TREATING SEIZURES DUE TO CNS NEOPLASMS: RATIONAL NEW CHOICES

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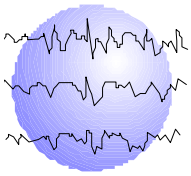

This paper has been prepared specifically for:

American Epilepsy Society Annual Meeting
New Orleans, Louisiana
December 3 - 8, 2004

Please consider this information to be preliminary findings.

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REVISED ABSTRACT

RATIONALE: CNS neoplasms are frequently the cause of new adult onset seizures. Treatment involves treatment of the neoplasm as well as adjuvant antiepileptic drug therapy (AED). Phenytoin has historically been used as the AED of choice. As a P450 3A4 metabolized AED, it may alter chemotherapy drug (CD) efficacy. Efficacy of new AEDs and CD efficacy needs to be evaluated in treatment of patients with CNS neoplasms.

METHODS: Retrospective review of patients referred for brain mapping or new onset seizures due to tumors from January 1999 to September 2004 was performed noting: tumor type, location, presenting symptoms, presence of seizures at onset, result of AED treatment, tumor treatment and functional status at last visit. Forty-four, patients ages 17-77, were reviewed (28 males, 16 females). Tumors were: 5 glioblastomas, 11 astrocytomas, 8 oligoastrocytomas, 12 oligodendrogliomas, 1 meningioma, 1 ganglioglioma, 2 DNET, 1 craniopharyngioma, 3 unknown. All received AEDs; 81% had resection; 59% had CD; 65% had radiation; 2% had cyberknife therapy. AEDs used: gabapentin (GBP) monotherapy (MT) 3; levetiracetam (LEV) MT 22 and polytherapy (PT) 7; oxcarbazepine (OXC) 4 MT and 3 PT; phenytoin 3 MT and 1 PT; topiramate (TPM) 2 MT. CDs utilized were temozolomide 34%; BCNU/CCNU 14%; and 2% each cisplatin, procarbazine, thalidomide, etoposide and 4% imatinib.

RESULTS: There were 5 deaths (11.3%) and 7 lost to follow-up. 93% presented with seizures. 79% of LEV patients were seizure free or only SPS. 75% OXC were seizure free or SPS only. 67% TPM patients were seizure free. 100% of GBP patients were seizure free. No phenytoin patients were seizure free. Tumor treatment resulted in survival and good functional outcome in 84.8%.

CONCLUSION: AEDs with no or minimal hepatic metabolism include GBP, LEV, TPM. OXC is reduced by a noninducible ketoreductase. CD metabolic pathways vary: temozolomide is conjugated; etoposide, BCNU and CCNU are hydroxylated; procarbazine, imatinib and vincristine are oxidized and inducible. Dexamethasone, frequently utilized initially, induces P450 AED metabolism. Choice of CD regimen is not often known at time of initial diagnosis. Choice of GBP, LEV, OXC or TPM would potentially avoid drug interactions and allow maximum CD effectiveness. All 4 AEDs showed excellent seizure outcome, whereas, phenytoin did not, although numbers are small. Patients with CNS neoplasms should be given maximum opportunity for successful outcome both for seizure control and survival. Treatment of seizures in these patients is effective utilizing GBP, LEV, OXC, and TPM with low risk of interfering with chemotherapy.

Introduction:

CNS primary neoplasms present with seizures in 20-80% of adult patients.[1,2] Pediatric patients with supratentorial tumors experience epilepsy with a prevalence of 38% due to either tumor or as a complication of treatment.[3] The occurrence of seizures was more likely to occur with higher grade tumors.[3]

Treatment of these patients involves treatment of the neoplasm, as well as adjuvant antiepileptic drug therapy (AED). Phenytoin has been the historical AED of choice. As an inducer of the P450 enzyme systems, it may alter the chemotherapeutic drug (CD) efficacy. Efficacy of the "new AEDs" and CD efficacy needs to be evaluated in treatment of patients with CNS neoplasms.

Methods:

Retrospective review of all patients referred for brain mapping or for new onset seizures due to primary brain tumors from January 1999 to September 2004 was performed. Evaluation of tumor type, location, presenting symptoms, presence of seizures at onset, result of AED treatment, tumor treatment and functional status at last clinic visit was noted.

Forty-four patients, ages 18-77, were reviewed (Table 1). Tumors were: 5 glioblastomas, 11 astrocytomas, 8 oligoastrocytomas, 12 oligodendrogliomas, 1 meningioma, 1 ganglioglioma, 2 DNET, 1 craniopharyngioma, and 3 unknown (Figure1) All patients received AEDs; 81% had debulking or gross total resection; 59% had CD; 65% had radiation treatment; 2% had cyberknife therapy.

AEDs used were: gabapentin (GBP) monotherapy (MT) 3; leviteracetam (LEV) MT 22 and polytherapy (PT) 7; oxcarbazepine (OCX) 4 MT and 3 PT; phenytoin 3 MT and 1 PT; topiramate (TPM) 2 MT.

CDs utilized were temozolomide 34%; BCNU/CCNU 14%; imatinib 4%; and 2% each cisplatin, procarbazine, thalidomide, etoposide. (Figure 2)

Results

There were 5 (11.3%) deaths (4 high grade astrocytomas, 1 glioblastoma) and 7 patients were lost to long-term follow-up. 93% presented with seizures at the time of diagnosis. 89% are seizure free or only have SPS (excellent outcomes). LEV monotherapy resulted in 86% excellent outcome of those treated with LEV MT. Of all patients treated with LEV, 79% achieved excellent outcomes; 57% of those with other AEDs in various combination with LEV (Table 2). 75% of OXC treated patients, 100% of GBP treated patients, and 67% of TPM treated patients achieved excellent results (Figure 3).

Discussion

CNS tumors are frequently present with seizures in 93% of our adult patients in a tertiary referral center. Resection for tumor and epileptogenic region is the most effective treatment for complete seizure control.[4] However, persistent seizures may require AED use.

Many patients require chemotherapy drug protocol, particularly in higher grade tumors. Some CDs have potential interactions with AEDs through liver metabolism or protein binding (Table 3). AED choice then becomes important in optimizing the CD efficacy since these CD agents have narrow therapeutic indices.[5] One new CD protocol with imatinib requires patients not to be on P450 inducing AEDs. Minimal interaction would be expected with the use of GBP, LEV, TPM, or OXC as AED choice, thus allowing maximum CD effectiveness. Although the number of patients is small in each group, all of the new AEDs resulted in excellent seizure outcome (seizure free or only SPS), whereas PHT did not. Our experience with LEV is the most extensive and supports LEV use as a first line option.

Conclusions:

Likewise, seizure control is important in maximizing cognitive performance and mental health scores on quality of life measures. Traditional AEDs were shown to worsen cognitive performance although mental and physical heath scores were most affected by ongoing seizures.[6] Unlike this literature report, our patients experienced better seizure outcome using "new AEDs" and are functioning well.

References:

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Table 1

Demographics

Number of Patients	44
Sex: Male Female	28 16
Age: Range at Diagnosis Mean Median	17-77 40 44
Follow-up	6 mo. – 5.5 yrs.
Deceased	5
Lost to Follow-up	7

Table 2

Experience with Leviteracetam in Primary Brain Tumors

Therapeutic Regimen	**N (% of all LEV)**	**% (SPS or sz free of subgroup)**
LEV Monotherapy	22 (76%)	19 86% of
LEV + OXC	2 (7%)	2
LEV + VPA	1 (3%)	1
LEV + TPM	1 (3%)	1
LEV + LTG + DIL	1 (3%)	0
LEV + OXC + ZNS	1 (3%)	?
LEV + PB + TPM	1 (3%)	Early
57% (28/44) of all patients received LEV 79% (23/29) are excellent outcomes		

Table 3

Chemotherapeutic Agents in Primary Brain Tumors

Agent	Mechanism	Metabolism	Tumor Type	Interactions
Temozolomide		Conjugation	Lymphoma Glioma Oligodendroglioma	
Cisplatin	DNA X-Links	Nonenzymatic	Oligodendroglioma	+
Carmustine (BCNU)	Alkylating	Hydrolysis	Glioma	
PCV Procarbazine Lomustine (CCNU) Vincristine	 Methylation Free Radicals Alkylating Block Mitosis Bind Tubulin	 P450 Hydrolysis P450	Lymphoma, Oligodendroglioma	+
Etoposide (VP 16)	Block Mitosis	Hydroxylation	Oligodendroglioma	+
Imatinib (Gleevac)	Tyrosine Kinase Inhibitor	P450	Oligodendroglioma, Glioma	
Methotrexate	Folate Antag	Protein Bind	Lymphoma	+
Steroids		Induce P450		

Figure 1

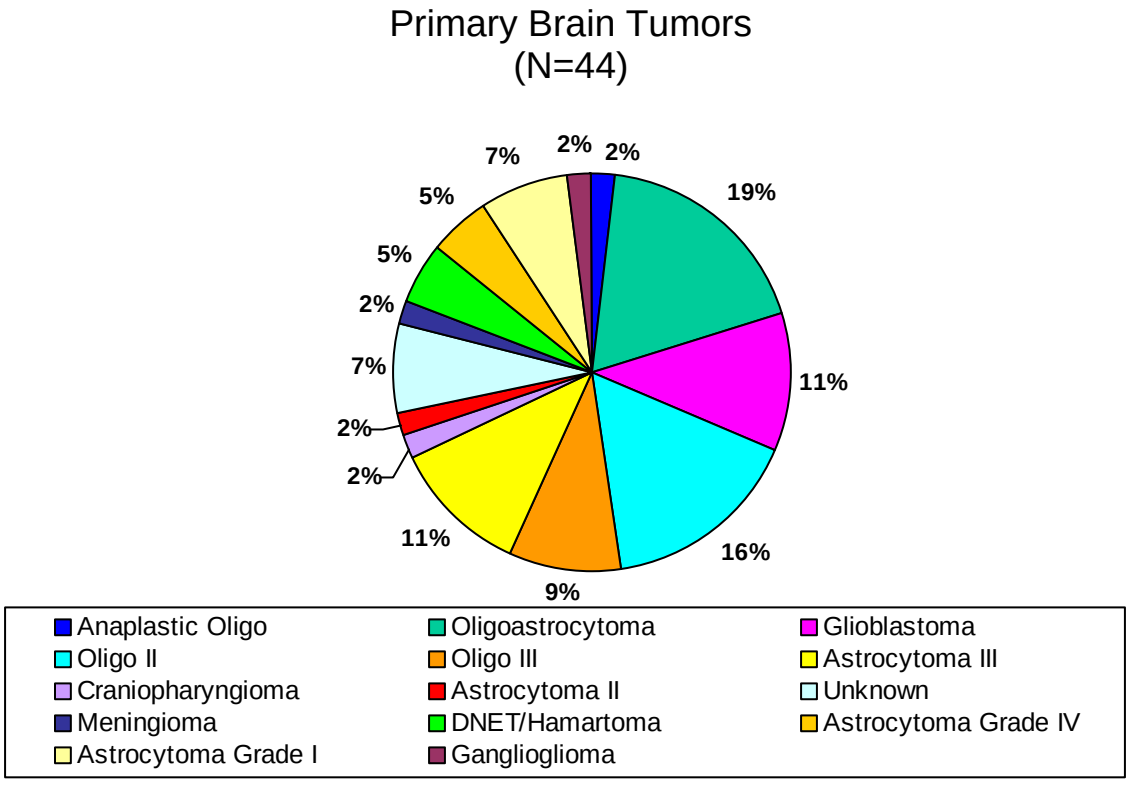
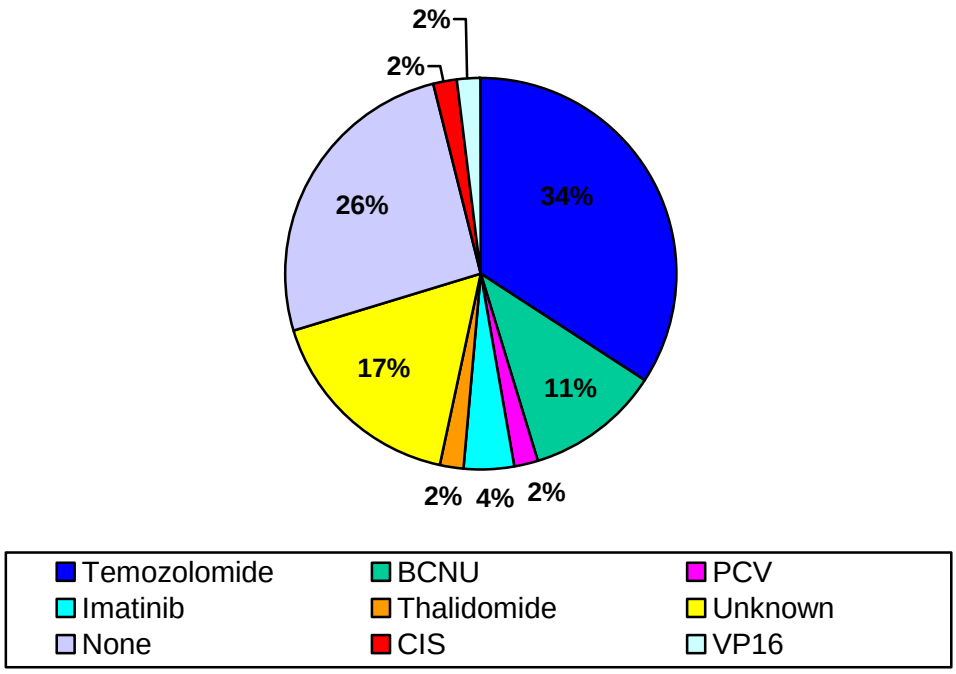


Figure 2



*some patients received multiple types

Figure 3