ANTISEIZURE MEDICATION IN PATIENTS WITH GLIOBLASTOMA- A COLLABORATIVE COHORT STUDY

Kristin M. Knudsen-Baas[1], Anette M. Storstein[2], Alessia Zarabla[3], Andrea Maialetti[3], Diana Giannarelli[4], Ettore Beghi[5], Marta Maschio[3]

[1]Department of Clinical Medicine, University of Bergen, Bergen, Norway; EMAIL: kriskn@ous-hf.no

ORCID:0000 0002 7805 1831

[2] Department of Neurology, Haukeland University Hospital, Bergen, Norway EMAIL: anette.margrethe.storstein@helse-bergen.no

[3]Center for Tumor-related Epilepsy, UOSD Neuroncology, Regina Elena National Cancer Institute IRCCS, Rome, Italy;

EMAIL: alessiazarabla@libero.it; andrea.maialetti@libero.it; marta.maschio@ifo.gov.it

ORCID: 0000-0002-2039-1331; 0000-0002-8428-4797; 0000-0002-3075-4108

[4]Biostatistic Unit, Regina Elena National Cancer Institute IRCCS, Rome, Italy; EMAIL: diana.giannarelli@ifo.gov.it

ORCID:0000-0002-6085-1195

[5]Laboratorio Malattie Neurologiche, IRCCS - Istituto "Mario Negri", Milano, Italy; EMAIL: ettore.beghi@marionegri.it

ORCID:0000-0003-2542-0469

Corresponding author:

Marta Maschio

Center for Tumor-related Epilepsy, UOSD Neuroncology, Regina Elena National Cancer Institute IRCCS, Rome, Italy

Via Elio Chianesi 53, 00144 Rome, ITALY

+390652665345

Marta.maschio@ifo.gov.it

ORCID: 0000-0002-3075-4108

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[2] Department of Neurology, Haukeland University Hospital, Bergen, Norway
EMAIL: anette.margrethe.storstein@helse-bergen.no

[3]Center for Tumor-related Epilepsy, UOSD Neuroncology, Regina Elena National Cancer Institute IRCCS, Rome, Italy;

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Corresponding author:

Marta Maschio

Center for Tumor-related Epilepsy, UOSD Neuroncology, Regina Elena National Cancer Institute IRCCS, Rome, Italy

Via Elio Chianesi 53, 00144 Rome, ITALY

+390652665345

Marta.maschio@ifo.gov.it

ORCID: 0000-0002-3075-4108

Highlights:

Retrospective analysis between epilepsy, antiseizure medications (ASM) and survival

Epileptic seizure as a GBM debut symptom did not lead to earlier hospital admission

Levetiracetam (LEV) was the most effective ASM compared to other ASMs

No differences emerged in the incidence of adverse events between LEV and other ASMs

Surprisingly, in our patients LEV and Valproic Acid are correlated with worse OS that other ASMs.

Abstract

Purpose

We investigated, whether epileptic seizures (ES) as presenting symptom in adult patients with GBM are associated with better Overall survival (OS) compared to ES presenting later during the course of GBM, and efficacy and safety of different antiseizure medications (ASMs)

Methods

Retrospective consecutive cohort study of adults with GBM: 50 from Norway and 50 from Italy. We compared the time to changing s ASM treatments. OS was investigated with a Cox regression model adjusted for time dependency.

Results

Median follow-up was 17 months from GBM diagnosis. ES were the presenting symptom in 49 patients. All patients received ASM treatment. LEV was the first ASM in the majority of patients and the most effective at one year from the first prescription, (p=0.004). Occurrence of adverse events (AEs) was similar between LEV and other ASMs (p=0.47). Poorer OS correlated with older age at GBM diagnosis, country and ASM therapy. A negative impact of ASMs on OS was observed for LEV in a univariate and multivariate analysis, and for VPA (only in multivariate analysis), even when adjusted for O6-methylguanine-DNA-methyltransferase (MGMT) methylation status. Patients with ES as the onset symptom of GBM and patients who had first ES later had similar OS (p=0.87).

Conclusion

ES as the GBM debut symptom did not lead to a longer OS. LEV was a more effective ASM compared to other treatments with no differences regarding AEs between LEV and other ASMs. Surprisingly, in our patients LEV and VPA were associated with worse OS than other ASMs. This result should be interpreted carefully due to the retrospective nature of this study along with the many variables which may affect the outcome in this population.

Keywords

Antiseizure medication, brain tumor, epilepsy, glioma, glioblastoma, overall survival, seizures

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Declarations

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Conflicts of interest

Dr Ettore Beghi reports grants from the Italian Ministry of Health, grants from SOBI, personal fees from Arvelle Therapeutics, outside the submitted work. Dr Diana Giannarelli has no conflicts of interest. Dr Kristin M. Knudsen-Baas has no conflicts of interest. Dr Andrea Maialetti has no conflicts of interest. Dr Marta Maschio has received support for travel to congresses from EISAI srl; has participated in scientific advisory boards for EISAI; has participated in pharmaceutical industry-sponsored symposia for UCB Pharma; has received research grants from UCB Pharma. Dr Anette Storstein has no conflict of interest. Dr Alessia Zarabla has no conflicts of interest.

Ethics approval

The study was approved by the Regional ethics committee (REC) in Western Norway, reference 2018/1412/REC West and by the ethics committee at the IRCCS Regina Elena National Cancer Institute(IRE), Rome, Italy, Prot. N° 0013912.27-11-2018. In view of the retrospective nature of the study, all the procedures performed were part of the routine care.

Consent to participate

All data were retrieved retrospectively. Patients signed a written consent for data treatment for research purpose.

Consent for publication

All data were retrieved retrospectively. Patients signed a written consent for data treatment for research purpose.

Availability of data and material

The data are available at GARR box:

https://gbox.garr.it/garrbox/index.php/s/8TM2ziSPsHhofoE

Code availability

Not applicable.

Authors` contribution

Research hypotheses, initiation of the collaborative study, data collection, interpretation of results and manuscript preparation were performed by Kristin M. Knudsen-Baas, Anette Storstein and Marta Maschio. Data collection was performed by Alessia Zarabla and Andrea Maialetti. Data analysis was performed by Diana Giannarelli. Advice during study planning and manuscript preparation was performed by Ettore Beghi. The first draft of the manuscript was written by Kristin M. Knudsen-Baas, Anette Storstein and Marta Maschio, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

All authors agreed with the content and all gave explicit consent to submit and obtained consent from the responsible authorities at the institute/organization where the work has been carried out.

Introduction

Glioblastoma (GBM) is the most common primary brain tumour in adults. Between 30 % and 60 % of the GBM patients experience at least one epileptic seizure as the debut symptom or during the course of the disease [1-3]. Epilepsy is often drug-resistant [4]. Epileptic seizures as the presenting symptom of GBM represent an essential aspect, as there have been reports on correlation with longer survival [5-6], while in another study this has not been confirmed [7]. In some studies, improved survival seems to be due to the prompt recognition of GBM in an earlier phase with seizures as the presenting symptom [8, 9, 10, 11]. Selecting the appropriate antiseizure medication (ASM) is important in this particular patient population. The efficacy on focal epileptic seizures, tolerability of treatment and potential drug-drug interaction must all be considered, as all these aspects can affect survival [7, 8, 12-14]. Throughout literature, studies regarding this topic have suggested that ASMs such as valproic acid (VPA) and levetiracetam (LEV) may enhance the efficiency of chemotherapy (CT) thus contributing to a decreased mortality rate in patients with GBM [13-14]. Furthermore, increasing sets of evidence indicate that genetic biomarkers play an important role, not only on survival of GBM patients [13], but also as predictors for epileptogenicity [16]. This may explain the difference in seizure frequency associated with particular types of tumours [15-21]. On the one hand, the methyl molecules attached to the promoter region of DNA repair protein O6-methylguanine DNA methyltransferase (MGMT) silence transcription and increase overall survival (OS) due to an improved efficacy of chemotherapy with temozolomide (TMZ), as previously demonstrated [18]. On the other hand, ASMs may have an unrecognized impact on modulating MGMT, playing an important role in tumour cell resistance towards alkylating agents [22]. A recent study highlighted this aspect of ASMs, in which LEV inhibited the transcription of MGMT, acting as a sensitizer for TMZ [22].

The first aim of our retrospective multicentric cohort study was to investigate whether the appearance of epileptic seizures as the presenting symptom of GBM are favorable regarding OS compared to the appearance of the first seizure occurring later during the course of GBM. Secondary objectives were efficacy and safety of different ASMs on seizure control and their impact on OS in patients with primary GBM and brain tumor-related epilepsy (BTRE) in the real world setting of two European countries (Norway and Italy).

Materials and Methods

This is an international, multicenter retrospective cohort study. The two centers were invited to participate in the study on a voluntary basis. Each center was required to send anonymized data regarding 50 consecutive patients with GBM and BTRE followed for at least one month. The inclusion criteria were age $\geq$ 18 years at the time of a histologically confirmed primary GBM diagnosis. Further criteria included at least one epileptic seizure either during the course of disease or within three months prior to GBM diagnosis, without any other cause of epileptic seizures. Patients with a history of seizures preceding the tumour diagnosis, considered unrelated to the tumour, were excluded. With reference to the onset of seizures after diagnosis, we did not use a specific cut-off rate as seizures at onset may occur at any stage of disease. We included 50 eligible patients treated at Haukeland University Hospital, Bergen or at the Central Hospital in Sogn and Fjordane County (HUS/CHS), Norway and 50 eligible patients treated at the Center for medical treatment of tumour-related epilepsy at the Regina Elena National Cancer Institute (IRE), Rome, Italy. The follow-up period was from the first hospital appointment due

to either seizure presentation or GBM diagnosis up until the last medical visit or last hospital appointment before death. The minimum length of hospital contact was set to one month. This study was approved by Ethics Committee of IRCCS Regina Elena National Cancer Institute (Prot. N° 0013912.27-11-2018) and Ethicsl Committee of HUS/CHS (2018/1412/REC West). Data were also collected from a collaborative prospective observational study of patients with WHO grade II-IV glioma and related epilepsy in two Western Norwegian countries. Data were collected from the patients` medical charts. The participating centers adhered to the standard follow-up of GBM patients and ASM treatment was chosen based on the guidelines of the International League Against Epilepsy (ILAE) [23]. All data were collected and combined through an anonymous Excel file developed and agreed upon by the participating centers. Completeness and quality control of collected data were performed before the statistical analyses. Centers were requested to answer specific queries whenever further clarification was necessary. To reduce selection bias, all patients present in the center's archives were screened and all consecutive patients fulfilling the selection criteria were enrolled.

The information included was date of GBM diagnosis, age at GBM diagnosis, gender, Karnofsky performance status (KPS) [24], MGMT methylation status, isocitrate dehydrogenase (IDH) 1 or 2 mutations, tumour site, date and extent of tumour resection, date of chemotherapy and radiotherapy (RT), use of systemic corticosteroids, date and type of first seizure, seizure types, seizures related to primary oncological treatment/tumour progression/treatment for tumour progression, time and type of first and subsequent ASMs, ASM regimen, ASM serum concentrations when available, ASM treatment changes, reason for ASM changes, any adverse events (AE) during ASM treatment and date of last follow-up.

An "adverse event" (AE) was defined as any unfavorable and unintended sign, symptom or disease temporally associated with the medical treatment administered. An AE may or may not be related to the medical treatment. Symptoms related to tumour progression were not considered to be an AE.

AEs were categorized as: sedation, mood disorder/irritability; vertigo; gastrointestinal; hematological, and rash. All AEs were recorded in our database. An AE was attributed to a specific ASM if the attending physician had evaluated that the AE in the medical chart was directly related to the drug or if the AE only occurred or aggravated after starting or increasing the dose of a specific ASM. We defined an AE intolerable if it led to a decrease in dose or cessation of an ASM.

Information on status of the molecular markers MGMT methylation and IDH 1 or 2 mutations were obtained from medical charts when available. MGMT methylation was analyzed for patients lacking this information when tumour tissue was available.

Endpoints

The primary endpoint was OS, calculated as the time difference from GBM diagnosis to date of death or censored at the date of last follow-up and its correlation with seizure onset. The secondary endpoint was the time until the first ASM switched to another ASM due to lack of efficacy and/or toxicity, defined as the retention time for the first ASM. The retention time was used as a measure of efficacy and tolerability for different ASMs.

Statistical analysis

We used the Kaplan-Meier method to assess OS and retention time until changing an ASM because of inefficacy and/or until switching an ASM due to AEs. We used the log-rank test to examine differences between groups. All patients who had received at least one dose of the drug were included in the analyses of toxicity. We calculated a 95% confidence interval (CI) for the retention time one year after starting treatment from the standard error in the survival table. Predictors for OS were assessed with Cox proportional hazard regression model (Cox regression); included variables were age at diagnosis, gender, KPS, treatment institution, extent of tumour resection, RT, TMZ, use of systemic corticosteroids, MGMT methylation status and the first ASM used. These features were considered in the univariate approach and thereafter were all included in a multivariate model where each hazard ratio was adjusted compared to all the others. Overall significance and all aspects related to each contrast were reported; in case of variables with only two categories the overall significance was related to a single contrast. Only the first ASM was considered in the Cox model. No selection criteria were applied. Information on tumour volume was not available for the cohort. Variables that were not associated with the aim of the study were excluded. No substitutions were made. Hazard ratios (HR) with 95% CI were calculated. The data were analyzed using IBM SPSS Statistics for Windows, version 21.0 (IBM, Corp., Armonk, NY, USA).

Results

Descriptive results

The study population consisted of 72 males and 28 females with primary GBM and at least one tumour-related epileptic seizure (Table 1).

We followed all patients until death or to the end of study on August 8, 2018. No patient was lost to follow-up during the study period. The median follow-up time for our cohort was 17 months from GBM diagnosis (range 3-145 months). Ten patients were still alive at the end of study on August 8, 2018.

Median age at GBM diagnosis was 54 years (range 26-85). Of the eleven patients aged 20-39, only two were <30 years old. The most common tumour site was the frontal lobe (right frontal in 19, left frontal in 17). All patients underwent surgery, of which twelve were biopsies. Of 92 patients who received RT, 89 received concomitant TMZ. There were 90 patients who received adjuvant chemotherapy with TMZ, and three patients received procarbazine, lomustine and vincristine (PCV). KPS at the time of the first hospital admission was >70 in 70 patients and ≤70 in 30 patients. During the first hospital stay related to GBM, 46 patients received systemic corticosteroids. At the last point of contact before death or at the end of study, 85 patients used systemic corticosteroids. The first epileptic seizure was GBM onset symptom in 49 patients. 14 patients had their first seizure within three months after radiological GBM diagnosis, and 12 patients within three to six months. In 25 patients, the first epileptic seizure appeared later than six months after GBM diagnosis. Details on seizure onset related to oncological therapy were registered (Table 2). Of the patients who had their first seizure as a GBM debut symptom, 26.7% had other seizures between RT and chemotherapy, and 36.7% had other seizures during adjuvant chemotherapy. Other prominent GBM debut symptoms than epileptic seizures were cognitive changes (20 patients), headaches (20 patients) and focal neurological deficits (eleven patients).

Pattern of epileptic seizures

There were 49 patients who had epileptic seizures as a GBM debut symptom. Of these, 19 had one focal aware seizure (38.8%), 16 had one focal to bilateral seizure (32.7%), eight had >two focal to bilateral seizures (16.3%), five had one focal unaware seizure (10.2%) and one had >two focal seizures (2.0%).

We evaluated whether patients who presented seizures at GBM onset had earlier access to hospital (<or> than a week) compared to patients who experienced other symptoms (cognitive changes, focal neurological deficits, headaches, other symptoms). The comparison between the two groups did not show any significant differences ($p = 0.99$).

There were no differences in timing of onset of epilepsy (early vs. late) regarding gender (males 47.2% vs. females 53.6%, p=0.57) or age (42.1% for <50 years, 54.2% for 50 and 69 years and 50.0% for >70 years, p=0.54). The incidence of seizures was higher for patients with temporal right-sided tumours (10/11 patients: 90.9%) and for patients with parietal tumours (14/25 patients: 56.0%). In general, there were no differences in type of seizure. Focal aware seizures were the most frequent type for late onset seizures (24/51: 47.1%) while focal to bilateral were the most frequent in patients with seizures as GBM debut symptom (24/49: 49.0%, p=0.55). During follow-up, 13 patients had at least one episode of status epilepticus (SE); between them, two had more than one SE. Progression of GBM was registered in 86 patients. In twelve of these patients, epileptic seizures led to the progression of diagnosis.

ASM therapy

As the first ASM in monotherapy, 71 patients received LEV (mean daily dosage ± SD: 1524.6±62.9 mg); ten patients VPA (mean daily dosage ± SD:1230.0±434.7 mg), five patients oxcarbazepine (OXC) (mean daily dosage ± SD: 600.00±212.1 mg), four patients lamotrigine (LTG) (mean daily dosage ± SD:187.5±62.9 mg), five patients carbamazepine (CBZ) (mean daily dosage ± SD:440.0±167.3 mg), three phenobarbital (PB) (mean daily dosage ± SD:100.0±0.0 mg) and two patients topiramate (TPM) (mean daily dosage ± SD: 300±141.4 mg). The patients had control appointments with a neurologist every three months after their GBM diagnosis and information was included at six month intervals. Because LEV was the first ASM in the majority of patients, we analysed the retention time for this group compared to the group of patients who had a different first ASM. Six months after GBM diagnosis, 82.5% of patients still alive were on ASM treatment, 89.9% of patients with LEV and 64.8% of patients with other ASMs. One year after the first prescription of an ASM, the retention rate was compared between patients with LEV and patients with other ASMs. Regarding patients treated with LEV as first ASM, 82.8% continued with LEV, while patients treated with other first ASMs 55.5% continued with unchanged ASM (p=0.004, Figure 1A). In regards to efficacy on seizure control, 89.3% of patients treated with LEV (95% CI 81.7-96.9) did not change ASM because of inefficacy, while 61.3% of patients treated with other ASMs (95% CI 44.7-81.5) did not switch ASMs because of inefficacy (p=0.004; Figure 1B).

Adverse events

Given that LEV was the first ASM in the majority of patients, we analysed the retention time for this group compared to the group of patients who had a different first ASM. In regards to AEs at one year, 92.9% of

patients on LEV (95% CI 86.0-99.8) and 88.3% on other ASMs (95% CI 72.4-100) did not change ASM therapy because of AEs, without significant differences between the two groups (p=0.47: Figure 1C).

In the whole population, 20 patients reported AEs on their first ASM (20%). There were 16/71 patients with LEV as first ASM with AEs (22.5%); eight patients had neuropsychiatric AEs (two with withdrawal of LEV), five patients had sedation or vertigo (one with withdrawal), one with allergic reaction (with withdrawal) and two non-specified AEs (both with withdrawal). There were 4/29 patients who received other first ASMs other than LEV with AEs (13.8%), three patients had sedation or vertigo (two with withdrawal) and one non-specified. There were no differences between the percentage of AEs in the two groups (p=0.32). Moreover, eight patients had hematological toxicity due to chemotherapy, five during LEV treatment (7%) and three (10.3%) with other ASMs.

Overall survival

Median OS for all patients was 18.9 months, (95% CI: 15.6-22.2); median OS was 20.8 months in the group of patients with seizure as GBM onset symptom (95%CI: 12.2-29.4) and 18.8 months (95% CI: 16.6-21.1) in the group with later first seizure, showing no significant differences (p=0.87).

In the univariate OS analysis (Table 3), older age at GBM diagnosis (50-69 years and ≥70 years) was associated with unfavorable OS compared to younger age (< 50 years). Correlation with OS was not proven for treatment institution (IRE vs HUS/CHS), gender, KPS, extent of surgery, use of systemic corticosteroids, seizures at debut vs seizures during the course of the disease. Conversely, regarding the correlation between OS and ASMs, the univariate analysis showed that they have a significant impact on survival (p=0.05); specifically, LEV is associated with worse survival than other ASMs(p=0.02).

Multivariate analysis (Table 3) confirms the results, both for the subgroup of 78 patients with MGMT methylation status, and for the entire group of patients, with the exception of "Treatment Institution", in which HUS/CHS was associated with favorable OS than IRE (p=0.012). Moreover, regarding the effect on OS of ASMs treatment, also VPA results associated with worse survival than other ASMs (p=0.05).

To eliminate the possible confounding effect on OS due to enzyme inducing ASMs (EIASMs), we removed those patients using EIASMs (5 patients with CBZ and 3 with PB) from the comparison group receiving LEV. Despite this change, the negative effect of LEV on OS remains stable (p = 0.04).

Discussion

The aim of our multicenter cohort study was to retrospectively evaluate whether epileptic seizures as a GBM debut symptom was a favourable prognostic factor for OS, compared to patients with a first seizure occurring later. Furthermore, we investigated efficacy on seizure control and the safety of different ASMs and the possible impact they have on OS.

In our population, half of the patients had epileptic seizures as a GBM debut symptom which was in accordance with previously reported rates of 52-53% [25-26]. There were no differences in timing of epilepsy onset or seizure type. Scientific literature highlights that epileptic seizures as a GBM debut symptom allowed patients to

receive an earlier diagnosis of the disease, with a positive impact on survival [3, 5, 9-11, 27]. Our results differ from these previous studies, because they showed that seizures as a GBM onset symptom did not lead our patients to earlier hospital access, compared to those who experienced other symptoms at disease onset such as cognitive or behavioural disturbances, focal neurological deficits (e.g. hemiplegia). Numerous advances in the diagnosis and treatment of brain tumours have been achieved [28, 29], by promoting the spread of specialized centers [30] and the use of advanced neuroimaging techniques [31]. We hypothesized that, in our patients, an increase in the availability of Magnetic Resonance Imaging (MRI) and physicians improved awareness of the neurological symptoms from GBM could be the reasons for equal time to hospital admission with and without seizures at GBM presentation.

Regarding ASM treatment, our results showed that LEV was the first ASM to be administered in more than two thirds of our cohort, in accordance with data in the literature [32-33]. In regards to the efficacy of different ASMs on seizure control, our results indicated that LEV was more effective as ASM compared to other ASMs (VPA, OXC, LTG, CBZ, PB, TPM) as shown from a lesser probability to change drug due to inefficacy, compared to patients treated with other ASMs (see Fig 1B). This is confirmed by retention time that was higher in patients treated with LEV (82.2%) compared to other ASM (55.5%), even at one year from the first prescription of an ASM. Our results are in line with a retrospective multicenter cohort study on 808 BTRE patients followed in 35 Italian centres of epilepsy [33]. The study showed a higher efficacy and a longer treatment time for patients treated with LEV, compared to patients treated with other ASMs. Furthermore, in a small trial of 52 patients with primary brain tumour comparing LEV to pregabalin (PGB), retention rates were found to be higher (59%) in the LEV group, compared to the PGB group (41%) [34].

Regarding ASM related AEs, we did not observe any significant differences in retention time between patients treated with LEV compared to patients receiving other ASMs at one year from first being prescrbed. Our data showed that after one year, 92.9% of patients with LEV and 88.3% of patients with other ASMs had no change in therapy due to AEs; furthermore, no significant differences in the percentage of AEs in the 2 groups were detected. A higher probability of discontinuing the first ASM due to AEs in patients with other ASMs than LEV has been reported [33]. Our data contrasts these results which may be due to the retrospective design of the study, and because physicians may have in addition underestimated patient's AEs given the lack of standardized reporting.

We performed a Cox regression in order to evaluate the possible effects of different variables on OS (sex, age, KPS, treatment institution, extent of surgery, use of systemic corticosteroids, seizures at debut of the disease, ASMs therapy). We did not observe significant correlations between OS and: sex, KPS, extent of surgery, use of corticosteroids, both in uni- and multivariate analyses. The only variables that correlated with poor OS were: older age at GBM diagnosis, treatment institution (IRE vs HUS/**CHS)** and ASM therapy. Regarding the significant correlation between poor OS and older age in uni- e multivariate analyses, this result is in accordance with previous studies [35]. We also found a significant correlation between poor survival and treatment at the IRE Institute -Italy, only in the multivariate analysis. This difference could be influenced by the retrospective nature of the study as well as to the fact that this is a multicenter international study. Disease management and data recording varies across centers and nations and this may have too affected the results of the study.

Regarding the role of epilepsy, the univariate analysis did not show significant differences in the mean survival between patients with first seizure at GBM onset (20.8 months) and patients with first seizure later during the course of disease (18.8 months) in our sample. The multivariate analysis confirmed those results both in the subgroup of 78 patients with MGMT methylation status and in the entire group of patients. Data in the literature indicated that epileptic seizures as a GBM onset symptom has a positive impact on patient survival [2, 8]. In our patients, the absence of impact of a first seizure as a GBM onset symptom on patient survival could be linked to what we observed as the time to hospital access, as mentioned above [7].

As to ASM therapy, our results indicated a negative impact of ASMs on OS, in particular for LEV, both in the univariate and multivariate analyses, and for VPA (only in multivariate analysis), compared to other ASMs, also after adjusting to MGMT methylation status. We did not expect this result, as it isnot in line with other studies which indicated that GBM patients may experience prolonged survival due to VPA administration [32] and that patients treated with VPA exhibit better outcomes than those treated with other ASMs [37]. Other studies demonstrate the positive role of LEV in enhancing the effectiveness of high-dose of CT [2, 36, 38], especially in GBM patients with methylated MGMT compared to unmethylated MGMT [13]. However, our result is in line with a study by Jaeckle and colleagues [39] which show that non-enzyme-inducing ASMs have a negative impact on patient survival compared to EIASMs and Happold et al. [14] whom, with a pooled analysis of clinical trials, did not found any association between the use of VPA or LEV and improvement of OS.

There are some critical issues that need to be considered concerning these results. Firstly, one of the major limitations was that only the first ASM drug prescribed was considered in the Cox model we performed, therefore we do not know if physicians made any changes in the therapeutic regimens during follow-up. Furthermore, we have to consider the possible co-incidence with tumour progression. We did not adjust for tumour progression in our analyses and we do not know if this could possibly explain the worsened prognosis in the group of patients with LEV treatment. Moreover, the three different groups include the nonhomogeneous: group with LEV larger (n=71) than that with VPA (n=10) or with other ASMs (n=19). Finally, this result may be influenced by the retrospective nature of our study. In this way, this data confirms the difficulties in studying the effects of ASM on OS in these patients, given the numerous variables that have to be considered in this population.

This study has several limitations. First, this is a retrospective study. Data were obtained from medical records whereas some data lacked standardized reporting and relied on the evaluations declared by the treating physicians. Secondly, treatment retention was assessed in an observational context. Physicians' and patients' judgment might have had a strong influence on the decision of when to start/stop the assigned treatment. All these limitations imply a more careful interpretation of our findings.

Conclusions

We found no survival benefit from a first seizure as a GBM onset symptom in our patient cohort. Half of the patients had an epileptic seizure as a GBM debut symptom but this did not lead to earlier hospital admission compared to patients with a first seizure occurring later during the course of the GBM disease. LEV was the first ASM chosen for over two thirds of the cohort and was more effective on epileptic seizures compared to other ASMs, but no differences in the incidence of AEs were detected. Surprisingly, in our patients LEV and VPA are

correlated with worse OS than other ASMs. This result has to be taken cautiously due to the limitations present in a retrospective study and to the difficulties in studying the effects of ASM on OS in these patients, given the numerous variables that have to be considered in this patient population.

Table 1: characteristics of the study population at study entry.

Characteristics		N = 100 patients
Gender	Male	72
	Female	28
Age at glioma diagnosis	<20	0
	20-39	11
	40-59	48
	60-79	39
	80+	2
Surgery	Radical resection	48
	Partly resection	40
	Biopsy	12
Radiotherapy	None	8
	13 fractions	6
	25-30 fractions	86
Temozolomide	Yes	90
	No	10
MGMT methylation status	Methylated	46
	Unmethylated	32
	Unavailable	22

Table 2: Time of the first epileptic seizure

Time of the first seizure	N = 100 patients
Debut symptom of the glioma	49
Between diagnosis and surgery	9
Between surgery and Standard RT plus Concomitant and Adjuvant TMZ	2
During Standard RT plus Concomitant and Adjuvant TMZ	4
Between Standard RT plus Concomitant and Adjuvant TMZ and tumor progression	11
At time of tumor progression ≤ 6 months after glioma diagnosis 4 >6 months after glioma diagnosis 8	12
After Standard RT plus Concomitant and Adjuvant TMZ, without tumor progression ≤ 6 months after glioma diagnosis 4 >6 months after glioma diagnosis 9	13

Legend:

RT: radiotherapy; CT: chemotherapy; TMZ: Temozolomide

405 **Table 3: Cox regression analysis of OS given as hazard ratio (HR) with 95% confidence interval (CI)**

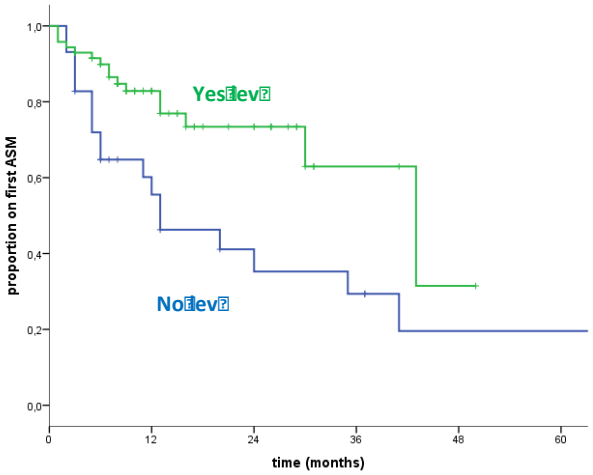
	Number of patients	UNIVARIATE HR (CI) N=100	MULTIVARIATE HR (CI) N=78	MULTIVARIATE HR (CI) N=100
INSTITUTION HUS/CHS IRE	50 50	0.71 (0.46-1.08) P=0.11 1.00	0.73 (0.38-1.40) P=0.34 1.00	0.52 (0.29-0.89) P=0.012 1.00
GENDER Male Female	72 28	0.91 (0.57-1.44) P=0.68 1.00	1.10 (0.60-1.99) P=0.76 1.00	0.93 (0.56-1.55) P=0.78 1.00
AGE <50 50-69 ≥70	38 48 14	P<0.0001 1.00 2.46 (1.53-3.97) P<0.0001 2.82 (1.46-5.44) P=0.002	P<0.0001 1.00 3.42 (1.77-6.58) P=0.001 4.35 (1.93-9.81) P=0.001	P<0.0001 1.00 3.01 (1.77-5.14) P=0.001 2.78 (1.38-5.64) P=0.004
KPS >70% ≤70%	70 30	0.75 (0.47-1.19) P=0.22 1.00	0.74 (0.39-1.41) P=0.36 1.00	0.77 (0.44-1.35) P=0.36 1.00
EXTENT OF SURGERY Partial Radical Biopsy	40 48 12	P=0.11 0.87 (0.45-1.68) P=0.68 0.57 (0.30-1.10) P=0.09 1.00	P=0.07 1.69 (0.74-3.88) P=0.21 0.81 (0.35-1.87) P=0.62 1.00	P=0.08 1.09 (0.53-2.21) P=0.82 0.50 (0.24-1.04) P=0.06 1.00

SYSTEMIC STEROIDS Yes No	93 7	1.98 (0.91-4.29) P=0.08 1.00	0.97 (0.22-4.34) P=0.97 1.00	1.64 (0.55-4.90) P=0.37 1.00
MGMT promoter status Methylated Unmethylated	46 32	0.76 (0.46-1.25) P=0.28 1.00	0.61 (0.35-1.04) P=0.07 1.00	---
SEIZURES AT DEBUT Yes No	49 51	1.04 (0.68-1.58) P=0.87 1.00	1.11 (0.66-1.85) P=0.70 1.00	1.22 (0.78-1.89) P=0.38 1.00
ASM Levetiracetam Valproate Other	71 10 19	P=0.05 1.86 (1.12-3.08) P=0.02 1.61 (0.71-3.67) P=0.26 1.00	P=0.04 2.16 (1.13-4.13) P=0.02 3.94 (1.20-12.91) P=0.02 1.00	P=0.03 1.97 (1.13-3.44) P=0.02 2.46 (1.00-6.03) P=0.05 1.00

Fig. 1A, 1B, 1C: Retention time on first ASM. Green line is patients with LEV as first ASM. Blue line is patients with other first ASM than LEV. Log-rank test for Fig. 1A, p=0.004, Fig. 1B, p=0.004, Fig. 1C, p=0.47.

1A: First ASM change

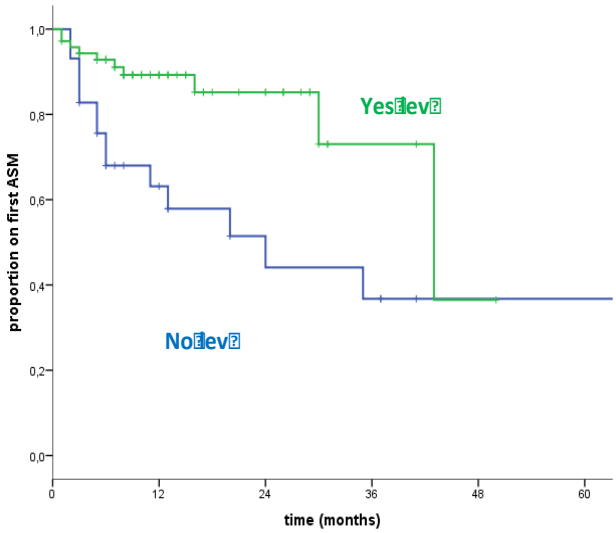
1A



P=0.004

415

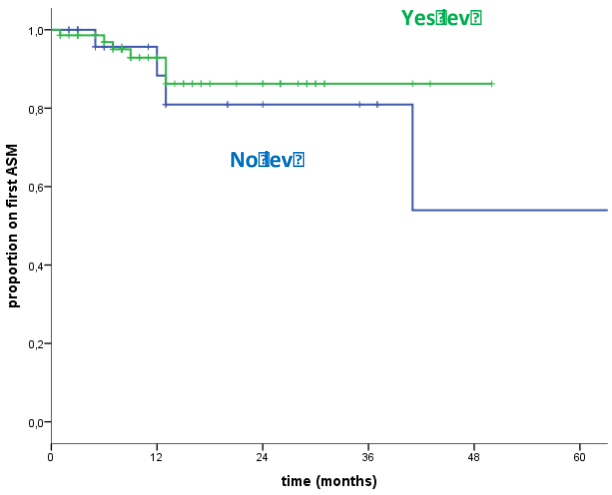
1B



P=0.004

416

1C


Yes
No
proportion on first ASM
1,0
0,8
0,6
0,4
0,2
0,0
0
12
24
36
48
60
time (months)

P=0.47

417

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ANTISEIZURE MEDICATION IN PATIENTS WITH GLIOBLASTOMA- A COLLABORATIVE COHORT STUDY

Seizure

Kristin M. Knudsen-Baas[1], Anette M. Storstein[2], Alessia Zarabla[3], Andrea Maialetti[3], Diana Giannarelli[4], Ettore Beghi[5], Marta Maschio[3]

[1]Department of Clinical Medicine, University of Bergen, Bergen, Norway;

[2] Department of Neurology, Haukeland University Hospital, Bergen, Norway

[3]Center for Tumor-related Epilepsy, UOSD Neuroncology, Regina Elena National Cancer Institute IRCCS, Rome, Italy;

[4]Biostatistic Unit, Regina Elena National Cancer Institute IRCCS, Rome, Italy;

[5]Laboratorio Malattie Neurologiche, IRCCS - Istituto "Mario Negri", Milano, Italy.

Corresponding Author:

Marta Maschio

marta.maschio@ifo.gov.it

Supplementary material

Fig. S1 : Overall survival according to MGMT status

Fig. S2: Retention time on first ASM for patients with non-methylated tumours

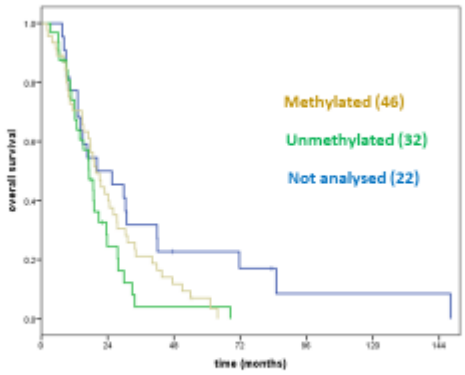
Fig. S3: Retention time on first ASM for patients with methylated tumours

Fig. S4: First ASM change because of inefficacy for patients with non-methylated tumours

Fig. S5: First ASM change because of inefficacy for patients with methylated tumours

Fig. S6: First ASM change because of adverse events for patients with non-methylated tumours

Fig. S7: First ASM change because of adverse events for patients with methylated tumours



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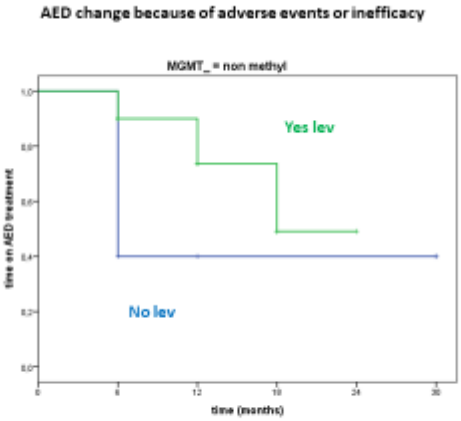

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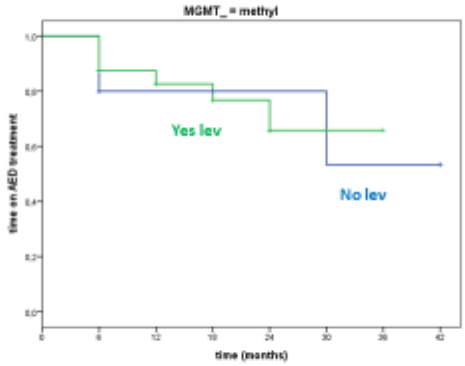
AED change because of adverse events or inefficacy



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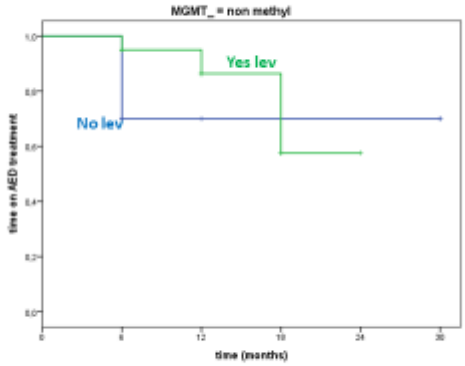
AED change because of inefficacy



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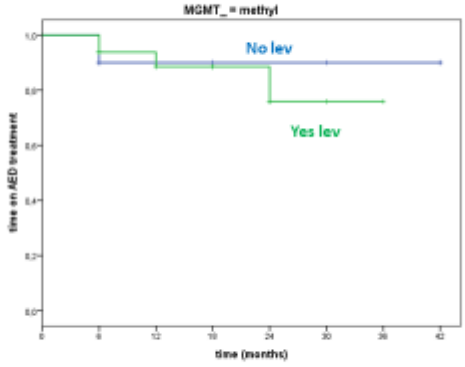

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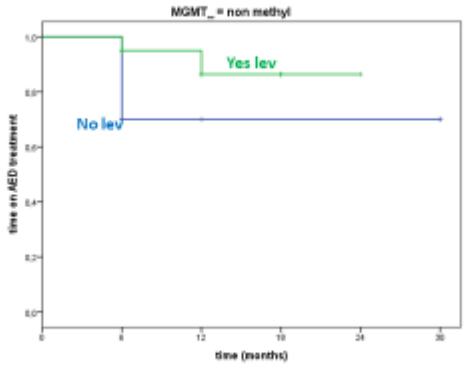

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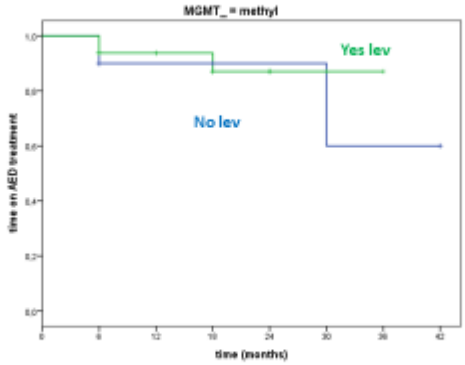

P=0.67

Declarations

Funding

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Conflicts of interest

Dr Ettore Beghi reports grants from Italian Ministry of Health, grants from SOBI, personal fees from Arvelle Therapeutics, outside the submitted work. Dr Diana Giannarelli has no conflicts of interest. Dr Kristin M. Knudsen-Baas has no conflicts of interest. Dr Andrea Maialetti has no conflicts of interest. Dr Marta Maschio has received support for travel to congresses from EISAI srl; has participated in scientific advisory boards for EISAI; has participated in pharmaceutical industry-sponsored symposia for UCB Pharma; has received research grants from UCB Pharma. Dr Anette Storstein has no conflict of interest. Dr Alessia Zarabla has no conflicts of interest.

Ethics approval

The study was approved by the Regional ethics committee (REC) in Western Norway, reference 2018/1412/REC West and by the ethics committee at the IRCCS Regina Elena National Institute for Cancer (IRE), Rome, Italy, Prot. N° 0013912.27-11-2018. In view of the retrospective nature of the study, all the procedures being performed were part of the routine care.

Consent to participate

All data were retrieved retrospectively. Patients signed a written consent for data treatment for research purpose.

Consent for publication

All data were retrieved retrospectively. Patients signed a written consent for data treatment for research purpose.

Availability of data and material

The data are available at GARRBox:

https://gbox.garr.it/garrbox/index.php/s/8TM2ziSPsHhofoE

Code availability

Not applicable.

Authors` contribution

Research hypotheses, initiation of the collaborative study, data collection, interpretation of results and manuscript preparation were performed by Kristin M. Knudsen-Baas, Anette Storstein and Marta Maschio. Data collection was performed by Alessia Zarabla and Andrea Maialetti. Data analysis was performed by Diana Giannarelli. Advice during study planning and manuscript preparation was performed by Ettore Beghi. The first draft of the manuscript was written by Kristin M. Knudsen-Baas, Anette Storstein and Marta Maschio, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

All authors agreed with the content and all gave explicit consent to submit and obtained consent from the responsible authorities at the institute/organization where the work has been carried out.

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