Antiepileptic treatment and survival in newly diagnosed glioblastoma patients: Retrospective multicentre study in 285 Italian patients

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ABSTRACT

Glioblastoma multiforme (GBM) has a dismal prognosis even with the best available treatment. Different studies have suggested a possible impact of antiepileptic drugs (AED) on survival in patients with GBM. A recent pooled analysis of prospective clinical trials in newly diagnosed GBM found no significant survival benefit in GBM patients treated with AED. We performed a retrospective study on adult patients with GBM in order to evaluate the impact of AED therapy on overall survival (OS), after adjusting for known prognostic factor (age, extent of surgery, Karnofsky performance status, radiochemotherapy).

A total of 285 patients were analyzed. Of them 144 received a non-enzyme-inducing (NEIAED) and 95 an enzyme-inducing AED (EIAED). At univariate analysis the OS of patients receiving AED was not significantly different from that of patients not receiving an AED (HR 0.98, 95%CI 0.69-1.4, p = 0.925), moreover OS was not significantly different between patients receiving EIAED or NEIAED. At multivariate analysis a trend to more prolonged survival (HR 0.8, 95% CI 0.59-1.08, p = 0.15) was detected in patients treated with NEIAED.

The question whether treatment with AED 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. In the meantime the use of AED in GBM patients, based on the presumed potential antitumour activity, is not recommended.

1. Introduction

Glioblastoma multiforme (GBM) is the most common and aggressive primary brain tumor in adults. It has a dismal prognosis even with the best available treatment. The standard of care, consisting of maximum tumor resection followed by radio-chemotherapy with temozolomide (TMZ), leads to a median survival of 14.6 months [1,2]. Epilepsy is common in GBM, with 40–60% of patients experiencing seizures [3,4]. It has been reported that GBM patients presenting with seizures survive longer [5], 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 [6–12]. The positive effects of VPA on survival could possibly be explained by the radiotherapy-sensitizing properties of VPA, including the inhibition of histone deacetylase [6]. In vitro studies indicate that LEV inhibits transcription of O-6-methylguanine-DNA-methyltransferase (MGMT) gene through the p53 mediated compressor complex and sensitize glioblastoma cells to temozolomide [13]. On the contrary, a recent pooled analysis of prospective clinical trials in newly diagnosed GBM [14] and a population-based study [15] 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).

2. Materials and methods

This is an Italian, multicentre, retrospective, cohort study. The patient's cohort includes 285 individuals with a newly diagnosed GBM.

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followed in 3 Lombardia Hospitals (Lecco, Niguarda, C. Besta); patients in Lecco were enrolled between 2004 and 2014, while patients from other hospitals were enrolled from 2007 to 2014.

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.

Major presenting symptoms were categorized as seizure, focal deficits, cognitive-behavioral symptoms, intracranial hypertension. EOR was categorized in macroscopical total resection (MTR), partial resection (PR), stereotactic biopsy (SB) as declared by the neurosurgeon and evaluated by neuroimaging 72 h post surgery.

Regarding adjuvant treatment strategies we recorded if the patient received no further treatment other than surgery, radiotherapy only, chemotherapy only, radiochemotherapy. 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 antiepileptic drugs (NEIAED) such as valproate or levetiracetam.

We also collected information regarding sex, age at onset, major presenting symptoms, tumor extension, Karnofsky performance status (KPS), extension of post-surgical intervention (radiotherapy alone, best supportive care alone), survival data were obtained from the death record registry of Lecco and Milan Province.

2.1. Statistical methods

The study endpoint was Overall Survival (OS) defined as the time from the date of surgery to the date of death. Patients alive at the last contact were right-censored. 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 for each concomitant tumoral treatment to detect and estimate statistical association between type of antiepileptic treatment (i.e. enzyme inducing versus non enzyme inducing antiepileptic 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. Statistical analysis was generated using SAS/STAT software, version 9.4 of the SAS System for Windows. (SAS Institute, Cary NC). Copyright (c) 2002–2012 by SAS Institute Inc., Cary, NC, USA.

3. Results

3.1. Patients characteristic

A total of 285 patients (178 males and 107 females) were analyzed. At the time of analysis (median follow-up of 3.1 years, IQR: 1.8–6.2 months) 50 patients were still alive and the remaining 235 had died. Mean age at onset was 64.2 years (range 28–83) and median age at onset 67 years. Mean KPS value was 75 (range 30–100) and median KPS 80. The extent of surgical resection was macroscopically total in 197/285 (69%) of cases and partial in 55/285 (19.3%). A biopsy was performed in 11.7% (33/285) of patients. Two hundred and five patients (71.9%) received radiochemotherapy according to the Stupp protocol, 33 patients (11.5%) received radiotherapy only, 47 patients (16.5%) received no further treatment other than surgery. Mean and median OS irrespective of treatment were 14.5 months (range 0.92–21) and 11 months. Major presenting symptoms, isolated or in combination, included focal deficits (137/285 = 48%), cognitive-behavioral symptoms (90/285 = 31.6%), symptoms related to intracranial hypertension (86/285 = 30%) and seizure (66/285 = 23.2%). At the time of diagnosis 46 tumors were plurilobar, 7 multifocal, 6 centrally located (basal ganglia and corpus callosum) and the remaining 226 were lobar–located tumors.

Sixty-six patients (23%) presented seizure at onset, however a prophylactic antiepileptic treatment was prescribed in 83% of patients (239/285) at the moment of diagnosis. The most common drug used was levetiracetam (122/239 = 51%), followed by oxcarbazepine/carbamazepine (45/239 = 19%), valproate (22/239 = 9%), phenobarbital (39/239 = 16%) and phenytoin (11/239 = 5%). In total 144 patients (60%) received a NEIAED (i.e. either levetiracetam or valproate), whereas 95 patients (40%) received a EIAED (phenobarbital, phenytoin, oxcarbazepine/carbamazepine).

Baseline clinical features were similar in patients receiving AEDs as compared with those not treated with AEDs, except for a trend to lower KPS in those not receiving AEDs and a lower proportion of patients undergoing MTR in this subgroup. When the 239 patients receiving AEDs were subdivided in those treated with EIAED versus NEIAED, only a trend to higher frequency of MTR in those treated with EIAED was detected. Patients treated with EIAED. NEIAED did not differ in their clinical features according to post-surgical intervention (radiochemotherapy versus radiotherapy alone) (Table 1).

3.2. Subgroup analysis and statistical results

At univariate analysis the OS of patients receiving an AED at baseline was not significantly different from that of patients not receiving an AED (HR 0.98, CI 0.69–1.4, p = 0.925), although median OS was 12.2 months (95% CI 9.9–13.4) in the former and 11.1 (95% CI 8.1–14.4) in the latter group respectively (Fig. 1). Moreover OS was not significantly different between patients receiving NEIAED or EIAED (HR 0.91, 95% CI 0.68–1.2, p = 0.512), despite median OS of 12.9 months (95% CI 9.9–14.8) and 11.4 (95% CI 7.2–13.3) months in the subgroups respectively (Fig. 2), nor between patients receiving levetiracetam or other AEDs (HR 1.18, 95% CI 0.89–1.56, p = 0.250) (median OS 13 months in levetiracetam-treated patients versus 10.9 months in those receiving other-AED) (Fig. 3). A further subgroup analysis comparing OS in patients receiving levetiracetam versus patients receiving EIAED was not statistically significant (HR 1.08, 95% CI 0.93–1.26, p = 0.291) (Fig. 4) and similar results were observed comparing patients receiving valproate versus patients receiving EIAED (HR 0.86, 95% CI 0.54–1.42, p = 0.585) (Fig. 5), although survival curves in patients treated with levetiracetam versus patients receiving other AED did never overlap.

At multivariate analysis a trend to more prolonged survival (HR 0.8, 95%CI 0.59–1.08, p = 0.15) was detected in patients treated with NEIAED versus those treated with EIAED, regardless of post-surgical treatment. (Fig. 6).

4. Discussion

Epilepsy is frequent in brain tumors and 40–60% of GBM patients suffer from seizures [3,4]. It has been reported that GBM patients with a history of seizures have a better prognosis than patients without seizures [5]. This observation raises questions about the possible impact of AED, especially those with antitumor functions, on survival.

Given the dismal prognosis of GBM with conventional therapy, and the low number of novel and promising pharmacological agents for treatment, there is growing interest in exploring the possible effect of AED on prognosis and the possible inclusion of these drugs into the standard of care for newly diagnosed GBM patients.

investigated the effects of EIAED or NEIAED on survival in 168 patients with GBM treated with surgery, radiotherapy and chemotherapy. A mild statistically significant difference in survival was observed between patients receiving a NEIAED (13.9 months) and those receiving an EIAED (10.8 months). In 2009 Jaeckle et al. [6] reported a positive correlation between EIAED use and OS and PFS in patients with newly diagnosed GBM. In 2011 Jaeckle et al. [6] examined clinical trial database of the European Organization for Research and Treatment of Cancer and of the National Cancer Institute of Canada to assess the impact of the interaction between AED use and chemo-radiotherapy on survival. The OS of patients who were receiving AEDs at baseline versus not receiving any AEDs was similar. Patients receiving valproic acid (VPA) alone appeared to derive more survival benefit from chemotherapy (HR 0.39, 95% CI: 0.24–0.63) than patients receiving EIAEDs only (HR 0.69, 95% CI 0.53–0.90) or patients not receiving any AEDs (HR 0.67, 95% CI 0.49–0.93). In 2013 also Weller et al. [7] underlined a positive effect of VPA on survival; the group of patients using VPA in combination with TMZ during at least 3 months had a significantly longer median survival of 69 weeks (95% CI: 61.7–67.3), compared with 61 weeks (95% CI: 52.5–69.5) in the group not using VPA.

In the same year Kerkhof [8] presented a review to investigate the

Table 1
Patients characteristics.

<table>
<thead>
<tr>
<th></th>
<th>Overall</th>
<th>AED</th>
<th>No AED</th>
<th>EIAED</th>
<th>NEIAED</th>
</tr>
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<tbody>
<tr>
<td>Total number</td>
<td>285</td>
<td>235/285</td>
<td>50/285</td>
<td>94/235</td>
<td>141/235</td>
</tr>
<tr>
<td>Female</td>
<td>N(%)</td>
<td>107(37.5)</td>
<td>89 (37.9)</td>
<td>18 (36.0)</td>
<td>38 (40.4)</td>
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<tr>
<td>Male</td>
<td>N(%)</td>
<td>178(62.5)</td>
<td>146 (62.1)</td>
<td>32 (64.0)</td>
<td>56 (59.6)</td>
</tr>
<tr>
<td>Age (at diagnosis)</td>
<td>N</td>
<td>285</td>
<td>235</td>
<td>50</td>
<td>94</td>
</tr>
<tr>
<td></td>
<td>Median</td>
<td>66.9</td>
<td>66.4</td>
<td>68.2</td>
<td>63.1</td>
</tr>
<tr>
<td></td>
<td>Min</td>
<td>27.8</td>
<td>27.8</td>
<td>29.9</td>
<td>31.1</td>
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<tr>
<td></td>
<td>Max</td>
<td>83.0</td>
<td>83.0</td>
<td>81.8</td>
<td>79.5</td>
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<tr>
<td>Karnofski performance status</td>
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<td>285</td>
<td>235</td>
<td>50</td>
<td>94</td>
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<tr>
<td></td>
<td>Median</td>
<td>80</td>
<td>80</td>
<td>70</td>
<td>80</td>
</tr>
<tr>
<td></td>
<td>Min</td>
<td>30</td>
<td>50</td>
<td>30</td>
<td>50</td>
</tr>
<tr>
<td></td>
<td>Max</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>90</td>
</tr>
<tr>
<td>Extent of surgery</td>
<td>Biopsy</td>
<td>N(%)</td>
<td>33(11.6)</td>
<td>24 (10.2)</td>
<td>9 (18.0)</td>
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<tr>
<td></td>
<td>MTR</td>
<td>N(%)</td>
<td>197(69.1)</td>
<td>167 (71.1)</td>
<td>30 (60.0)</td>
</tr>
<tr>
<td></td>
<td>Partial</td>
<td>N(%)</td>
<td>55 (19.3)</td>
<td>44 (18.7)</td>
<td>11 (22.0)</td>
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<tr>
<td>Adjuvant treatment</td>
<td>Stupp protocol</td>
<td>N(%)</td>
<td>205(71.9)</td>
<td>176 (74.9)</td>
<td>29 (58.0)</td>
</tr>
<tr>
<td></td>
<td>Radiotherapy</td>
<td>N(%)</td>
<td>33 (11.6)</td>
<td>27 (11.5)</td>
<td>6 (12.0)</td>
</tr>
<tr>
<td></td>
<td>No other treatment</td>
<td>N(%)</td>
<td>47 (16.5)</td>
<td>52 (13.6)</td>
<td>15 (30.0)</td>
</tr>
</tbody>
</table>

AED Antiepileptic drug.
EIAED enzyme-inducing antiepileptic drug.
NEIAED non enzyme-inducing antiepileptic drug.
Min-max minimum and maximum values.
MTR macroscopical total resection.

Fig. 1. Kaplan-Meier curves of OS in patients receiving an AED (A) vs patients not receiving an AED (B).
role of VPA as an antitumor agent in the management of patients with GBM. Patients treated with AEDs had a significantly longer survival than those who were not (Mantel-Cox log-rank test 19.617, p = 0.001) and patients treated with VPA had a significantly longer survival than those who received other AEDs (Mantel-Cox log-rank test 5.303, p < 0.02).

A meta-analysis of five studies on the effect of VPA on OS [12], concluded that this treatment was beneficial and could prolong the life of patients with GBM when compared to patients not receiving AED (HR 0.74, 95% CI 0.59–0.94) or receiving an AED different from VPA (HR 0.66, 95% CI 0.52–0.84).

In 2015 Kim et al. [10] analyzed the benefit of levetiracetam (LEV) compared with other AED as a chemosensitizer to TMZ. The median PFS (9.4 months; 95% CI: 7.5–11.3 months) and OS (25.7 months; 95% CI: 21.7–29.7 months) for patients who received LEV in combination with TMZ were significantly longer than those for patients who did not receive LEV (PFS: median, 6.7 months; 95% CI, 5.8–7.6 months; p 0.010; OS: median, 16.7 months; 95% CI, 12.1–21.3 months; p 0.027). Thus, there has been a number of reports suggesting that some antiepileptic drugs might be considered as candidates also in the context of repurposing strategies in patients with high grade glioma, although other reports have been contradictory. In this context, results from laboratory investigations have indeed produced results that are conflicting, possibly due to differences in experimental design of the studies; while Phiel and colleagues [16] have shown hyperacetylation of histones in cultured cells at therapeutic levels, Rocca and colleagues [17] in a study in patients with advanced melanoma were able to detect significant histone acetylation levels in peripheral blood mononuclear cells only in patients receiving a supratherapeutic dose of valproic acid.

Unfortunately a recently pooled analysis of prospective clinical trials in newly diagnosed GBM patients [14] reported that VPA use at start of radiochemotherapy was not associated with improved PFS or...
OS compared with all other patients pooled (PFS: HR 0.91, 95% CI 0.77–1.07, p = 0.241; OS: HR 0.96, 95% CI 0.8–1.05, p = 0.633), similarly no association with improved outcomes was observed for LEV (PFS: HR1.14, 95% CI 1.10–1.28, p = 0.029, OS: HR 1.05, CI 0.92–1.2, p = 0.462). Furthermore PFS and OS of patients taking VPA or LEV both at the beginning of and still after radiochemotherapy were not different from those without AED. Similarly, in a retrospective nationwide analysis of 1263 GBM patients diagnosed in Norway between 2004 and 2010 [15], none of the six AED 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 AED on overall survival, moreover no statistically significant difference was observed between patients receiving a NEIAED versus EIAED, even if a trend of more prolonged survival was detected in those receiving NEIAED, particularly for levetiracetam. The interesting result of our study is that the advantage in OS outcome was confirmed independently of the adjuvant treatment strategies, thus suggesting that putative antitumor effects of NEIAEDs may not be strictly related to the radiochemotherapy phase of adjuvant treatments.

Our paper, as most of the studies regarding the impact of AED on survival of GBM patients, presents some limits. First of all, the data derive from unplanned retrospective analysis, secondly the sample size is small, finally the selection of AED depend on the investigators’ preferences and local practice and the dose and duration of treatment was heterogeneous.

Despite these problems, our data reflect the wide spread attitude of the neurooncological community in the overtreatment of GBM patients with AED regardless of seizure occurrence [18,19]. Only a small proportion of seizure-free patients did not receive AED; no major differences in clinical features or outcome (i.e. survival) were detected between these two groups; the retrospective nature of the study does not

Fig. 4. Kaplan-Meier curves of OS in patients receiving levetiracetam (A) vs patients receiving an EIAED (B).

Fig. 5. Kaplan-Meier curves of OS in patients receiving valproate (A) vs patients receiving an EIAED (B).
exclude a selection bias produced by the treating physicians’ preferences. Among the available drugs, levetiracetam is by far the most prescribed, perhaps due to its ease in titration, low frequency of severe side effects and low profile of interaction with other drugs; however, some studies warn about a possibly higher frequency of serious side effects on ideation and mood in patient treated with levetiracetam for frontal tumors [20]. Although overall treatment with NEIADs was the most frequent choice, a non negligible proportion of patients still received EIAIDs; this was mostly due to treatment started by the neurosurgeon and subsequently felt by patients and or physicians difficult or hazardous to stop or modify.

The question whether treatment with AED may increase OS in GBM patients remains unanswered and extremely large randomized controlled clinical trial would be necessary to elucidate the possible impact of AED on prognosis. Nevertheless recently discovered common pathways of epileptogenesis and tumor growth in gliomas [21,23] 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.

On behalf of all authors, the corresponding author states that there is no conflict of interest.

References


Fig. 6. Forest plot of the effect of antiepileptics treatment type on OS according to the different adjuvant strategies.