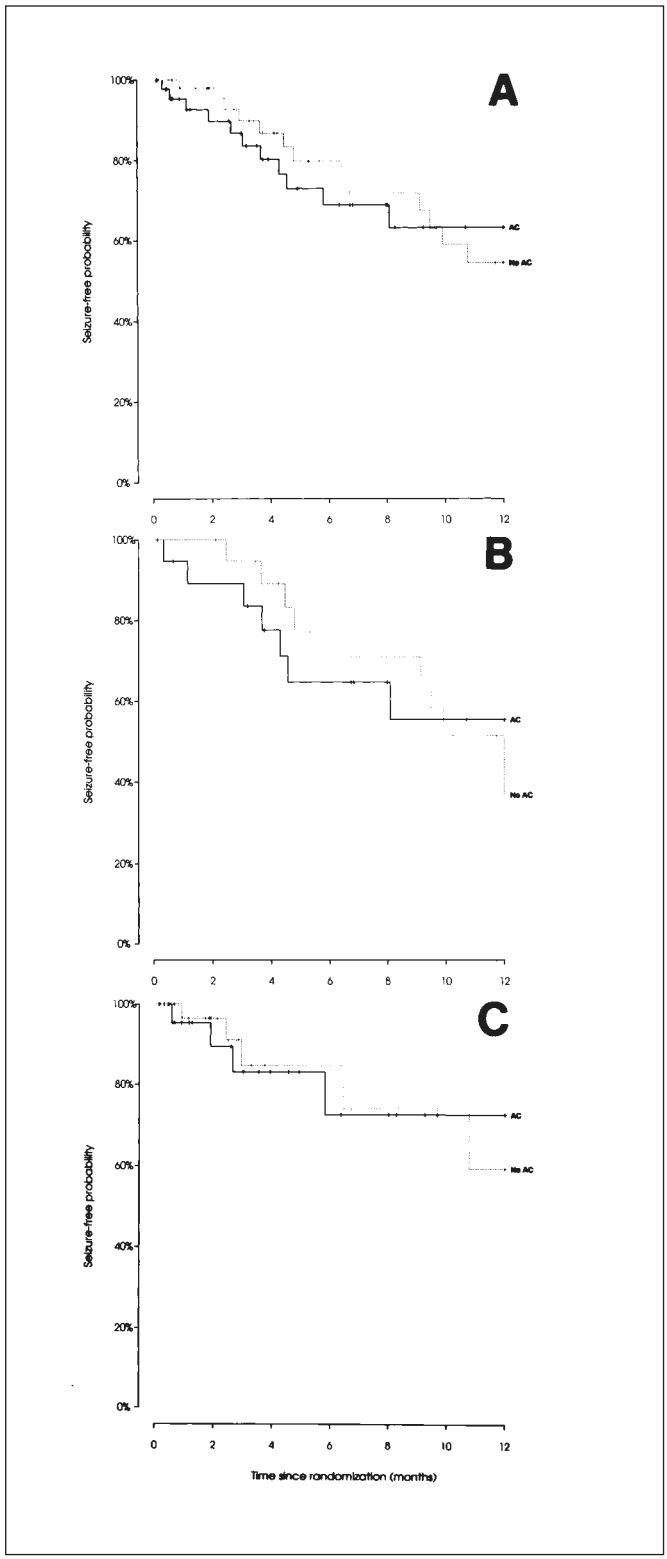


***Figure:*** *Seizure-free survival according to treatment group.* ***A)*** *For the whole group there was no difference whether patients received prophylactic anticonvulsants (AC) or not (No AC) (log rank test; p = 0.595 ).* ***B)*** *There was also no difference for patients with primary (log rank test; p = 0.95), or* ***C)*** *metastatic (log rank test; p = 0.90) brain tumours.*

**Table 2:** Reasons for Termination of Follow-up According to Treatment Group

| ALL PATIENTS<br>**Variable** | **AC Grp N=46** | **No AC Grp N=54** |
|---|---|---|
| Reason: | | |
| Seizure | 11 | 15 |
| lost to follow-up | 1 | 4 |
| patient preference | 3 | 0 |
| death | 26 | 28 |
| still enrolled | 3 | 6 |
| other | 2 | 1 |
| Duration of follow-up at withdrawal (no. of patients) | | |
| <3 months | 17 | 22 |
| 3-6 months | 11 | 8 |
| 6-12 months | 11 | 10 |
| >12 months | 7 | 14 |

three (3%) patients (all in the AC Group) requested withdrawal from the study (Table 2). Nine (9%) stayed with the study until the time of termination without death or seizure. We continued to collect information on seizure frequency and toxicity in patients who had seizures (regardless of their original treatment assignment).

## Results

One hundred patients were studied; their clinical characteristics are summarized in Table 1. Sixty patients had metastatic, and 40 had primary brain tumours. The characteristics of the study groups were balanced although there was a slightly higher percentage of patients with metastatic tumours in the No AC Group (57% vs. 63%). Forty-six patients were randomized to the AC Group and 54 to the No AC Group. Of the patients in the AC Group 26 (56%) had brain metastases and 20 (43%) had primary brain tumours. In the No AC Group 34 patients (62%) had brain metastases and 20 (38%) had primary brain tumours.

Detailed information regarding the number of patients screened was available at one centre (Tom Baker Cancer Centre) where 52 patients were accrued for 13 months. Over this period there were 360 potentially eligible patients of whom 266 were screened; 74 did not meet the eligibility criteria, 51 patients declined participation, 31 could not be contacted and 58 were not enrolled for other reasons. One patient had a seizure one week postoperatively before he was evaluated for study enrolment. No other patient had a seizure during the one month allowed between tumour diagnosis and randomization.

### Seizure incidence

The median follow-up was 5.44 months (range 0.13 - 30.1 months) for individuals who did not experience a seizure; almost



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**Table 3:** Side Effects of Medication[1]

| Side Effect | Number (Percent) |
|---|---|
| **Systemic Toxicity** | |
| Nausea | 4 (9) |
| Rash | 3 (7) |
| Sore gums | 1 (2) |
| Myelosuppression (lowest WBC=2000 and plts=100,000) | 1 (2) |
| Increased lactate[2] dehydrogenase (<1.5 X normal) | 1 (2) |
| **Neurotoxicity:** | |
| Vertigo and blurred vision | 1 (2) |
| Tremor | 1 (2) |
| Gait ataxia[3] and confusion | 1 (2) |

[1]definitely or probably related to anticonvulsant. [2]due to chemotherapy.
[3]due to tumours progression
WBC = white blood cell count
plts = platelets

25% had at least one year of follow-up. All but one patient was followed for at least three months unless a seizure or death intervened (Table 2). At the time of analysis 26 patients had experienced a seizure. Of these, 11 (24%) were in the AC Group and 15 (28%) in the No AC Group. At three months following randomization 87% (95% CI 76 to 98%) of the patients in the AC Group, and 90% (95% CI 80 to100%) of the No AC Group were seizure-free (Figure). There was no significant difference between the two groups as a whole (log rank test, p=0.98; Figure A; hazard ratio = 1.01, 95% CI 0.46 to 2.21) or for those with primary (log rank test p=0.95) or metastatic (log rank test p=0.90) brain tumour (Figure B&C). There were too few patients with metastases from melanoma[8] or hemorrhagic lesions[17] to be analysed separately; only one melanoma patient (in the No AC Group) had a seizure.

### Prognostic factors for seizures

Gender was the only potential prognostic factor which has a relationship to seizure incidence; the risk ratio for females as compared to males was 2.6 (95% CI 1.01 - 6.71). Age, KPS, tumour location or surgical resection did not predict development of a seizure.

### Anticonvulsant compliance

Compliance was measured qualitatively by patient self-report and quantitatively by serum anticonvulsant levels. Forty-three (93%) patients reported they took the prescribed medication according to schedule. Serum levels were obtained from 38 AC Group patients a median of two times (range, 1-10). Overall, 53% of patients were compliant. Anticonvulsant blood levels were deemed adequate if ≥ one trough level was therapeutic or serum level obtained at the time of a seizure was therapeutic. The number of patients with at least one therapeutic level was not different for those who had a seizure (6/11 or 55%) versus those who did not (14/35 or 40%). This was true both for the AC group as a whole and for patients with metastatic or primary brain tumour.

### Survival

By the end of the study period 70 patients had died; 32 in the AC Group (median survival = 6.8 months) and 38 in the No AC Group (median survival = 5.6 months; log rank test, p=0.50). Only 24 (24%) patients survived one year or longer; 7 (12%) with metastatic and 17 (43%) with primary brain tumour. The most frequent causes of death were progressive intracranial tumour in 34 patients (14 in the AC Group and 20 in the No AC Group) and progressive systemic cancer in 32 (15 in the AC Group and 17 in the No AC Group). There were other causes of death (e.g. pulmonary embolism) in four patients. No patient died as a result of a seizure or its treatment.

### Seizure type and their associated morbidity

Seizures were generalized in 13 (50%) patients, (six in the AC Group and seven in the No AC Group) which is not significantly different. The remainder of the seizures were focal motor or sensory. One patient in the No AC Group with multiple brain metastases had an episode of status epilepticus that required intubation and ICU admission; she recovered after several days. No other patient had prolonged seizures and none had long lasting sequelae from their seizures. The most common cause of a seizure in both groups was progressive brain tumour, seen in 17 (65%) patients. In the AC Group the most common causes of a seizure were progressive disease alone (five of 11 or 45% of patients), subtherapeutic phenytoin levels alone (two of 11 or 18%), or both (two of 11 or 18%). Two (18%) other patients had seizures but without progressive disease or subtherapeutic levels.

### Side effects of medication

Side effects definitely or probably related to the anticonvulsant are listed in Table 3. The most common were nausea in four of 46 (9%) patients and rash in three (7%). Side effects were severe enough to warrant withdrawal from the study in three (6%) patients. One had a rash which resolved when the anticonvulsant was stopped. Two others were withdrawn for myelosuppression and ataxia which were ultimately attributed to chemotherapy and progressive tumour respectively.

## Discussion

We were unable to definitively determine, from our study alone, if prophylactic anticonvulsants were effective in preventing the first seizure in patients with a brain tumour. Our data suggest that we could only rule out a risk reduction of more than 46% if patients took anticonvulsants prophylactically. However, when considered in conjunction with other randomized trials (or portions thereof[7,38,39]), and a meta-analysis,[37] the results suggest prophylactic anticonvulsants are ineffective. The lower than expected seizure and survival rates we found in our patients suggested we needed to accrue ≥ 900 patients to have an adequately powered study; this was clearly not feasible or reasonable and we terminated the study.

Our data are useful for several reasons. First it is important to be able to review the data on which meta-analyses are based so clinicians can make informed decisions about prescribing anticonvulsants to brain tumour patients. Second, since the data are prospective and randomized they are clinically useful in showing seizures are uncommon but occasionally result in status epilepticus and side effects of anticonvulsants can be significant.

Finally, clinical trialists, considering conducting a trial of seizure prophylaxis in subsets of brain tumour patients with higher rates of seizures (e.g. in anaplastic astrocytoma patients) or longer survivals (e.g. excluding glioblastoma multiforme or brain metastases patients), should consider our data in constructing sample size and outcome estimates.

Our study has three other limitations. First, the study was not blinded or placebo-controlled and this might introduce bias in terms of determination of endpoints, treatment allocation, and differential use of co-interventions. All seizures in this study were generalized or simple partial seizures that are readily recognized and unlikely to be disproportionately reported in one group versus another; no patient had partial complex seizures that were difficult to diagnose.

Second, the study population was somewhat heterogeneous (e.g. included patients with brain metastases and a few low-grade gliomas) and smaller sample sizes may be feasible in a more homogenous population with a more uniform natural history. Finally, we allowed one month to elapse between brain tumour diagnosis and randomization. Some may argue that this "pre-selects" patients who are unlikely to have a seizure but we found only one patient of the 266 screened who had a seizure after diagnosis and before randomization. Therefore this selection bias would not account for the lack of efficacy we observed.

In contrast, the frequency of side effects was very biased by both the patients' and investigators' knowledge that anticonvulsants were being used. Interestingly Glantz and colleagues[37] found similar toxicities for treated and untreated patients using a double-blind, placebo-control design, corroborating our finding that major anticonvulsant toxicities were not particularly common in these patients.

We were unable to identify significant patient characteristics that would predict patients most likely to have a seizure. Age, KPS, tumour location or a craniotomy was not predictive. However, there were only a small number of patients thought to be at high risk for seizure, such as those with hemorrhagic lesions or melanoma. Several retrospective reports find a high frequency of seizures in these two groups,[2-4,8] leading some to recommend anticonvulsant prophylaxis in these patients only. Unfortunately our small patient number precludes an appropriate subgroup analysis and left this question unanswered.

The most common cause of seizures in our patients was progressive intracranial disease indicating that patients with a new seizure must be re-evaluated for tumour recurrence. Sub-therapeutic anticonvulsant levels were not specifically associated with the development of a new seizure but they may still have played a contributory role. Rapid decline in levels can precipitate a seizure or fluctuations in the level can make a patient more vulnerable. We cannot attribute most seizures to a subtherapeutic level but, if anticonvulsants are used, they should be maintained in the therapeutic range. Nevertheless, this is clearly difficult to achieve despite frequent monitoring and protocol-mandated escalations in anticonvulsant doses. While part of the problem may be drug interactions[20,23-25] (virtually all brain tumour patients use dexamethasone) many patients may have been partially noncompliant. It is difficult to enforce compliance for prophylactic treatments in general and especially in patients who may be cognitively impaired and take a number of other medications.

The publication of the AAN guidelines,[37] which recommend no seizure prophylaxis in brain tumour patients, and our own difficulties (i.e. lower than expected seizure and survival rates) suggested to us that this trial should not be attempted in the future. In retrospect (one of us conceived of this trial during residency) the clinical problem is probably not important enough to justify an expensive and long-term prospective double-blind randomized clinical trial in patients with high-grade gliomas or brain metastases (unless their survival rates improve dramatically with new treatments). Rather, it should only be contemplated in subgroups of brain tumour patients such as those with low-grade gliomas. Patients with low-grade gliomas are more likely to have seizures, they survive much longer than glioblastoma multiforme patients (increasing their period at risk of a seizure) and, consequently, the implications of having a seizure (e.g. losing a driving license or the ability to work) may be more important.

We conclude that seizure prophylaxis offers no benefit to brain tumour patients or that benefit may be minimal at best. In the absence of benefit, we do not recommend prophylactic anticonvulsants for patients with brain metastases or primary brain tumour.

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