

Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Lee JW, Bromfield EB, Kesari S. Antiemetic properties of the antiepileptic drug levetiracetam. *N Engl J Med* 2008;359:1853.

Table 1: Patient baseline characteristics and statistical analysis (n=161)

A: Baseline characteristics¹			B: Univariate analysis³		C: CINV counts⁴			
	LEV (66)	non-LEV (95)	All patients	P-value	All patients	LEV	non-LEV	No AED
Mean age, y (SD)	56.8 (12.5)	55.6 (11.6)	LEV use	0.0027	CINV	8	32	14
Gender, M/F, n (%)	41 (62)/25 (38)	55 (58)/40 (42)	Older age	0.0272	No CINV	58	63	25
			Male gender	0.2906			P=0.0016	P=0.0059
Chemo: TMZ alone	48	52	Chemo	0.4187	TMZ alone			
Chemo: TMZ + other²	18	43	Dexamethasone use	0.9673		LEV	non-LEV	No AED
					CINV	6	21	9
Dexamethasone use (%)	37 (56)	52 (55)			No CINV	42	31	13
Phenytoin	10	39					P=0.0030	P=0.0117
Valproic acid	1	9			D: Logistic regression⁵			
Gabapentin	0	4			All patients	Adjusted Odds Ratio	95% CI	P-value
Carbamazepine	1	4			LEV use	4.067	1.668-9.920	0.0020
Other AEDs	1	5			Older age	1.043	1.008-1.079	0.0161
No AEDs	N/A	39			Male gender	1.757	0.792-3.900	0.1660
					Chemo	1.755	0.776-3.970	0.1767
					Dexamethasone use	1.003	0.466-2.161	0.9929

Abbreviations: AED-antiepileptic drug, Chemo-chemotherapy, CI-confidence interval, CINV-chemotherapy-induced nausea/vomiting, LEV-levetiracetam, N/A-not applicable, TMZ-temozolomide.

¹Retrospective IRB approved chart review of GBM patients with KPS=>60 seen in neuro-oncology clinic at Dana-Farber/Brigham and Women's Cancer Center between 3/1/2000 and 8/31/2006. Two authors (JWL, SK) independently reviewed the first 2 cycles (=2 months) of adjuvant TMZ based chemotherapy and noted baseline characteristics and AED use before starting chemotherapy and presence of CINV (absent or present noted in clinical notes as reported by patient or physician) in either one of these 2 cycles; these early cycles were chosen so as to not confound the effects of disease progression which often happens within 6 months in patients with GBM. This was done in a non-blinded fashion and independently validated the datasets. We initially reviewed 200 consecutive GBM cases between 2000 and 2004 and only included patients whose treatment was administered locally so that adequate treatment and side-effect information was available in the medical records. Because only ~50% of these initial cases were eligible, we then expanded our review to 2006, for a total of 400 cases of which 161 had enough information to include in this final analysis. The median dose of LEV at baseline was 1000mg divided BID (range of 1000mg to 4000mg daily) and most patients were on 1000mg (56%) or 1500mg (19%) daily. Emetogenicity categories: Most brain tumor specific regimens are classified as moderate including TMZ and irinotecan. Thalidomide, erlotinib and R115777 are investigational agents and classified as minimal. Per standard clinical practice, all patients are routinely premedicated with conventional antiemetic agents (all with ondansetron, a 5-HT(3) antagonist, at our institution) during chemotherapy and usually add or switch to other drugs (e.g., metoclopramide, prochlorperazine, lorazepam, and new agents as clinically indicated) if nausea not controlled after these cycles.

²Most patients (87%) received thalidomide (35 pts) or irinotecan (18 pts), the rest received erlotinib (5) or R115777 (3). The imbalance in LEV vs. non-LEV is an historical artifact during this time of avoiding AEDs altogether due to potential interactions with new chemotherapy regimens and also due to a trend towards tapering AEDs in patients who have not had prior seizures.

³Univariate analysis using logistic regression of factors associated with reduced CINV. Age was analyzed as a continuous variable.

⁴Numbers of patients who did or did not have CINV. In 3 of the 32 non-LEV patients with CINV, the nausea resolved after LEV initiated. In 1 of the 58 LEV patients without CINV, nausea emerged after LEV tapered. In 1 of the 63 non-LEV patients without CINV, nausea emerged after LEV initiated. In all these cases the change in LEV was for unrelated reasons. The reported P-values are Fisher's exact test used to determine the significance between the comparator group-LEV.

⁵Multivariate logistic regression (SAS version 9.2, SA Institute, Inc.) modeling the adjusted odds of not developing CINV with LEV, gender, age, chemotherapy, and dexamethasone use and confirmed using stepwise and backward modeling. Dexamethasone's well-known efficacy against CINV was likely not appreciated because of the retrospective nature of this study and patients selected to receive dexamethasone may have also been at greatest risk for CINV. Likewise the anti-nausea effect of LEV may be underestimated due to co-administration of dexamethasone and traditional antiemetic agents.