De novo glioblastoma and relationship of anti-epileptic treatment with overall survival: a study on 285 patients from 3 Lombardia hospitals

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Introduction

Epilepsy is common in GBM, with 40-60% of patients experiencing seizures. It has been reported that GBM patients presenting with seizures survive longer, this notion raises questions about the reason of improved survival, whether antiepileptic drugs (AEDs) play a role, and whether all AEDs have the same effect. Different studies have suggested a possible impact of antiepileptic drugs (AEDs), in particular valproate (VPA) and levetiracetam (LEV), on survival in patients with GBM treated according to current standards of care. On the contrary, a recent pooled analysis of prospective clinical trials in newly diagnosed GBM and a population-based study on 1263 GBM patients from Norway found no significant survival benefit in GBM patients treated with AED. We performed a retrospective study on adult patients with GBM followed in 3 Lombardia Hospitals in order to evaluate the impact of AEDs therapy on overall survival (OS), after adjusting for known prognostic factor (age, extent of surgery, Karnofsky performance status, radiochemotherapy)

Methods

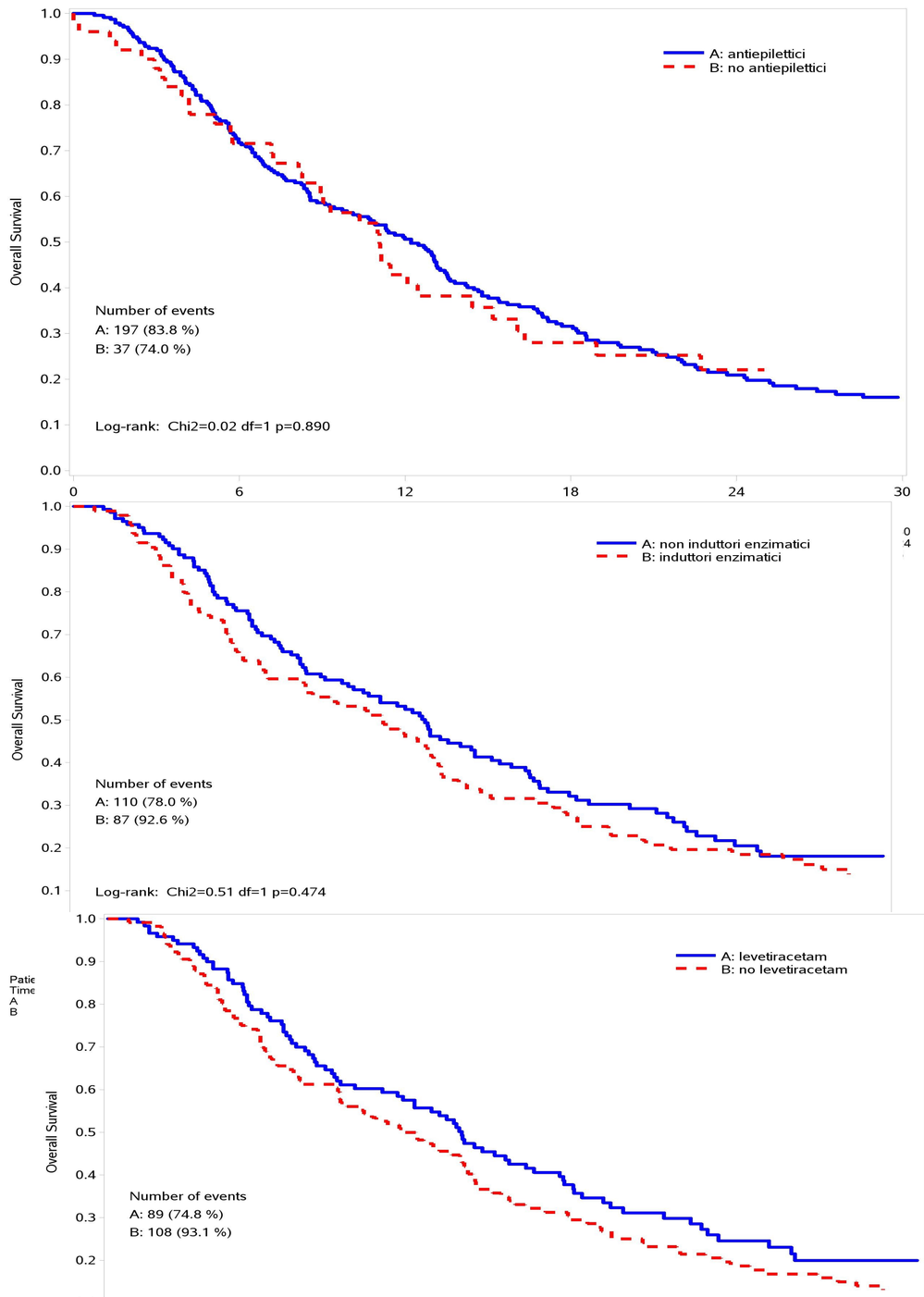
The patient's cohort includes 285 individuals with a newly diagnosed GBM. In all cases the diagnosis was supported by histological data. We collected data regarding sex, age at onset, major presenting symptoms, tumor location, Karnofsky performance status (KPS), extension of surgical resection (EOR), adjuvant treatment, antiepileptic therapy, survival data.We also collected information regarding the presence/absence of seizure at presentation and the use of antiepileptic drugs (AED),in particular regarding AED we recorded if the patients received enzyme-inducing AED (EIAED) or non enzyme-inducing AED (non-EIAED) such as valproate or levetiracetam. Survival data were obtained from the death record registry of Lecco and Milan Province.

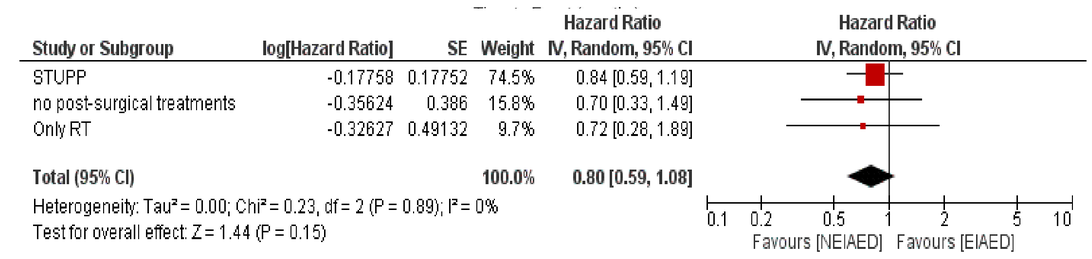
Statistical methods

The study endpoint was Overall Survival (OS) defined as the time from the date of surgery to the date of death.Baseline covariate and treatment distributions were summarized using descriptive statistics (median and range for continuous variables, and absolute and percentage frequencies for categorical variables). Survival functions were estimated by the Kaplan-Meier method. Median follow-up was estimated by the reverse the Kaplan-Meier method. Cox model was used by each concomitant antitumoral treatment to detect and estimate statistical association between type of antiepilectic treatment (i.e. enzyme inducing vs non enzyme inducing antiepilectic drugs) and OS. In multivariable regression models predictor variables were identified a priori. A random-effects meta-analysis model was used to estimate an average effect size. The DerSimonian and Laird method was used to estimate the between-subgroups variance. Q and I2 statistics were used respectively to detect and estimate heterogeneity.

Results

At univariate analysis the OS of patients receiving an AED at baseline was not statistically significantly different from that of patients not receiving an AED (p=0.925, HR 0.98, 95% CI 0.69-1.4), althought median OS was 12 months and 11.1 months in the latter group, respectively. Moreover OS was not statistically significantly different between patients receiving EIEAD or non EIAED (p=0.512, HR 0.91, 95% CI 0.68-1.2), despite median OS of 12.9 months and 11.4 months in the subgroups respectively, nor between patients receiving levetiracetam or other AEDs (p=0.250, HR 1.18, 95% CI 0.89-1.56) (median OS 13 months in levetiracetam-treated patients versus 10.9 months in those receiving other-AED) (figure con Kaplan Meyer).
At multivariate analysis a trend to more prolonged survival was detected in patients treated with NEIAED versus those treated with EIAD, regardless of post-surgical treatment.





	Overall	AED	No AED	EIAED	NEIAED
Total number	285	235/285	50/285	94/235	141/235
Female	107	89	18	38	51
Male	178	146	32	56	90
Age at diagnosis					
Median	66.9	66.4	68.2	63.1	67.5
Min	27.8	27.8	29.9	31.1	27.8
Max	83	83	81.8	79.5	83
Karnofski					
Median	80	80	70	80	80
Min	30	50	30	50	50
Max	100	100	100	90	100
Extent of surgery					
Biopsy	33	24	9	8	16
MTR	197	167	30	77	90
Partial	55	44	11	9	35
Adjuvant treatment					
Stupp	205	176	29	71	105
Radiotherapy	33	27	6	7	20
No other treatment	47	32	15	16	16

Conclusion

Given the dismal prognosis of GBM with conventional therapy, there is growing interest in exploring the possible effect of AEDs on prognosis and the possible inclusion of these drugs into the standard of care for newly diagnosed GBM patients. Some retrospective clinical studies and a metanalysis suggested a possible impact of treatment with AED on survival in patients with newly diagnosed glioblastoma.Unfortunately a recently pooled analysis of prospective clinical trials in newly diagnosed GBM patients reported that VPA use at start of radiochemotherapy was not associated with improved PFS or OS compared with all other patients pooled , similarly no association with improved outcomes was observed for LEV. Similarly, in a retrospective nation-wide analysis of 1263 GBM patients diagnosed in Norway between 2004-2010 , none of the six AEDs valproate, levetiracetam, carbamazepine, oxcarbazepine, lamotrigine or phenytoin significantly influenced overall survival. In line with these papers, in our patients we did not observe a positive impact of AEDs on overall survival, moreover no statistically significant difference was observed between patients receiving a non EIAED versus EIAED, even if a trend of more prolonged survival was detected in those receiving NEIAED. The question whether treatment with AEDs may increase OS in GBM patients remains unanswered and randomized extremely large controlled clinical trial would be necessary to elucidate the possible impact of AED on prognosis. Neverthless recently discovered common pathways of epileptogenesis and tumour growth in gliomas hold promise in identifying other potential targets of therapy, in the meantime the use of AED in GBM patients, based on the presumed potential antitumour activity,is not recommended.