Journal of the Neurological Sciences 390 (2018) 14–19

Contents lists available at ScienceDirect

Journal of the Neurological Sciences

journal homepage: www.elsevier.com/locate/jns

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

Andrea Rigamonti[a,*], Francesca Imbesi[b], Antonio Silvani[c], Paola Gaviani[c], Elio Agostoni[b], Luca Porcu[d], Irene De Simone[d], Valter Torri[d], Andrea Salmaggi[a]

[a] Neurological Department, ASST Lecco, Via Dell' Eremo 9-11, 23900 Lecco, Italy
[b] Neurological Department, ASST, Grande Ospedale Metropolitano Niguarda, Piazza Ospedale Maggiore 3, 20162 Milano, Italy
[c] Neuro Oncology Unit, Fondazione IRCSS Carlo Besta, Via Celoria 11, 20133 Milano, Italy
[d] Pharmacological Research Institute, IRCSS Mario Negri, Via La Masa 19, 20156 Milano, Italy

ARTICLE INFO

Keywords:
Antiepileptic drugs
Glioblastoma
Survival
Epilepsy

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 radiotheraphy-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 p-53 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

* Corresponding author.
E-mail addresses: rig74@libero.it, andrea.rigamonti@asst-lecco.it (A. Rigamonti).

https://doi.org/10.1016/j.jns.2018.04.004
Received 28 November 2017; Received in revised form 7 March 2018; Accepted 3 April 2018
Available online 05 April 2018
0022-510X/

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, radiochemoterapy. 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 (NEIAED) such as valproate or levetiracetam. Antiepileptic use was defined as treatment at diagnosis and for at least 3 months (i.e. encompassing the time lapse between surgery and end of concomitant radiochemiotherapy in patients receiving both treatments, or still ongoing 3 months after diagnosis in patients treated with radiotherapy alone or 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 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. 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 0,2–92,1) 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 remaning 226 were lobar -located tumors.

Sixty-six patients (23%) presented seizure at onset, however a prophylatic 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 tretated 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), althought 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 NEIEAD 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 (HR0.86, 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 EIAD, 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 question 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.

Some retrospective clinical studies [6–11] and a metanalysis [12] suggested a possible impact of treatment with AED on survival in patients with newly diagnosed glioblastoma. Bobustuc et al. [11]