Seizure 23 (2014) 830–835

Contents lists available at ScienceDirect

Seizure

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

Survival analysis for valproic acid use in adult glioblastoma multiforme: A meta-analysis of individual patient data and a systematic review

Yang Yuan [a,1], Wang Xiang [a,1], Mao Qing [a,*], Liu Yanhui [a], Luo Jiewen [a], Mao Yunhe [b]

[a] Department of Neurosurgery, West China Hospital, Si Chuan University, Chengdu 610041, China
[b] West China Medical School of Si Chuan University, Chengdu 610041, China

ARTICLE INFO

Article history:
Received 19 May 2014
Received in revised form 22 June 2014
Accepted 29 June 2014

Keywords:
Glioma
Valproic acid
Survival
Meta-analysis

ABSTRACT

Purpose: Glioblastoma multiforme (GBM) is the most lethal type of primary brain tumor, and patients that undergo the maximum tumor resection that is safely possible and standard radiochemotherapy only achieve a median survival time of 14.6 months. Several clinical studies have reported that valproic acid could prolong survival of GBM patients. However, the results of these studies are inconsistent. We examined relevant studies and conducted a meta-analysis to assess the effects of VPA on survival times and recurrence.

Methods: A bibliographic search was performed in the EMBASE, MEDLINE, ClinicalTrials.gov and Cochrane Central Register of the Controlled Trials databases to identify potentially relevant articles or conference abstracts that investigated the effects of VPA on the outcome of glioma patients. Five observational studies were included.

Results: Pooled estimates of the hazard ratio (HR) and 95% confidence intervals (CI) were calculated. Our meta-analysis confirmed the benefit of using VPA (HR, 0.56; 95% CI, 0.44–0.71). Sub-group analysis shows that patients treated with VPA had a hazard ratio of 0.74 with a 95% confidence interval of 0.59–0.94 vs. patients treated by other-AEDs and a hazard ratio of 0.66 with a 95% confidence interval of 0.52–0.84 vs. patients treated by administration of non-AEDs. No heterogeneity was observed in the subset analysis.

Conclusion: The results of our study suggest that glioblastoma patients may experience prolonged survival due to VPA administration. Sub-analysis confirmed the benefit of VPA use compared to a non-AEDs group and an other-AEDs group. Further RCTs of this subject should be performed.

1. Introduction

Glioblastoma multiforme (GBM) is the most lethal and most frequent type of astrocytic brain tumor in adults.[1] It is a malignant, highly recurrent intracranial neoplasm with a rapidly progressive and fatal outcome. Patients who undergo the maximum tumor resection that is safely possible and standard radiochemotherapy with temozolomide (TMZ) only achieve a median survival time of only 14.6 months, and the 5-year survival rate of patients is less than 10%.[2] Glioma-associated seizures (GAS) frequently occur among glioma patients. Approximately 30%–50% of GBM patients will experience seizure activity before surgery, and 6%–45% experience seizures post-diagnosis.[3] However, it has been reported that GBM patients with a history of seizures will have a better prognosis than patients without seizures, which raises questions about whether the antiepileptic drugs, especially those with anti-tumor functions, play a role in this process.

Valproic acid (VPA) has evolved beyond its original use in the 1960s, as an established anticonvulsant drug and mood stabilizer, into an anticancer drug.[4] Preclinical studies within the last decade have suggested that VPA and its analogs could affect tumor cells in many respects, such as inhibition of a subset of histone deacetylases (HDAC) and cellular kinases, which could affect gene transcription through histone hyperacetylation, DNA hypomethylation, and modulation of the MAPK signaling pathway.[5] As a

* Corresponding author at: Neurosurgery Department, West China Hospital, Waiguoxuexiang No. 37, Chengdu 610041, Sichuan Province, China. Tel.: +86 18980601506; fax: +86 02885422488.
E-mail addresses: 76896489@qq.com (Y. Yuan), 4589235@qq.com (W. Xiang), qingmao2000@163.com (M. Qing), 827005432@qq.com (L. Yanhui), 4155343@qq.com (L. Jiewen), 297913442@qq.com (M. Yunhe).
[1] These authors contributed equally to this work and are considered co-first authors.

http://dx.doi.org/10.1016/j.seizure.2014.06.015
1059-1311/

consequence, VPA could inhibit tumor angiogenesis and induce differentiation and apoptosis in diverse types of tumor cells. Some clinical studies have reported the outcome of GBM patients with valproic acid for seizure prophylaxis or treatment, and it appears that most, but not all, of these reports have suggested that VPA could prolong overall survival in GBM patients.[6] However, the combination of the results of these studies in our meta-analysis increases the statistical power and may provide sufficient information to show a credible survival benefit of VPA treatment.

Therefore, we conducted a survival analysis for valproic acid treatment of adult glioblastoma multiforme. Using meta-analysis, we initiated time-to-event analyses, which are extremely important for malignant tumors such as glioblastoma multiforme. Novel methods in the treatment of this devastating cancer are urgently needed.

2. Methods

2.1. Search strategy

In February 2014, a bibliographic search was performed in the EMBASE, MEDLINE, ClinicalTrials.gov and Cochrane Central Register of Controlled Trials databases to identify potentially relevant articles or conference abstracts that reported the outcome of patients diagnosed with glioblastoma multiforme, and we initiated the survival analysis of patients treated with or without valproic acid. The search was limited to studies written in English. Two investigators (Y.Y and W.X) independently evaluated papers with respect to the inclusion and exclusion criteria, and any controversies were settled by discussion and consensus. The references contained in the identified trials were also examined to identify any other relevant published or unpublished articles. We used combinations of the following search terms: glioma, valproic acid, outcome and brain tumor (details of the search criteria are provided in Supplemental file 1).

2.2. Inclusion and exclusion criteria

The inclusion criteria were as follows:

(a) Because drug use may involve ethical issues and limited or no RCTs, all comparative studies (i.e., trial, cohort, case–control and observational studies) of the relevant AEDs were included.
(b) The glioma cases were histologically confirmed, and all included patients had undergone surgery or biopsy; the age of all patients was >17 years.
(c) The articles provided survival status, hazard ratio (HR), and 95% confidence intervals (CIs) or information sufficient to calculate these variables from the raw data (including distinct Kaplan–Meier survival curves, number of patients of the research and control team, and follow up time).

We excluded studies for the following reasons:

(i) Either the HR data were not available or other raw data were insufficient to conduct a meta-analysis.
(ii) The patients had only received a biopsy or radiochemotherapy.
(iii) The article type was a letter, editorial or review.

2.3. Data extraction and end points

The first two authors (Y.Y. and W.X) extracted the data from each eligible article with a standardized form. Disagreements were resolved through discussion or consultation with another author (M.Q). Study designs, patient characteristics, operational definitions, combination therapy, patient outcomes, HR, and 95% CIs were extracted from the articles. We also sent emails to the corresponding authors requesting missing information, as appropriate.

Overall survival (OS) is based on death from any cause. Progression-free survival (PFS) is the length of time during and after surgery in which the disease being treated does not get worse. Data for patients alive without progression were censored on the date of last follow-up evaluation.

2.4. Statistical analyses

Our primary outcome was the overall survival of the GBM patients. We conducted meta-analyses when data were available from more than one study. Hazard ratio (HR) and 95% confidence intervals presented in the studies were used to estimate the pooled risk. If the HR was not reported in the article, we used the Engauge Digitizer 4.1 (QT) to extract the time-to-event data from Kaplan–Meier survival curves, and estimated the Hazard ratio (HR) and 95% confidence intervals by the methods recommended by Tierney.[8] The heterogeneities of the studies were assessed using Cochran's Q statistic and the I^2 statistic. When the p value was ≤ 0.1 and the I^2 value was >50%, the heterogeneity was considered significant. Publication biases were estimated using Egger's tests, and p values below 0.05 were considered evidence of publication bias. All p values were two-sided. All analyses were performed with STATA version 11 (STATA/SE, College Station, TX). Because the characteristics of eligible patients, study designs, and usage of valproic acid were not consistent across the articles, we performed further subset and sensitivity analyses to explore possible explanations of heterogeneity and to assess the potential effects of these variables on the outcomes.

The Newcastle–Ottawa Quality Assessment Scale, which was recommended by the Cochrane Non-Randomized Studies Methods Working Group, was used to assess our included studies.

3. Results

3.1. Search results and study characteristics

Fig. 1 shows the flow diagram of the electronic literature search and selection of articles. A total of 166 unique publications were identified after the exclusion of duplicates, and the titles or abstracts of these articles were examined to exclude unrelated studies. Ultimately, 53 relevant articles were identified as primary studies, and the full texts of these articles were retrieved. Next, we identified six studies as eligible for our meta-analysis. The authors of these studies were contacted for further information if the data presented in the article was insufficient for our needs, e.g., the paper reported by Me'lanie S. M. van Breemen[8] only provided K–M curves, but did not include numbers of patients and the follow-up time. The meta-analysis was ultimately based on five studies (this information is summarized in Table 1). One of the studies was conducted in North America, one was conducted in Asia, and three were conducted in Europe. All studies were published recently (published during 2011–2013).

Table 1 displays the design characteristics of the five studies that were included in our meta-analysis. Overall, 1634 patients were included; all patients had been diagnosed with glioblastoma multiforme. The largest cohort study was conducted by M. Weller et al.[15] (2011) and included 587 GBM patients. Among the included studies, 59% of patients received chemotherapy, most of them were treated with temozolomide, and 94.3% of the patients underwent radiotherapy. Phenytoin and levetiracetam were the most commonly used antiepileptic drugs beyond valproic acid used to treat patients. Only two percent of the total patients had missing data (Table 2).