*Brief Communication*
# Brief report: pediatric high-grade gliomas treated with vinorelbine and valproic acid added to temozolomide

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**Abstract:** Children and young adult with high grade gliomas (HGG) have dismal prognoses and treatment options remain limited. We present 19 patients diagnosed with anaplastic astrocytoma (AA) or glioblastoma (GBM) treated with concomitant and adjuvant 20-30 mg/m$^2$/dose of vinorelbine and 30 mg/kg/day valproic acid (VA) in combination to consolidated TMZ and focal RT after maximal surgery. We evaluated the feasibility of treating children diagnosed with HGG. The median follow-up time was 51.4 months (range, 6.2-106.6 months). The 5-year OS was 57.9% (CI 95%, 33.2-76.3) and the 5-year PFS was 57.9% (CI 95%, 33.2-76.3). Eight patients (42.1%) have progressed so far, with a median time to progression of 9 months from diagnosis (range, 4.6-34.7 months). All of them died for disease progression. At time of analysis, 11 patients were still alive with no evidence of disease. It is notable that all events occurred within 35 months from the start of therapy. All 19 treated patients reported low-grade drug-related adverse events (AEs). The treatment was well tolerated in our limited cohort of patients without significant toxicity. Further studies of the efficacy and safety of combination of vinorelbine/VA to consolidated RT/TMZ therapy in children with HGG are underway in a clinical trial setting.

**Keywords:** High-grade gliomas, anaplastic astrocytoma, glioblastoma, radiotherapy, temozolomide, vinorelbine, valproic acid

## Introduction

High-grade gliomas (HGG) are rare in the pediatric age group (5% to 10% of all childhood brain tumors). Anaplastic astrocytoma (AA) and glioblastoma (GBM) are an aggressive malignancy and frequent cause of cancer-related mortality and morbidity in childhood [1]. Although the outcome of pediatric HGGs seems slightly better than adults, it remains poor despite aggressive treatments [2]. Current standard of care for HGG consists of surgical resection, radiation therapy and chemotherapy. The DNA alkylator temozolomide (TMZ) represents the frontline chemotherapy treatment for adult and pediatric HGG [3-5], TMZ together with surgical resection and radiotherapy has improved the prognosis for HGG patients [1, 6-10]; however, despite improvements in therapeutic treatment, quality of life and prognosis

remain very poor. Moreover, the management of HGG patients is complicated by the presence of drug resistance mechanisms that are a common cause for therapeutic failure of several drugs, including TMZ.

Vinorelbine (VNR) is a vinca alkaloid derivative used mostly to treat various tumor types, including GBM and midline diffuse gliomas [11]. Vinorelbine acts by depolymerizing microtubules, causing interference in M-phase by microtubule function disruption and preventing mitosis completion. In 1998 Matthew et al. described that vinorelbine possesses antineoplastic activity against human tumor xenografts derived from pediatric gliomas [12].

Histone deacetylases inhibitors such as valproic acid (VA) act on the acetylation status condensing chromatin and preventing access to

transcription factors. Histone deacetylases are involved in a series of pathways as environmental information processing, cellular processes, cell growth and death [13]. VA is a radiation sensitizer of tumor cells by using in vitro and in vivo model systems [14]. Retrospective analyses have shown that the use of VA at a dose of 25 mg/kg divided into 2 daily doses to standard RT/TMZ therapy may improve the survival of adult patients with newly diagnosed GBM [15, 16]. These data had been confirmed by following Krauze's phase II study, on adult patients with GBM. He showed a median overall survival (OS) of 29.6 months (range, 21-63.8 months) compared previous studies where it ranged from 8.6 to 19.3 months, with the same toxicity [17]. Interesting is the Wolff's et al study, where they reported the use of valproic acid in pretreated pediatric patients with high grade glioma. The study included 44 pediatric patients (from 3 to 18 years old) with newly diagnosed DIPG or grade III or IV HGG. Treatment stared with standard radiotherapy and chemotherapy (8 cycle (2 cycle simultaneous of radiotherapy) with the PEV, cisplatin, etoposide and vincristine and vincristine weekly). Subsequently VA was given in additional maintenance treatment. After 4 cycles, if the tumor remained stable, treatment with VA and maintenance therapy was started earlier; in case of tumor relapse patients were offered valproic acid as relapse treatment. Median OS was 1.33 years (at 5 years OS was 44% and 14% for first line and relapse patients respectively). The drug was well tolerated, especially if it was given on individual tolerance and efficacy [18].

According to the clinical practice of the center, we report our experience in the treatment of pediatric and young adult with high grade gliomas treated with the consolidated protocol for adult HGG with concomitant and adjuvant temozolomide to focal radiotherapy [5] with the addition of vinorelbine and valproic acid.

Our retrospective study considered patients enrolled since 2012, therefore not all new molecular investigations were performed, according to the latest 2016 and 2021 WHO classifications [19]. We reported the molecular characteristics of pediatric HGG, also looking for H3.3K27M mutations, H3F3A G34R/V and BRAF V600 E.

## Materials and methods

### Patients population

Pediatric oncology patients with HGG diagnosed at Meyer Children's Hospital in Florence, from May 2012 to January 2017 were identified.

Diagnoses were confirmed by MRI imaging at diagnosis and post operatively (to evaluate the extent of resection) and tumor histology. The tumor pathology was confirmed both by an institutional neuropathologist and outside hospital pathologists. All patients were fitted with a central line catheter before beginning the chemotherapy. All images used for tumor diagnosis as well as for re-evaluation during and after treatment were reviewed in a multidisciplinary meeting program.

Patients were previously untreated, with a Lansky or Karnofsky performance status ≥50, adequate organ function, and no MRI evidence of neuraxis dissemination.

We reported all treatment details with toxicity, time to tumor progression and overall survival.

This case series study was approved by Comitato Etico Istituzionale - Meyer Children's Hospital IRCCS number 39/2023.

### Treatment

Disease depending on the extent at diagnosis was assessed on cranial and spinal MRI and cerebrospinal fluid (CSF) cytology in all patients. All patients received surgical treatment. According to the clinical practice of the center, patients undergone radiotherapy and chemotherapy. Radiotherapy consisted of fractioned focal irradiation at a dose of 1.8 Gy per fraction given five days a week until a total dose of 54-60 Gy was reached depended on extent of tumor at diagnosis, on the age of patients and on tumor location. Radiotherapy was delivered to the gross tumor volume with a 2-to-3-cm margin for the clinical target volume. Concomitant chemotherapy consisted of temozolomide at a dose of 75 mg/m$^2$/dose on days, given orally 7 days per week. During radiation, weekly vinorelbine, 20 mg/m$^2$/dose injection was administered until the last week of radia-
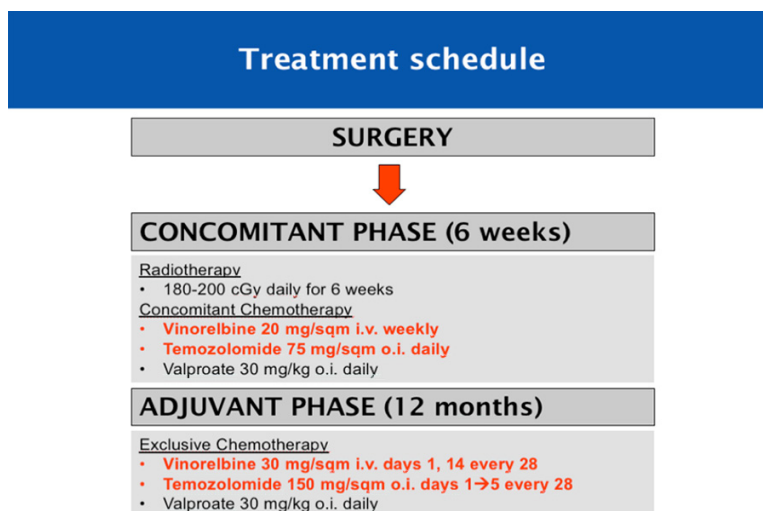
**Figure 1.** Treatment schedule.

tion therapy. Valproic acid treatment was administerd as radio-chemosensitizing drug.

VA was given orally, starting with 20 mg/kg/day in week 1 and 30 mg/kg/day in week 2. Serum trough levels were then analyzed and the dosage adjusted to reach target serum levels of 50-100 mg/L, unless unwanted side effects had already occurred.

Maintenance chemotherapy started after a 4-week break in concomitance with the MRI control after radiotherapy consisting of TMZ, 150-180 mg/m$^2$ five days every 28 days and VNR 30 mg/m$^2$/dose every 15 days for 12 months (**Figure 1**).

Surviving patients were also included in a program of endocrinological, ophthalmological and neuropsychological follow-up to monitor disease and iatrogenic sequelae and to establish a personal program aimed at rehabilitation.

*Evaluation of response*

At the end of therapy, all patients were maintained in active follow-up. Radiological evaluation was performed by cranial and spinal MRI scans every four months for the second and third years and every six months thereafter. Tumor response was defined using the response assessment in neuro-oncology (RANO) criteria by two-dimensional measures on MRI images [20] Progressive disease was defined as > 25% increase in the radiographic size of the lesion while partial response was defined as > 50% decrease in the radiographic size of the lesion. Stable disease was defined as that which cannot be classified. In the case of stable tumor volume with clinical improvement without steroids availment, disease was considered as stable for the purposes of statistical analysis in this report.

*Statistical methods*

Progression-free survival (PFS) and Overall Survival (OS) were computed in months according to the Kaplan and Meier method, considering failure and toxicity events from the date of treatment start and censoring data for progression and survival at the last follow-up visit. Difference in survival among patients' group were evaluated by using the log-rank test. Statistical analysis was performed using Fisher's exact test. Differences with *P* value < 0.05 were considered to be statistically significant.

*Evaluation of toxicity*

Patients were assessed by medical history, physical examination (including performance status), and laboratory evaluations at least monthly, with certain laboratory parameters assessed weekly during radioterapy. Targeted toxicities included all hematologic parameters, nausea, vomiting, infection, astenia, anorexia, skin rash and neurologic cognitive status.

**Results**

Nineteen patients with a diagnosis of histopathological confirmed HGG were treated at Meyer Children's Hospital from May 2012 to January 2017.

Clinical and pathological characteristics of HGG patients are shown in **Table 1**. This group consisted of 11 males and 8 females. Median age at diagnosis was 10 years (range, 6-25 years). Six patients (31.6%) had a GBM and thirteen (68.4%) had an AA. One AA patient had neurofibromatosis type 1 (NF1). According to localiza-

**Table 1.** Clinical and pathological characteristics of pediatric HGG patients

| | |
|---|---|
| Total Patients | 19 |
| Gender | |
| *Male* | 11 (58%) |
| *Female* | 8 (42%) |
| Histological Diagnosis | |
| Glioblastoma | 6 (32%) |
| Anaplastic Astrocytoma | 13 (68%) |
| Site of Tumor Origin | |
| *Supratentorial* | 15 (79%) |
| Thalamus | 5 |
| Hypothalamic/chiasm | 1 |
| Pineal | 1 |
| Hemispheric | 8 |
| *Infratentorial* | 4 (21%) |
| Cerebellum | 2 |
| Midbrain | 1 |
| Brainstem | 1 |
| Type of surgery | |
| Total resection (R0) | 7 (37%) |
| Partial resection (R2) | 12 (63%) |

tion, 15 tumors (78.9%) were supratentorial and four (21.1%) were infratentorial.

Twelve patients had received a partial excision of tumors with a macroscopic residue seen at the MRI done after surgery (R2) and gross total tumor resection was achieved in seven of nineteen cases (R0). In many cases, it has not been possible to perform all the genetic and molecular characterization due to the small amount of material analyzed after biopsy.

MGMT promoter methylation was present in 3 of 11 HGG analyzed. Two midline gliomas showed H3.3 K27M mutation, today classifiable as diffuse midline glioma, H3 K27-altered (WHO IV), whereas one hemispheric glioblastoma had G34V mutation (Diffuse hemispheric glioma, H3 G34-mutant). Eight of 14 HGG had BRAF V600E mutation. No analyzed cases showed neither EGFR amplification nor IDH1-2 mutation. Ten of 10 analyzed cases had absence of 1p19q co-deletion. Molecular characteristics are reported on **Table 2**.

The median time from diagnosis to the start of multimodal treatment was 3 weeks.

The median follow-up time was 51.4 months (range, 6.2-106.6 months). The 5-year OS was 57.9% (CI 95%, 33.2-76.3) and the 5-year PFS was 57.9% (CI 95%, 33.2-76.3). Eight of 19 patients (42.1%) died after relapse. It is notable, that all events occurred within 35 months from the start of therapy (**Figure 2**). OS appeared to be superior in patients who underwent gross total tumor resection (28.6%) versus partial total resection (50.0%). Of the seven patients who underwent gross total resection, two died during a median follow-up period of 13 months (range, 8.5-16.5 months). Of the twelve patient who underwent a partial resection, six died during a median follow-up period of 13.5 months (range, 6.5-3477 months). The extent of resection did not however have a significant effect on PFS (P = 0.63), and neither gender nor tumor location had prognostic relevance to OS or PFS. There are no significant differences in OS (P = 0.61) and PFS (P = 0.57) between AA and GBM as shown in **Figure 3**. Eight patients have progressed so far, with a median time to progression of 9 months from diagnosis (range, 4.6-34.7 months). One AA patient died soon after radiotherapy for progression disease. Five patients (26.3%) had a disease progression during the maintenance phase. The median maintenance duration for those patients was 5.4 months (range, 1.8-6.7 months). Those patients were treated later with second-line chemotherapy, usually PCV and just only one GBM patient was treated with fotemustine. All of them died for disease progression. Thirteen patients were able to complete the maintenance therapy without serious adverse events. Two patients with AA of the left thalamus relapsed. Both patients were treated with salvage chemotherapy (PCV). Both died for disease progression, 3 weeks and 3 months later, respectively.

The BRAF V600E mutation allows BRAF to signal as a monomer to activate MEK and thus ERK. Targeted therapies to BRAF V600E inhibit this monomeric signal transduction and should be effective therapeutic options.

To date we not used BRAF inhibitors as monotherapy or in combination with MEK inhibitors, therapeutic options to be considered in case of relapses.

At time of analysis, 11 patients (7 AA and 4 GBM) were still alive with no evidence of disease.

**Table 2.** Molecular characteristics of pediatric HGG treated with temozolomide and vinorelbine combination during and after radiotherapy

| Molecular Analysis | n patients (%) |
|---|---|
| MGMT promoter methylation status | |
|    Methylated | 3 (25%) |
|    Non methylated | 9 (75%) |
|    Unknown | 7 |
| BRAF V600E | |
|    Mutated | 6 (43%) |
|    Non mutated | 8 (57%) |
|    Unknown | 5 |
| EGFR amplification | |
|    Amplified | 0 |
|    Non amplified | 10 (100%) |
|    Unknown | 9 |
| H3.3 | |
|    Mutated | 3 (21%) (2 K27M, 1 G34V) |
|    Non mutated | 11 (79%) |
|    Unknown | 5 |
| IDH 1-2 | |
|    Mutated | 0 |
|    Non mutated | 13 (100%) |
|    Unknown | 6 |
| 1p19q co-deletion | |
|    Co-deleted | 0 |
|    Non co-deleted | 10 (100%) |
|    Unknown | 9 |

*Toxicity*

Toxicities grades data are presented in **Table 3**. Hematologic toxicity was the most common, with 58.3% of patients experiencing grade 3 or 4 leucopenia (52.4% neutropenia). Grade 3 or 4 nontargeted toxicities were infrequent and required transfusion of platelets and peripheral red blood cells (42% grade 1 and grade 2 anemia).

No any infections have been found. Two patients reported neurocognitive defects.

**Discussion**

Despite different approaches for pediatric HGGs, their outcome has remained dismal. Clinical studies showed a 5-year OS ranging from 15 to 35% [21-24].

However, today could be difficult to define a range of OS for pHGGs, indeed it could change substantially depending on patient's age at the diagnosis and the histology. Actually, as our case, we have to consider that the major studies on pediatric high grade glioma included heterogeneous groups of disease as GBM, AA and DIPG, that we know well they are distinct diseases, with different behavior.

Maximal surgery followed by focal irradiation to the tumor bed, plus concomitant and adjuvant chemotherapy is a main treatment approach [25, 26]. Many studies confirmed the prognostic value of GTR (gross total resection). Despite a historical report showed that, only around 20% of patients undergo near-total resection or GTR [27], 37% of patients received a GTR (R0) and 63% a partial tumor resection (PTR) (R2). In recent years the standard of care treatment for newly diagnosed HGG of pediatric age, when possible, is maximal tumor resection.

Over the subsequent years, several biologic and chemotherapeutic agents have been tested in combination with focal radiotherapy.

The role of chemotherapy in combination with radiotherapy in patients newly diagnosed with HGG had already been documented by CCG-943 trial and the randomized phase III trial CCG-945, historical protocols of Children's Cancer Group (CCG).

In the CCG-943 trial, children with HGG were randomized to receive either focal radiation therapy alone to a dose of 54 Gy or the same radiotherapy with a combination of concomitant and maintenance chemotherapy (weekly vincristine during radiation followed by eight maintenance chemotherapy cycles consisting of prednisone, lomustine, and vincristine (pCV) each given approximately 6 weeks apart).

The results highlighted that five-year EFS was 46% in the chemotherapy treated group versus 18% in the radiation alone group; however, subsequently a central pathology review showed that many of the patients included in this study were LGGs.

In trial CCG-945 HGGs were randomized to one of two chemotherapy regimens in addition to focal radiotherapy. The conventional arm was the same chemotherapy given in the CCG-943
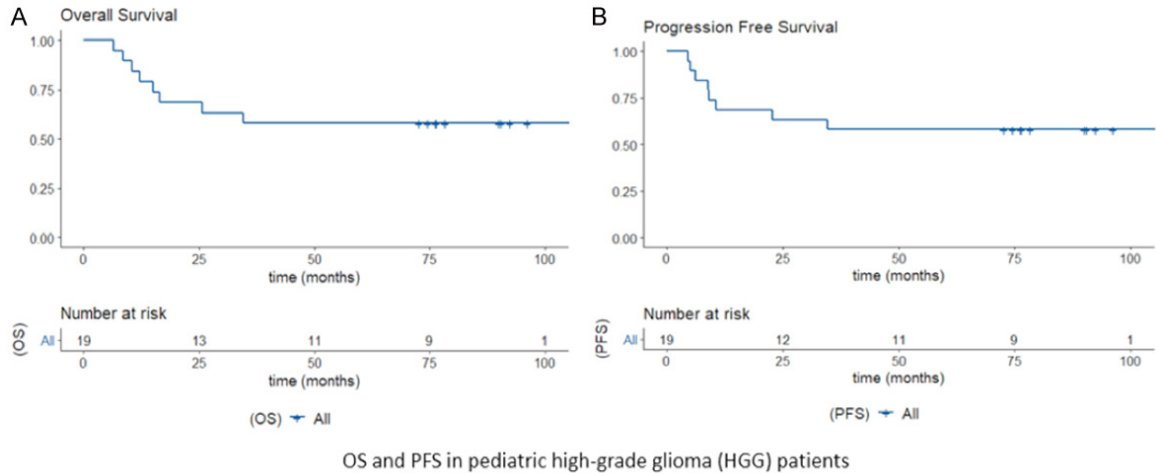
**Figure 2.** Overall survival (A) and Progression-free survival (B) and of the series.
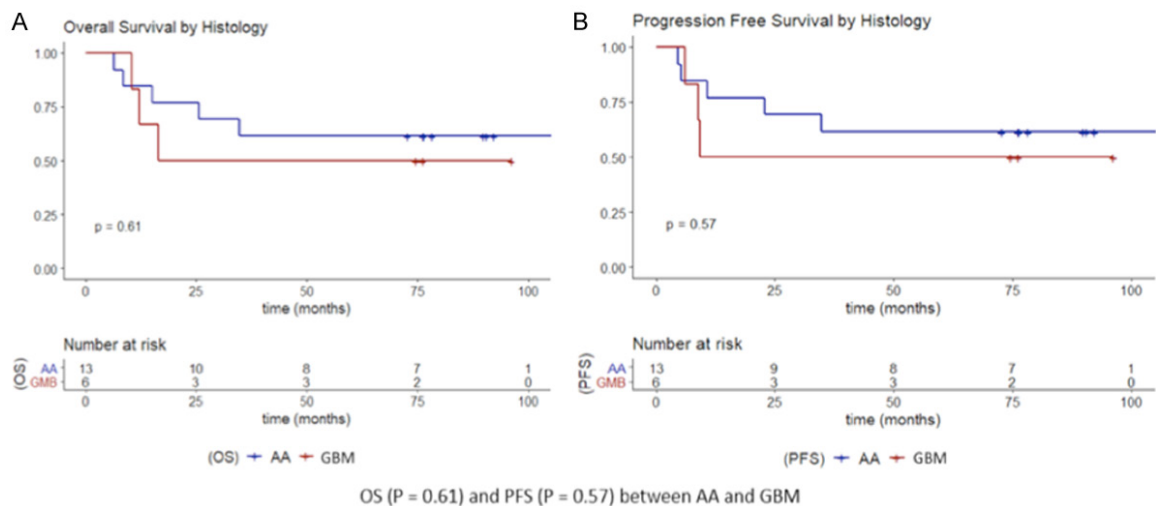


**Figure 3.** Overall survival (A) and Progression-free survival (B) and of the series according to histology (glioblastoma vs anaplastic astrocytoma).

trial (pCV) and the experimental arm was the so called "8 in 1", 8-drugs-in-l-day' (vincristine, hydroxyurea, procarbazine, CCNU, cisplatin, cytosine arabinoside (Ara-C) high-dose methylprednisolone, and either cyclophosphamide or dacarbazine). The results were not promising, there was no statistical difference between the two arms and the trial not reached the outcomes reported in the CCG-943 trial, suggesting that the addition of LGGs in this cohort modified the survivals reported [28].

The Stupp protocol has become standard of care for the treatment of adult GBM since its publication in 2005 and has led to significant outcome improvement [29].

However the results of following ACNS0126 trial were discouraging.

They used concomitant TMZ with radiotherapy followed by 10 courses of adjuvant TMZ, but this did not seem to result in an improved outcome [24].

In 2007 Donson hypothesized that the unsatisfactory results of the use of temozolomide in children with HGG, are in part linked to overexpression of DNA repair proteins, particularly O6-methylguanine-DNA methyltransferase (MGMT) [30].

The COG ACNS0423 study aimed to evaluate the efficacy of the addition of CCNU to radio-

**Table 3.** Disease and treatment related deficits and treatment toxicities

| Disease and treatment related deficits (13 evaluable patients) | | | | |
|---|---|---|---|---|
| Visual | 4 | | | |
| Endocrine | 0 | | | |
| Neuro-Cognitive | 2 | | | |
| Toxicities (highest grade for patient) | | | | |
| Hematologic toxicities | G1 | G2 | G3 | G4 |
| -Anemia | 3 (15.8%) | 5 (26.2%) | - | - |
| -Thrombocytopenia | 1 (5.2%) | 1 (5.2%) | - | - |
| -Leukopenia | 2 (10.5%) | 3 (15.8%) | 9 (47.8%) | 2 (10.5%) |
| -Neutropenia | 2 (10.5%) | 1 (5.2%) | 5 (26.2%) | 5 (26.2%) |
| Non-hematologic toxicities | G1 | G2 | G3 | G4 |
| -Asthenia | 6 (31.5%) | 2 (10.5%) | - | - |
| -Anorexia | 1 (5.2%) | - | - | - |
| -Skin rash | - | 1 (5.2%) | - | - |
| -Nausea | 3 (15.8%) | 1 (5.2%) | - | - |
| -Vomiting | 1 (5.2%) | - | - | - |

therapy plus temozolomide compared with the preceding ACNS0126 study. They hypothesized that MGMT-mediated resistance could be overcome by dual-alkylator regimen.

The addition of lomustine resulted in a significantly better EFS (P = 0.019). Indeed, the addition of CCNU to a TMZ and radiation appears to confer a significant survival benefit in particularly for subgroups known to have a worse outcome (incomplete resection, and overexpression of O6-DNA methylguanine-methyltransferase (MGMT)) [31].

In light of these different results we wonder what will be the best approach. Previous single arm adult study in newly diagnosed glioblastoma patients they demonstrated favorable results.

However, despite Jakacki et al's conclusion, in pediatric populations this association of two drugs seems to be more toxic than adjuvant treatment with TMZ [32, 33].

Intriguingly, in 2011, a group from the EORTC showed that the use of valproic acid in combination to standard RT/TMZ therapy may improve the survival of adult patients with newly diagnosed GBM [15, 16, 34, 35].

These results have been questioned in 2016 in Happold et al study. In fact, they counter that previous studies on the use of VA in newly diagnosed glioblastoma were retrospective, with small sample sizes, and there were few data on VA exposure in terms of dose and time.

They demonstrated that the additions of VA in different approaches regimes for GBM (AVAGlio (Avastin in Glioblastoma; NCT00943826), CENTRIC (Cilengitide, Temozolomide, and Radiation Therapy in Treating Patients With Newly Diagnosed Glioblastoma and Methylated Gene Promoter Status; NCT00689221), CORE (Cilengitide, Temozolomide, and Radiation Therapy in Treating Patients with Newly Diagnosed Glioblastoma and Unmethylated Gene Promoter Status; NCT00813943), and Radiation Therapy Oncology Group 0825 (NCT00884741), it did not add advantages in terms of PFS and OS.

Therefore, the use of VA was justify only for seizure control in patients with newly diagnosed glioblastoma outside clinical trials.

These study have several strengths as notably size (patients cohort n = 1.869) and prospective capture of outcome data, however, the VA was used at study entry only and after radiochemotherapy in a subset of patients. There seems to be no valid biostatistical strategy of controlling for change in treatment from VA to another antiepilettic drugs or vice versa [34].

The same not encouraging results were shown in a phase 2 study of valproic acid and radiation, followed by maintenance valproic acid and bevacizumab in children with DIPG and HGG.

Su et al reported this schedule: radiation therapy and VA at 15 mg/kg/day and dose adjusted to maintain a trough range of 85 to 115 µg/mL. VA was continued post-radiation, and bevacizumab was started at 10 mg/kg intravenously biweekly, four weeks after completing radiation therapy. The median OS was 10.3 months and 12.1 months, respectively for DIPG and HGG suggesting addition of VA and bevacizumab to radiation was well tolerated but did not appear to improve EFS or OS in children with DIPG or HGG [35].

All this doesn't mean that we can consider using VA for glioma treatment topic of discussion come to an end [34]. Indeed, in the study they underline 19% rate of pseudoprogression, in the middle of protocol therapy, compared with < 10% in adult trials incorporating up-front bevacizumab, suggesting the potential of VA's radiation enhancement. So we could consider that VA may have radiation enhancement potential, and thus early clinical and/or radiographic progression should alert clinicians to consider treatment for pseudoprogression [35].

The heterogeneous nature of HGG patients (degree of resection, location, histology, etc.) have to be considered. It could preclude a meaningful conclusion.

Other therapeutic approach was studied, recently, the randomized multicentric HERBY trial analyzed the efficacy and safety of adding bevacizumab to standard Stupp protocol in pediatric patients with newly diagnosed, localized HGG. Similarly to adult, adding bevacizumab to radiotherapy plus temozolomide did not improve the outcome in pediatric HGG patients [36].

Over 2 decades ago it has been shown that vinorelbine possesses antitumor activity against childhood high-grade gliomas with marked activity in the presence of DNA mismatch repair deficiency of glioma tumor xenografts [12].

Of great interest is an early study from 1996 showing that vinorelbine diffusely opens the blood-brain-barrier, BBB [37]. This means vinorelbine has potential for a dual mode of action: 1] opening the BBB to allow better access to glioma tissue by drugs that might not otherwise cross the BBB, and 2] have cytotoxicity to the tumoral cells.

Of all the recent work on high-risk glioma, the work of Massimino et al seems the most promising [11], although in diffuse intrinsic pontine glioma (DIPG), they gave vinorelbine 20 mg/m²/dose i.v. once weekly with an anti-EGFR antibody (nimotuzumab) and a complex radiation regimen. It was unclear if it was one, the other or the combination that marginally lengthened from expected the median progression free survival, PFS, and overall survival, OS, to 8.5 and 15 months respectively.

The same group had documented the long-term response of a young-adult recurrent glioblastoma to vinorelbine administered at a dose of 30 mg/sqm on days 1, 8, q21 [38].

The efficacy of vinorelbine on glioma cells has been recently demonstrated by a phase II study on progressive unresectable LGGs and particularly optic pathway gliomas, with low toxicity and excellent quality of life [39].

Our series of 19 patients treated with vinorelbine plus VA combined to standard RT/TMZ demonstrated a low-grade toxicity with a good quality of life for poor prognosis patients. The better prognosis of our series than other HGG series could be explained by the fact that all our patients underwent a GTR (36.8%) or a PTR (63.2%) without just a biopsy. Intriguingly we had 4 long-survival pediatric GBM patients still alive with no evidence of disease after a median follow-up time was 47.9 months (range, 6.2-79.2 months). Therefore, whenever possible, efforts should be made to completely resect these tumors before adjuvant therapy.

The limitations of our series are to be considered, in particular, the histological heterogeneity: GBM (WHO-grade IV) and AA (WHO-grade III), which may have different prognoses (patients with a WHO grade III tumor have improved survivals as compared to those with WHO grade IV tumors) and this may have biased the results. In addition, our study has a small court (n: 19 patients).

## Conclusion

We are confident that the combination of vinorelbine/VA to standard RT/TMZ had good survival outcomes and no significant adverse events. Adjuvant chemotherapy seems to be crucial for a better outcome. Maximal surgery and radiotherapy is still an important step for

obtaining tumor control. Despite the encouraging data, we suggest that properly designed prospective studies be carried out to determine whether vinorelbine and VA added to consolidated radiotherapy/TMZ, can improve pediatric HGG outcomes.

## Acknowledgements

Informed consent was obtained from all subjects involved in the study.

## Disclosure of conflict of interest

None.

## Abbreviations

HGG, high-grade glioma; CNS, central nervous system; RT, radiation therapy; CCSS, Childhood Cancer Survivor Study; AA, anaplastic astrocytoma; GBM, glioblastoma; DIPG, diffuse intrinsic pontine glioma; DMG, diffuse midline glioma; PFS, progression-free survival; OS, overall survival; GTR, gross total resection; EFS, event-free survival; MRI, magnetic resonance imaging; PTR, partial tumor resection; TMZ, Temozolomide; VA, valproic acid; VNR, vinorelbine.

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