Survival of children with malignant brain tumors receiving valproate: a retrospective study

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Abstract

Purpose The treatment of pediatric patients with malignant brain tumors has evolved considerably in the past decades. However, results are still unsatisfactory for some patients. Valproate has been shown to positively affect the survival of adult glioblastoma patients. We have been giving prophylactic antiepileptic drugs to newly diagnosed children with brain tumors. Since then, we noted a trend towards a better survival from our patients. In order to study this, we performed a retrospective evaluation in our institution.

Methods Standard survival analysis was used, calculating survival until death by all causes or censoring. Comparisons were made by Cox's proportional hazards model regression.

Results Between 2000 and 2010, 94 patients were treated (12 with high-grade gliomas, 56 medulloblastomas, and 26 ependymomas); median and mean ages were 7.7 and 7.8 years. Median follow-up was 60 months (35 for treated and 109 for untreated patients). Of these, 47 received valproate 10–15 mg/kg/day every 8–12 h and 47 did not. Patients who received valproate had a median survival of 34 months, whereas the other group had a median survival of 24 months (hazard ratios=0.99, 0.57–1.75, $p=0.99$).

Conclusions These results do not prove that valproate prophylactic treatment in pediatric patients with malignant brain tumors had an influence on their survival. However,

our cohort showed an effect of higher size than the recent European Organization for Research and Treatment of Cancer trial analysis, even though not significant. Clinical trials with valproate in pediatric malignant brain tumors should be carefully planned, in order to detect a possible effect of this drug in survival.

Keywords Malignant primary brain tumors · Valproic acid · Survival analysis · Treatment outcome

Introduction

The treatment of pediatric patients with malignant brain tumors has evolved considerably in the past two decades. However, results are still unsatisfactory for a subset of patients. Innovative treatments for these patients are a hot research area. Recently, Weller et al. [1] reported the effect of seizure treatment with valproate in the survival of adult glioblastoma patients. Valproate is frequently used to treat childhood epilepsy. Prophylactic use of antiepileptic drugs (AED) in brain tumor patients has been discouraged [2], but a recent meta-analysis was not conclusive [3]. We decided to give prophylactic AED to newly diagnosed children with brain tumors because of local issues [4]. We chose valproate because it is a non-hepatic enzyme-inducing AED. Since we started prophylaxis, we noted a trend towards a better survival from our patients. In order to study this, we submitted a retrospective study to the ethical board of our institution. This study is ongoing, and we have published preliminary data recently [4]. We sought to verify if valproate prophylactic treatment had impact on the overall survival of pediatric patients with malignant brain tumors (high-grade gliomas, medulloblastomas, and ependymomas) diagnosed between January 2000 and December 2010, and treated with chemotherapy or radiotherapy (or both).

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Fig. 1 Demographics and treatment characteristics of both valproate-treated (*VPA*) and non-treated patients. Age depicts a boxplot, whereas the others show stacked columns. No difference was statistically significant

Methods

Data collection and analysis has been described elsewhere [5]. Standard survival analysis was used, calculating survival until death by all causes or censoring (follow-up to July 1, 2011). R 2.12 for Windows [6, 7] was used for all calculations and graphs. Survival curves were created from Kaplan–Meier estimates by the Kalbfleisch and Prentice method. Comparisons were made by Cox’s proportional hazards model regression using the Andersen and Gill approach [6, 7]. Results were expressed as hazard ratios (HR) and 95 % confidence interval (95CI).

Results

Between 2000 and 2010, 94 patients were consecutively diagnosed and treated in our hospital (12 with high-grade gliomas, 56 medulloblastomas, and 26 ependymomas); median and mean ages were 7.7 and 7.8 years. Median follow-up was 60 months (35 for treated and 109 for untreated patients). Of these, 47 received valproate 10–15 mg/kg/day every 8–12 h and 47 did not. Ten patients used other AED. Most of the

patients who received valproate ($n=41$) were diagnosed after 2006 (when we have begun prophylactic administration), whereas most of the patients who did not receive valproate were diagnosed before 2007 ($n=45$). There were no significant differences between the two groups regarding surgical resection, radiotherapy, chemotherapy, and demographic data

Fig. 2 Kaplan–Meier survival curves of children with malignant brain tumors (high-grade gliomas, medulloblastomas, ependymomas) treated with chemotherapy and/or radiotherapy, diagnosed between 2000 and 2010. Blue line: Patients treated with valproate prophylaxis

(Student's *T* test, Pearson's chi-squared test, and Fisher's exact test) (Fig. 1). In the Cox regression model, complete surgical resection accounted for statistically significant higher survival (HR=0.49, 95CI=0.28–0.84, $p<0.01$). Extent of surgical resection, metastasis at diagnosis, and demographic data were added. Radiotherapy and chemotherapy were not added to the model, once most of the patients received them. Patients who received valproate had a median survival of 34 months, whereas the other group had a median survival of 24 months (HR=0.99, 0.57–1.75, $p=0.99$; Fig. 2).

Discussion

These results do not prove that valproate prophylactic treatment in pediatric patients with malignant brain tumors may have had an influence on their survival. Retrospective and underpowered design may be responsible for this. Patients in our series used platinum-based chemotherapy, the standard for the treatment of medulloblastoma and high-grade gliomas in children [8]. It is possible that valproate effects on chemotherapy, either by modifying drug pharmacokinetics or altering gene expression by chromatin remodeling, are more pronounced for temozolomide than for platinum drugs. The heterogeneity of patients' diagnoses can also mean that valproate does not act in the same fashion in different malignant brain tumors and possibly has a more important epigenetic effect in specific types or subtypes of tumor, like glioblastoma in the European Organization for Research and Treatment of Cancer (EORTC) trial. Other important difference of our cohort is that we used low prophylactic doses, whereas the patients in the EORTC group received full therapeutic doses. It is also conceivable that valproate effects are not the same in adults and children. Recently, the ACNS0126 trial results showed that temozolomide is not as effective as expected for children with high-grade gliomas [9]. However, our cohort showed an effect of higher size than the EORTC trial, even though it was not significant (a difference of 10 months in median survival, against 3 months in the Weller et al. study). Our preliminary study cannot be conclusive, but it does not indicate that a similar effect of valproate in the survival of pediatric patients with malignant brain tumors could be likely, although further prospective research may be warranted. Finally, we do not advocate widespread use of prophylactic

valproate, as we have done so because of local constraints. We believe that clinical trials with valproate in pediatric malignant brain tumors should be carefully planned, selecting single histopathological entities and possibly using cytotoxic drugs other than platinum, like temozolomide.

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Conflict of interest The authors declare no potential sources of conflicts of interest and state that the manuscript is not being considered for publication elsewhere and will not be submitted elsewhere while under consideration for publication.

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