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CLINICAL STUDY

Does the choice of antiepileptic drug affect survival in glioblastoma patients?

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Abstract Patients with glioblastoma (GBM) often suffer from symptomatic epilepsy. Older antiepileptic drugs (AEDs) which affect the enzyme system cytochrome P450 have been in extensive use, but there is an increasing focus on interactions with other drugs. This study investigated whether newer AEDs with little or no enzyme effect are increasingly preferred. Previous research has indicated that valproate improves survival in GBM. We investigated the impact of AEDs on overall survival in GBM patients. All GBM patients diagnosed in Norway 2004–2010 were included through a linkage of national registries, and follow-up data on the malignancy and drug usage were analyzed. In a multivariate cox proportional-hazards regression, AEDs were adjusted for each other and for relevant factors. Immortal time bias was eliminated with time-dependent variables. The study population was 1263 patients with histologically confirmed GBM. Carbamazepine was the most frequently prescribed AED to patients diagnosed with GBM during 2004–2006, while levetiracetam was increasingly prescribed to patients diagnosed later. Taking AEDs on a reimbursement code of epilepsy was not beneficial for survival. None of the six AEDs valproate, levetiracetam, carbamazepine, oxcarbazepine, lamotrigine or phenytoin significantly altered overall survival. There has been a shift in the prescriptions of AEDs to GBM patients from older to newer AEDs over time. We found no significant survival benefit in GBM patients neither from treatment with AEDs for epilepsy in general, nor from the usage of six separate AEDs.

Keywords Antiepileptic drugs · Epilepsy · Glioblastoma · National registries · Overall survival

Introduction

Glioblastoma (GBM) is the most common and aggressive primary brain tumor [1]. Standard treatment consists of maximum safe tumor resection followed by external beam radiation therapy (RT) with concomitant and adjuvant temozolomide (TMZ) chemotherapy. This strategy yields a median survival of 14.6 months, with 2- and 5-year survival rates of 27.2 and 9.8 %, respectively [2, 3]. More effective therapies are needed to improve GBM outcomes.

Epilepsy is frequent in brain tumors, and 40–60 % of GBM patients suffer from seizures [4–6]. Initiation of antiepileptic treatment is justified after a first and single seizure in patients with brain tumors [7]. Optimal choice of antiepileptic drugs (AEDs) is of special importance in these patients. Most of the older AEDs affect the enzyme system cytochrome P450 and interact with chemotherapy and systemic corticosteroids. Increased hematological toxicity is of particular concern. AEDs also often have cognitive side effects, which are especially unfortunate as the life expectancy is short and quality of life is a crucial aspect for these patients. We wanted to investigate whether AED

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prescription preferences for GBM patients have changed over time as newer AEDs have become available. The first aim of this study was to analyze trends in the prescription of AEDs to GBM patients in Norway during the years of 2004–2010.

A debated issue is whether epilepsy and using AEDs is associated with an improved prognosis in GBM patients [8]. Our second aim was to investigate whether use of AEDs for epilepsy was in favor of overall survival (OS).

There are several studies on the impact of different AEDs on GBM survival [9–23]. Previous research reports that valproate use improves survival in GBM patients [11, 12, 17–19]. Tsai et al. found survival benefit from valproate in univariate analyses but not in stratified analyses [13]. The third aim of our study was thus to investigate whether the different AEDs affected OS in GBM patients in a nationwide, unselected database.

Material and methods

Cancer registry of Norway (CRN)

The CRN was established in 1951. All medical doctors are instructed by the Norwegian law to notify new cancer cases to the CRN. The CRN data are based on clinicians' reports, subsequent pathology reports and frequent co-ordination with the Cause of Death Registry of Norway, securing a high grade of completeness [24]. There was a mean clinical reporting degree of 98.6 % on patients diagnosed with GBM during 2004–2010 and GBM diagnoses were morphologically verified with a mean value of 88.0 % for 2004–2010 [25].

The Norwegian Prescription Database (NorPD)

NorPD was established in 2004 and is maintained by the Norwegian Institute of Public Health. The database contains information on all prescription drugs expedited at every pharmacy in Norway, covering the entire population. The registration is mandatory with monthly automatically generated updates from all pharmacies. For in-hospital patients and patients living in nursing homes, all data on dispensed drugs are collected, but at an institutional level. Therefore, drugs dispensed at institutions are not included in our study. Medication for chronic diseases is reimbursed. The reimbursement codes together with the ICD-10 and ICPC-2 codes function as a proxy of diagnosis. International Classification of Diseases, 10th revision (ICD-10), and/or the International Classification of Primary Care, 2nd edition (ICPC-2) have been recorded since 2008. For epilepsy, a local reimbursement code (7) was used until 2008, after which ICD-10 (G40) and ICPC (N88) were used.

Linkage of registries

Norway has a population of 5 million people, all of which have a unique identification number, allowing reliable linkage of registries. By using the identification number, data from CRN and NorPD were combined for each patient with a registered diagnosis of glioma in the CRN. Registry data was updated until death, censored or end of follow-up on 31 October 2013. All patients with a histologically confirmed GBM were identified and included. Information on gender, age at GBM diagnosis, date of GBM diagnosis, extent of surgery and RT were available in the data from CRN. The Regional Committee for Medical Research Ethics (REK 2011-02280) preapproved all aspects of this study.

Statistical analyses

The study population was 1263 patients with histologically confirmed GBM diagnosed in Norway between 1 and 2004 and 31 December 2010. The first 3 months of 2004 were excluded to be certain that all drug prescriptions on patients included in the study were registered in NorPD.

AEDs are often classified according to their impact on the enzyme system cytochrome P450 [26]. Enzyme-inducing AEDs (EIAEDs) are phenobarbital, primidone, phenytoin, ethosuximide, carbamazepine and oxcarbazepine. Enzyme-inhibiting AEDs are valproate and felbamate. AEDs without enzymatic effects on the cytochrome P450 enzyme system are often called non-EIAEDs. We chose to investigate the six AEDs most frequently prescribed to the GBM patients with symptomatic epilepsy in this material; levetiracetam, valproate, carbamazepine, oxcarbazepine, phenytoin and lamotrigine. Patients exposed to these six AEDs were chosen for statistical analyses. Topiramate was considered but excluded because only seven patients in the study population were treated with this AED.

OS was defined as the time from glioma diagnosis till death. A multivariate cox proportional hazard regression analysis was adjusted for age at GBM diagnosis in a categorical variable with five age groups: <20, 20–39, 40–59, 60–79 and ≥80 years. Other factors adjusted for were gender, extent of resection (none, biopsy, incomplete surgery or complete surgery), RT (RT and gamma knife treated patients versus no RT) and co-medication with TMZ and systemic corticosteroids. Patients using AEDs were included and the analysis was adjusted for collecting AEDs on a reimbursement code of epilepsy as a proxy for the diagnosis of epilepsy.

Immortal time refers to a period of follow-up during which, by design, death or the study outcome cannot occur. Time between start of follow-up and first prescription of medication must be registered as untreated time. Immortal time bias was eliminated using time-dependent variables on all medications (AEDs, TMZ, systemic corticosteroids) [27].

Hazard ratios (HR) with 95% confidence intervals (CI) were calculated. A significance level of 5% was used. IBM SPSS Statistics for Windows, version 22.0 and 23.0 (Armonk, NY, USA: IBM Corp.) was used for all statistical analyses.

Results

Of the 1263 patients diagnosed with GBM, 731 were males and 532 were females (Table 1). On 31 October 2013, 1159 patients had died and 104 patients were still alive. No patients were lost to follow-up. Of the 1263 GBM patients, 443 were ≥70 years old at time of glioma diagnosis (35.1%). The number of patients diagnosed with GBM was 467 during the years of 2004–2006, 378 during 2007–2008, and 418 during 2009–2010. Complete surgery was performed in 859 patients (68.0%), of whom 799 also received RT. Incomplete surgery was performed in 137 patients (10.8%), of whom 112 also received RT. In total 966 patients (76.5%) received RT, of whom 663 were also treated with TMZ. In total 721 patients (57.1%) used TMZ. 1005 patients (79.6%) used systemic corticosteroids during the course of disease. The median OS irrespective of treatment was 8.8 months (95% CI 8.1–9.4); 8.4 months in female patients (95% CI 7.4–9.4) and 9.0 months in males (95% CI 8.2–9.8). 1-year survival was 39%, 2-year survival was 16% and 5-year survival was 7%. For patients under the age of 70, median OS was 12.6 months (95% CI 11.7–13.4), for female patients 12.9 months (95% CI 11.2–14.7) and for males 12.4 months (95% CI 11.4–13.4).

Table 1 Characteristics of the study population at start of follow-up

Characteristic	Cohort (n)	Deaths (n)	Person-months
Gender			
Males	731	672	10,116
Females	532	487	7608
Age at diagnosis, years			
1–29	23	21	472
30–39	40	27	1328
40–49	104	88	2116
50–59	264	232	5239
60–69	389	356	5640
≥70	443	435	2929
Year of diagnosis			
2004	132	128	1880
2005	173	171	2218
2006	162	151	2861
2007	188	182	2382
2008	190	182	2408
2009	207	184	2842
2010	211	161	3133
Total	1263	1159	17,724

1-year survival for patients aged below 70 years was 52%, 2-year survival was 22% and 5-year survival was 10%.

Females had about 1 month shorter median OS than males when not adjusted for any other prognostic factors, but not statistically significant ($P=0.86$) (Fig. 1a). Patients aged 49 or younger at time of GBM diagnosis had median OS 16 months (95% CI 14.0–18.0), patients aged 50–69 had median OS 12 months (95% CI 11.0–13.0) and patients who were 70 years or older had 4 months median OS (95% CI 3.5–4.5) (Fig. 1b). The results for OS in different age groups were statistically significant ($P<0.001$). RT gave median survival of 11 months (95% CI 10.2–11.8) versus 2 months (95% CI 1.6–2.4) without RT ($P<0.001$) (Fig. 1c).

Of the 1263 GBM patients, AEDs were prescribed to 526 patients (41.6%) on a reimbursement code of epilepsy. Of these, 186 used EIAEDs, 183 enzyme-inhibiting AEDs and 303 non-EIAEDs. Within these three groups, 24 patients used both EIAEDs and enzyme-inhibiting AEDs, 61 used both EIAEDs and non-EIAEDs and 73 used both enzyme-inhibiting AEDs and non-EIAEDs. Carbamazepine was the most frequently prescribed AED (15.4%) to patients diagnosed with GBM during 2004–2006 (Table 2). Of the patients diagnosed with GBM in 2007–2008, 16.7% were treated with valproate. The non-EIAED levetiracetam was increasingly prescribed, and 22.7% of the patients diagnosed in the latest period of time were treated with levetiracetam. Age at time of glioma diagnosis was 50–69 years in 45.6–66.1% of cases in the different AED groups. There were no major differences in type of AED prescribed to the younger versus the older age groups.

There was no difference in OS in the six AED groups (Fig. 2). In all the survival analyses, patients not using AEDs are the standard comparison group. In the time-dependent variables, the patient is first registered as in treatment with a drug at the actual time of the prescription of the current drug. Each of the six AED groups was separated into subgroups of patients who were only exposed to one AED during the whole study period 2004–2010 or to more than one AED. The numbers of patients who were only exposed to one AED were 76 patients for levetiracetam, 89 for valproate, 79 for carbamazepine, 30 for oxcarbazepine, 30 for phenytoin and 20 for lamotrigine. In time-dependent variables that take into account at what time the patient first received the AED and with adjustment for all the same factors (Fig. 2), there was no positive effect on OS in any AED subgroup. Applying age at GBM diagnosis as a continuous variable did not influence the results. TMZ treatment was in favor of survival ($P<0.001$), HR 0.51 (95% CI 0.44–0.60). Subgroup analyses of patients exposed to TMZ and patients not exposed to TMZ did not have statistically significant impact on survival from any of the six AEDs.

Usage of systemic corticosteroids was in disfavor of survival ($P<0.001$), HR 2.01 (95% CI 1.71–2.37). Treatment

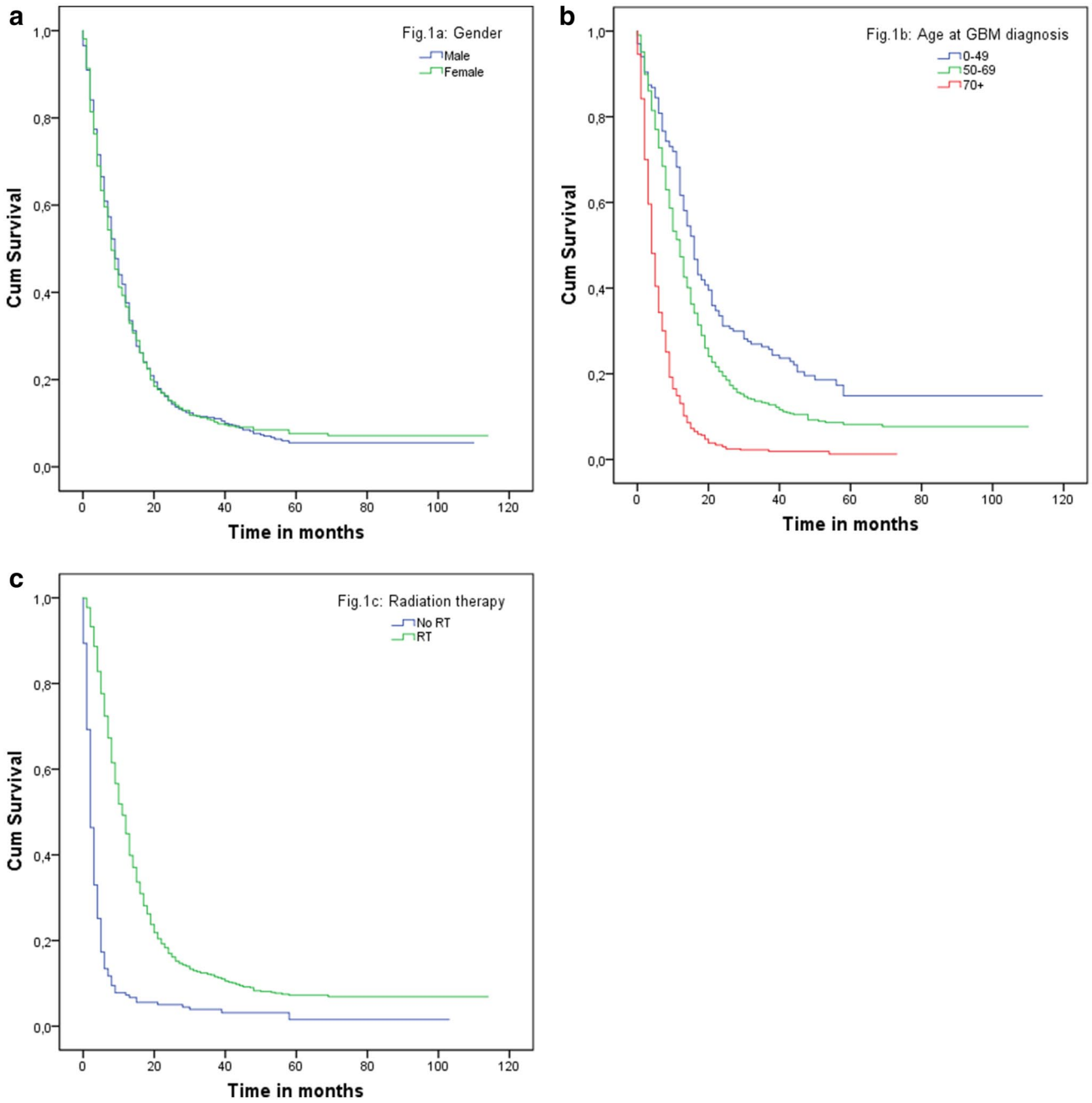

Fig. 1 **a** Kaplan–Meier plot with survival duration based on gender. **b** Kaplan–Meier plot with survival duration based on age. **c** Kaplan–Meier plot with survival duration based on RT

with AEDs on a reimbursement code of epilepsy gave HR 1.03 (95 % CI 0.82–1.29).

Discussion

Does the choice of AED affect survival?

The general survival data irrespective of AED use showed that patients of older age have reduced OS compared to younger patients, in accordance with previous studies. Reasons for this might be co-morbidity, worse performance status, the fact that older patients often do not receive full standard oncological treatment and the general shorter remaining life-time expectancy in older patients, independent of GBM [28]. The survival results are quite comparable to what is reported in US patients from the same period [29].

None of the six investigated AEDs had a significant effect on OS in GBM patients diagnosed in Norway 2004–2010. Previous studies have indicated that GBM patients exposed

Table 2 Characteristics of glioblastoma patients (n = 1263) using anti-epileptic drugs

Characteristic (n)	Carbamazepine	Oxcarbazepine	Phenytoin	Valproate	Levetiracetam	Lamotrigine	All GBM patients
Gender							
Male	107	48	41	112	113	28	731
Female	56	34	18	74	82	29	532
Age at glioma diagnosis							
0–49 years	28	19	14	37	46	22	167
50–69 years	98	50	39	111	112	26	653
≥70 years	37	13	6	38	37	9	443
Year of glioma diagnosis							
2004–2006	72	36	33	60	39	19	467
2007–2008	54	23	12	63	61	17	378
2009–2010	37	23	14	63	95	21	418
Total	163	82	59	186	195	57	1263

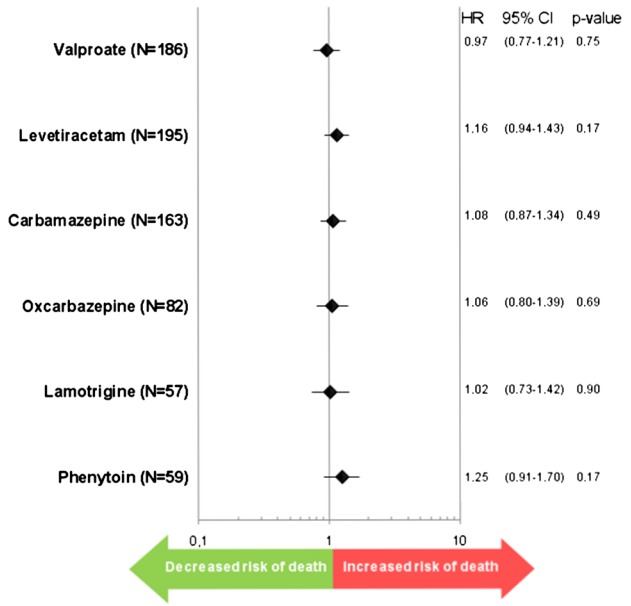

Fig. 2 Cox proportional-hazards regression with time-dependent variables for AEDs. The comparison group is patients not using AEDs. All variables are adjusted for each other, age groups, gender, extent of surgery, RT, epilepsy and time-dependent variables for TMZ and systemic corticosteroids. *HR* hazard ratio, *CI* confidence interval

to valproate have longer OS, possibly because of inhibition of tumor angiogenesis and induction of differentiation and apoptosis in tumor cells [11, 12, 17]. A meta-analysis of five studies on the effect from valproate on OS in adult GBM found HR 0.74 with 95% CI 0.59–0.94 versus patients using other AEDs, and HR 0.66 with 95% CI 0.52–0.84 versus patients with no AED treatment [30]. However, the data were from retrospective analyses including a low number of patients, and the selection of the AEDs depended on the investigators' preferences and local practices [30, 31]. A recent pooled analysis of prospective clinical trials did not show impact of valproate or levetiracetam on survival [21]. Our study supports the results of that analysis, examining a nation-wide, unselected patient material that reflects nationwide prescription trends and not the preferences of individual clinicians or hospitals. A retrospective in vivo study of GBM survival according to AED use has been warranted [32]. The present study clarifies the issue as none of the six AEDs we investigated had any positive effect on OS.

The impact of epilepsy on survival

Whether glioma patients with symptomatic epilepsy benefit with regard to OS has been a matter of debate [22, 23, 33–35]. We found that AED treatment for epilepsy did not influence OS in the GBM subgroup. AED treatment on an epilepsy reimbursement code is likely to be a good marker for epilepsy [36, 37]. GBM patients without seizures do not receive prophylactic AEDs as a routine in Norway. Thus, prescription of anticonvulsants is highly indicative of at least one seizure.

The excitatory neurotransmitter glutamate plays an important role in seizure development [38]. Abnormalities include increased expression of specific glutamate receptor subtypes, low activity of glutamine synthetase, high glutamate concentrations in glioma cells, and almost absent intracellular uptake with excessive extracellular levels. These changes correlate with higher seizure frequency and may affect tumor progression [39, 40]. Radiological investigations after a first seizure may lead to the diagnosis and treatment at an earlier stage than in patients without epileptic seizures. Brain tumors causing seizures are often easier to operate and target effectively with RT because of localization in a cerebral hemisphere. Occurrence of postoperative seizures did not significantly influence OS in 147 HGG patients [41]. In one study of 340 GBM patients, epilepsy was a significant prognostic factor in a univariate analysis. However, the multivariate analysis did not confirm this

finding, as the patients with epilepsy had additional favorable prognostic factors [42]. The adjustments for relevant factors in our survival analysis might be the reason why there was no survival benefit from having epilepsy.

AED prescription trends

Carbamazepine was prescribed predominantly in the earliest period, 2004–2006. Levetiracetam was prescribed to an increasing degree towards the latest period, 2009–2010. This shows a shift in prescription trends from EIAEDs to non-EIAEDs during the study period. One reason for this shift may be clinicians´ wish to avoid potential interactions between EIAEDs and other relevant drugs [26]. Another explanation for the increasing use of levetiracetam might be the prompt effect and easy dose titration. Levetiracetam is also an efficient AED for focal seizures, which represent the majority of GBM seizures. The newer AEDs have less sedative and cognitive effects, which is especially beneficial in a patient group prone to similar symptoms caused by the disease and oncological therapy.

The fraction of valproate treated patients was nearly constant during the study period. Most patients treated with valproate were aged 50–69 years of age, similar to all other AED groups. We found that the choice of AED was independent of age at GBM diagnosis. First-line choices for treatment of symptomatic localization-related epilepsy in patients with brain tumors differ from those for epilepsy in general because of increased risk of drug interactions, particularly with anticancer agents, and the use of EIAEDs is discouraged [43]. Levetiracetam may be a reasonable choice of AED, not least due to lack of interactions with other drugs including chemotherapeutic agents and systemic corticosteroids [5, 44]. The risk of hematological toxicity is tolerable for both levetiracetam and valproate [18, 45].

Thus, the choice of AED for glioma patients should place emphasize on aspects as side effect profiles, interactions and co-morbidities, and our data do not support the notion that specific AED types have independent survival benefits.

Increased incidence of glioblastoma

Throughout the study period 2004–2010, the number of diagnosed GBMs increased. This corresponds with the incidence pattern for adult GBM patients in the Dutch population [46]. In that study, the incidence was accompanied by a decrease in other subtypes including anaplastic astrocytomas and astrocytomas with unknown malignancy grade, and the authors speculate whether availability of TMZ had increased identification of GBMs. We did not compare GBM frequencies with those of other brain tumors in our study. The increase in diagnosed GBMs may also be due to steady increase in MRI availability, improvements in diagnostic techniques, changes in histological classification, and aging of the population [47].

Survival and systemic corticosteroids

We found an increased risk of death in patients treated with systemic corticosteroids. In vitro studies show that dexamethasone works as an antagonist on TMZ-induced apoptosis in human GBM cells, suggesting that the combination of TMZ and dexamethasone may be counteractive in treating GBM [48]. Recent clinical and experimental data suggest that corticosteroids shorten survival in GBM [49]. The findings with three large independent patient cohorts gained further support in a correlative retrospective analysis of 73 patients with GBM showing that dexamethasone use during RT with concurrent TMZ correlated with reduced OS [50]. Cerebral edema is a common side effect of chemo radiotherapy for GBM, necessitating glucocorticoid management throughout anti-tumor treatment [51]. Some GBM patients are kept on steroids because of worsened symptoms due to dose tapering. Other patients need an increase in corticosteroids because of focal neurological symptoms due to tumor expansion and increased edema. In clinical practice, corticosteroids are administered more often to patients with aggressive tumor growth, resulting in a significant selection bias. Study patients have also been identified early in the course of disease during initial anti-tumor treatment and corticosteroids were still an independent predictor of poor outcome, but clarifying randomized controlled clinical trials are unlikely to ever be performed [49].

Methodological considerations

The main strength of this study is the population-based design including all patients from high quality national registries. The study population was unselected unlike previous retrospective studies on AEDs and survival, and the choice of AED reflects national practice rather than individual preferences. In our study, 186 GBM patients received valproate, whereas previous studies include patient populations of 24–108 [11–17]. Another advantage of the present study is that immortal time bias was eliminated by application of time-dependent variables in a multivariate analysis.

The registries do not give access to detailed clinical information for individual patients. We were not able to investigate whether the patients collecting their prescribed drugs from the pharmacy were actually ingesting the drugs. However, breakthrough seizures often cause considerable distress in GBM patients, due to the fear of tumor recurrence, and hospital physicians follow this group closely. Both factors are likely to facilitate good medication compliance. The Norwegian law denies re-identification of the patients registered in NorPD and validation of the data is

therefore not possible. However, only dispensed and collected prescriptions are included in NorPD and previous studies find the register data to be more complete than medical records [36, 37].

Conclusions

In a nation-wide material, the choice of AED was of no significant importance for the OS in GBM patients. Treatment with AEDs for epilepsy did not improve survival. The results were not influenced by selection bias or immortal time bias. There has been a recent shift in the prescriptions of AEDs to GBM patients from EIAEDs to non-EIAEDs, and levetiracetam is now the most prescribed AED on a national basis. This is most likely due to an increased awareness of drug interactions and side effect profiles when treating brain tumor patients.

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Compliance with ethical standards

The study employs anonymous data in mandatory national registries only and complies with the ethical standards for use of these registries.

Conflict of interest The authors declare no conflict of interest.

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