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CLINICAL STUDY

Single agent vinorelbine in pediatric patients with progressive optic pathway glioma

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Abstract The management of progressive unresectable low-grade glioma remains controversial. Treatment options have included radiotherapy, and more recently chemotherapy, usually following an initial period of observation. Within this context, we evaluated vinorelbine, a semi-synthetic vinca alkaloid that has shown evidence of activity against glioma. From July 2007 an institutional protocol with vinorelbine (30 mg/m^2 days 0, 8, 22) for a total of 18 cycles, has been conducted at IOP/GRAACC/UNIFESP for children with optic pathway glioma (OPG). The main objectives were clinical and radiological response, as well as toxicity profile. Twenty-three patients with progressive OPG with a mean age of 69 months (4–179) were enrolled. Three patients had a diagnosis of neurofibromatosis type 1. Twenty-two patients were assessable for response with an overall objective response rate of 63 %, with eight patients showing stable disease. The most important toxicity was hematologic (grade III/IV neutropenia) observed in four patients. Gastrointestinal toxicity (grade I/II vomiting) was observed in seven patients and only 1 patient showed grade I peripheral neuropathy. The median progression-free survival (PFS) was 33 months (6.9–69) with a 3 and 5 year PFS of 64 ± 19 and 37 ± 20 %, respectively, for an overall 3 and 5 year-survival of 95 ± 10 %. This study suggests that vinorelbine may be an interesting option for pediatric low-grade gliomas, showing low toxicity profile and providing a good quality of life for patients with such chronic disease.

Keywords Progressive unresectable low-grade glioma · Optic pathway glioma · Vinca alkaloid · Vinorelbine

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Introduction

Low-grade gliomas (LGGs) represent 30–40 % of all childhood brain tumors [1]. Optimal treatment, when possible, is surgical resection [2–4]. However, for patients with midline or recurrent tumors, appropriate management remains unclear. Although radiotherapy afford some disease control, it may promote long term adverse effects, especially in younger children and patients with neurofibromatosis type1 (NF1) [5, 6]. Therefore, chemotherapy has become the mainstay treatment for children with progressive unresectable LGG. A variety of regimens have showed efficacy, inducing mostly objective tumor response [7–18]. However, given the chronicity of these conditions, administration of repeated lines of chemotherapy can lead

to undesirable side effects [8–12, 14, 15]. In this context, and based on evidence of activity of single agent vinca alkaloids, the authors evaluated vinorelbine; this semi-synthetic vinca alkaloid preferentially binds to the mitotic spindle instead of axonal neurons, promoting less neurotoxicity than other compounds in this class [17–19]. Despite evidence of activity on solid tumors, there are few reports on vinorelbine in brain tumors [20–24]. We conducted this study in children and adolescent with optic pathway gliomas (OPG).

Materials and methods

This phase II study was approved by the local Institutional Research Ethics Board and opened to accrual in July 2007 at IOP/GRAACC/Federal University of São Paulo. Data were collected and analysed in June 2013.

Eligibility criteria

The following criteria were required for enrolment in the study: (1) Patients with newly diagnosed OPG that required immediate treatment due to progressive symptoms or patients with indolent OPG that showed progression on consecutive imaging studies and/or visual deterioration. (2) Patients with recurrent/refractory tumors, recurrence defined as progression following completion of previous treatment and refractoriness as progression during chemotherapy; (3) age $\leq$ 21 years old when originally diagnosed; (3) Histologic confirmation at diagnosis was recommended. However, histology was not mandatory for patients with intrinsic chiasmatic tumors and OPG associated with NF1; (4) Patients with evidence of dissemination were eligible for the study; (5) Recurrent/refractory patients must have evidence of radiographic progression, (i.e. >25 % enlargement on magnetic resonance imaging (MRI), and/or clinical deterioration such as impairment of visual acuity; (6) interval of at least 4 weeks from previous treatment; (7) Corticosteroids were allowed to control progressive symptoms, if necessary. Patients must be on a stable or decreasing dose for at least 1 week prior to enrolment; (8) adequate hematologic, renal and hepatic functions; (8) written informed consent as approved by local institutional board. Cytologic examination of the cerebrospinal fluid and MRI scan of the neuroaxis was recommended but not mandatory.

Treatment

The treatment plan consisted of the administration of intravenous vinorelbine at a dose of 30 mg/m^2 on days 0, 8 and 22, during eighteen 4 weekly cycles for a total of 54 injections. For children weighting <10 kg, doses were calculated by body weight (1 mg/kg/dose). Before each cycle the absolute neutrophil count was to be $\geq$500/mm^3, platelet count >100.000/mm^3, creatinine level <1.5 mg/dL and transaminases <1.5× the institutional normal level. Therapy was delayed if the patient did not meet the criteria, and in case of fever and neutropenia until recovery, with decrease by 25 % of the dose, depending on individual situations. In case of grade III/IV vinorelbine-related neurotoxicity, treatment was withheld until evidence of improvement and the dose was reduced by 25 % during the following cycle.

Evaluation of response

Initial staging consisted of a brain MRI without/with contrast administration ± neuroaxis if clinically indicated. Patients underwent a detailed clinical examination at study entry. Whenever possible, visual assessment was performed at the time of inclusion, during and after treatment. Assessment was obtained using the Snellen linear chart method and single field analyses. A 2-line decrease in visual acuity compared with the pre-chemotherapy examination was defined as worsening. Similarly, improvement was defined as a 2-line increase in acuity. For visual fields, deterioration was defined as a loss of 25 % or more of the field. In children who were not able to proceed with this method, visual acuity was assessed using visual-evoked potentials.

MRI assessments were performed after the 4th, 8th, 12th and 18th cycles and every 4 months after the treatment. Tumor measurements were assessed by two physicians (FAS and EB) blinded from clinical information and calculated on bi-or tri-dimensional measures, depending on the shape of the lesion and in the non-enhanced FLAIR and enhanced T1-weighted images. Complete response (CR) was defined as no radiological evidence of tumor. Partial response (PR) as $\geq$50 % reduction in the product of the two greatest tumor diameters ($\geq$65 % for 3D measurement). Minor Response (MR) as 25–50 % reduction (40–65 % for 3D measurement). Stable disease (SD) < 25 % decrease (40 % for 3D measurement) and Progressive disease (PD) as >25 % increase (40 % for 3D measurement) in the tumor size. Because previous studies have shown some early progression followed by stabilization or response, progression had to be confirmed by a second scan at 4–8 weeks showing further increase in tumor size. In this trial, objective response (OR) was defined as CR, PR or MR with stable or improved clinical findings. In addition and independently of radiological changes, children who showed visual deterioration on two consecutive visual assessments were deemed to have PD.

Statistical considerations

The primary endpoint of the trial was response rate to single agent vinorelbine and secondary endpoints were the 3 and 5-year progression free and overall survival, safety and duration of response. The best response rates reported in the literature using single agents are 36 % with vinblastine and 29 % with carboplatin [11, 18]. A two-stage design was used for patient accrual, based on the occurrence of OR. Initially, ten patients were to be accrued. If $\leq$2 patients responded to vinorelbine, the study would be discontinued due to lack of efficacy. If $\geq$3 patients had responded, ten additional patients would be enrolled and treated (Simon's optimal two stage design). With adjustment for potential incomplete data, the required sample size would be 23 patients. Response was evaluated clinically and with MRI scan overall survival (OS) was defined as the time in months to death from any cause from date of entrance into the study. Progression-free survival (PFS) was defined as the time in months to first disease progression, disease recurrence or disease related-death from date of entrance into the study. Survival times (OS and PFS) were calculated according to the Kaplan–Meier methods.

Results

Patient characteristics

A total of 23 patients with a diagnosis of OPG were enrolled in the study. Eleven patients had biopsy proven low grade glioma and 12 patients—including three with NF1—had lesions that were considered typical on radiology, therefore were not confirmed histologically. There were 15 males. Three patients had NF1, three presented with features of diencephalic syndrome and one had disseminated disease at diagnosis. The mean age at diagnosis was 69 months (range 4–179 months). The mean time between the initial symptoms and diagnosis was 14 months (range 1–48 months). Eighteen patients were newly diagnosed and chemotherapy naïve, whereas five patients had previously been treated with $\geq$1 line of chemotherapy (range 1–4). Eligibility criteria were met for all patients: nine patients on observation were included due to visual deterioration, including two with concomitant radiographic progression; 14 patients had radiographic progression or large tumors that were considered for immediate treatment including three with diencephalic syndrome. Patients' characteristics are listed in Table 1. Eleven patients underwent surgery, including six partial resections and five biopsies. On histology, ten tumors were consistent with the diagnosis of pilocytic astrocytoma and one was described as grade two astrocytic tumors. Two patients were on steroids (dexamethasone, 0.10–0.15 mg/kg/dose BID) at the time of treatment initiation.

Table 1 Patient characteristics

Sex	
Male	8
Female	15
Age, months	
Mean	69.6
Median	50.9
Range	4.4–179.5
NF1	3
DS	3
Initial signs and symptoms	
Decreased vision	16
Proptosis	2
Diabetes insipidus	3
Precocious Puberty	4
Intracranial Hypertension	9
Surgery	
Biopsy	5
Partial resection	6
Histology	
Grade I astrocytoma	10
Grade II astrocytoma	1
Prior treatment	
One line of chemo	1
Two lines of chemo	2
Three lines of chemo	1
Four lines of chemo	1
Radiotherapy	0

*NF*1 neurofibromatosis type 1, *DS* diencephalic syndrome, *chemo* chemotherapy

At the time of last follow-up analysis in June 2013, all OPG patients had completed therapy or had discontinued treatment because of progression, toxicity or death. The median follow-up for the population was 45.8 months (range 6.8–69.4 months).

Toxicity

One patient developed atypical pneumonia after 8 cycles of chemotherapy. This patient was receiving steroids for symptom control with SD on MRI scan. He rapidly deteriorated, required intubation and died despite mechanical ventilation. Outside this complication, treatment was mostly well tolerated. Overall 1,124 doses of vinorelbine were administered, and 48 adverse events that were likely related to the treatment were reported in 14 patients. The most common toxicity observed was hematologic with eight patients experiencing 13 episodes of grade I/II

anemia. Grade I/II neutropenia was observed in three patients (4 episodes) and grade III/IV in four patients (7 episodes). Two patients under the age of 3, experienced severe neutropenia. The first developed febrile neutropenia and sepsis after two doses of vinorelbine and was taken off study. The second patient developed 2 episodes of febrile neutropenia, treated with IV antibiotics in an outpatient setting, with temporarily reduction in 25 % of vinorelbine's dose. No patient required platelet or red cell transfusion.

Seven patients experienced gastrointestinal toxicity (12 episodes) with grade I/II vomiting. Neurotoxicity was observed in four patients and included grade I abdominal pain (6 episodes) and grade I peripheral neuropathy in one patient.

Response

All patients were assessable for response except for one patient who discontinued treatment after two doses of vinorelbine due to sepsis. Responses to vinorelbine are listed in Fig. 1. The best response observed for the 22 evaluable patients was 1CR, 9PR, and 4MR, for an overall OR rate (CR + PR + MR) of 63 % (95 % CI 43–81 %) and a mean of 8 cycles to achieve the best response (Fig. 2). The response rate including only CR + PR was 45 % (95 % CI 27–65 %). The remaining patients (n = 8, 36 %) had SD.

The three NF1 patients initiated treatment after a period of observation with evidence of tumor progression. One patient with a 3 cm chiasmatic glioma extending to the right optic nerve initiated treatment due to radiological progression on consecutive scans. No surgery was performed. He achieved a CR after 12 cycles, with disappearance of contrast enhancement and normalisation of chiasmatic and optic nerve enlargement. The two other NF1 patients showed MR and SD, respectively. All three children with diencephalic syndrome demonstrated clinical response, two with radiological improvement (1MR and 1PR).

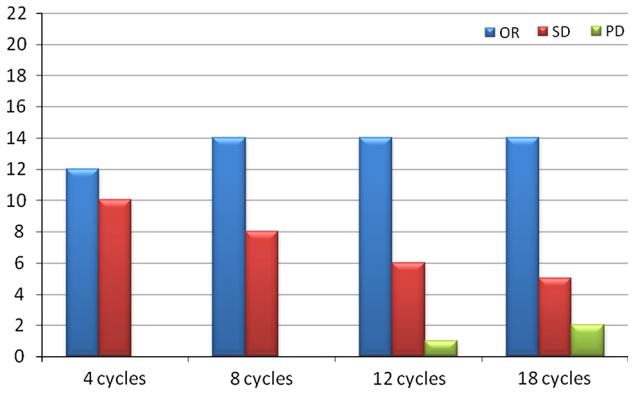

Fig. 1 Assessable patient's response according to cycles. *OR* objective response, *SD* stable disease, *PD* progressive disease

Of the nine patients who had baseline visual assessment, four were stable and five showed improvement, one of them with recovery of color vision. Other patients were considered to be too young to have their vision reliably assessed at the time of initiation of vinorelbine.

During treatment, two patients experienced radiological progression, with previous SD and MR, 11 and 12 months after starting treatment, respectively; seven other patients experienced progression 4 months to 2 years and 10 months after completion of treatment. In four patients, progression was diagnosed on imaging, while in the other three was based on deterioration of visual field with SD on MRI. Among the five patients who received vinorelbine after failure of previous chemotherapy regimens, two showed SD, 2MR and 1PR by the end of treatment. Three of them experienced further progression after completion of treatment. One of these three patients had previously experienced early progression with previous chemotherapy regimens (carboplatin/vincristine, vinblastine, cisplatin/etoposide and temozolomide). He showed sustained stabilization with vinorelbine until progression occurred, based on visual impairment while the tumor remained stable on imaging.

Median PFS for the 22 evaluable patients was 33 months (range 6.9–69 months), with a 3-year PFS and OS of 64 % (95 % CI 45–83 %) and 95 % (95 % CI 85–100 %), respectively; and an estimated 5-year PFS of 37 % (95 CI 17–57 %) and OS of 95 (95 % CI 85–100 %) (Fig. 3).

Discussion

The results of this phase II study support the use of single agent vinorelbine in the management of pediatric patients with LGG of the optic pathway. These tumors account for 5 % of all childhood brain tumors and represent a relatively homogeneous group of progressive unresectable LGG. Most OPG arise in children younger than 5 years of age although they may also be seen in teenagers. The behavior of these tumors is highly unpredictable [25]. The main threat associated with OPG is visual impairment and ultimately blindness [26]. Still, some OPG can also show aggressive behavior and may lead to death, particularly in the younger population [25]. Treatment with surgery is usually associated with a risk of serious morbidity, including visual loss and endocrine impairment [27]. The role of radiotherapy remains controversial and is reserved to older children and patients who have failed chemotherapy [28]. While there is certainly some role for observation in the context of indolent OPG, increasingly, physicians are

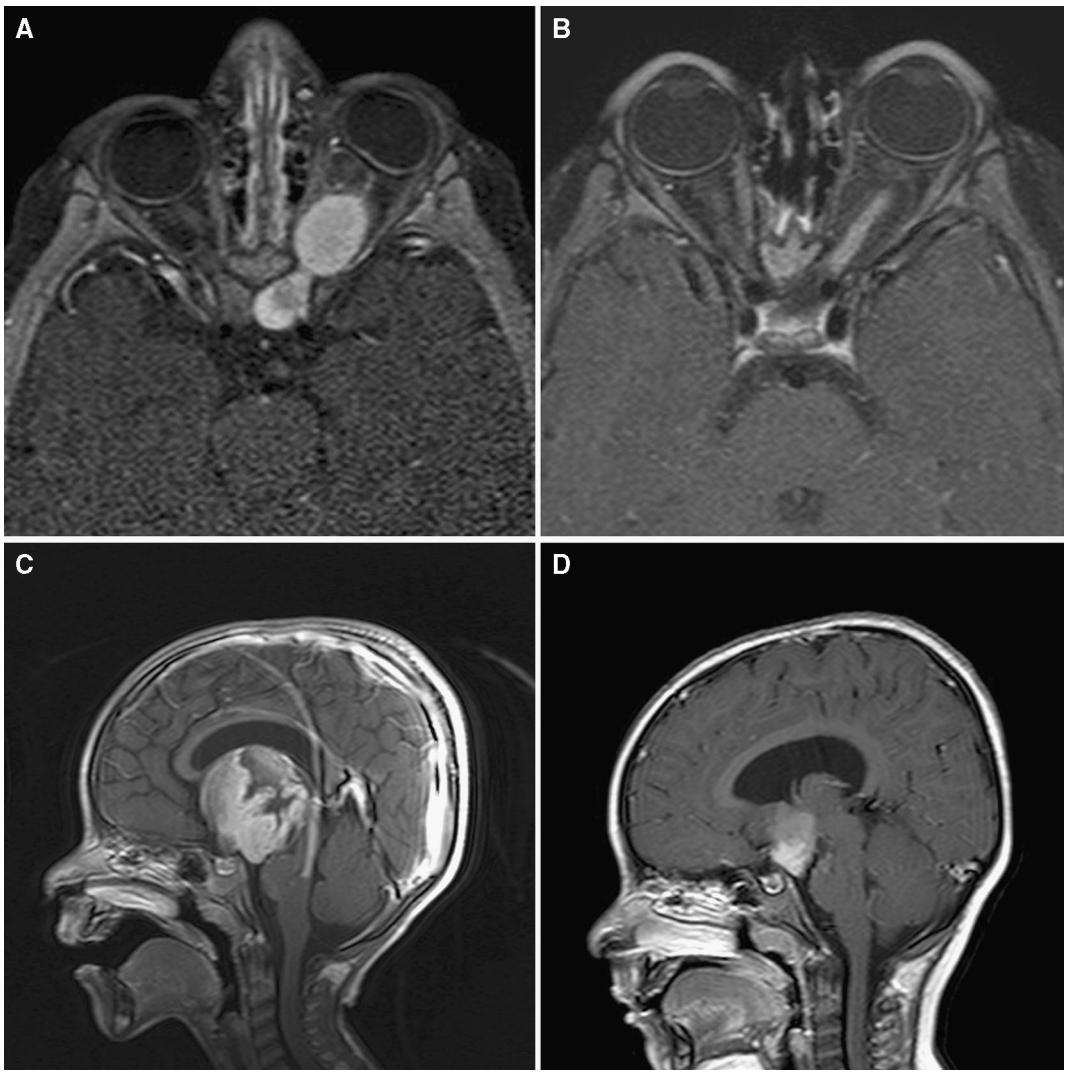

Fig. 2 **a** 4 month old boy at diagnosis, with divergent strabismus and proptosis, **c** 4 years old boy with Diencephalic Syndrome, **b**, **d** both showing partial response after 18 cycles of vinorelbine

using chemotherapy as a standard first line treatment for progressive unresectable LGG. Over the last 30 years, various protocols of chemotherapy have been investigated. Several agents and combinations have demonstrated activity, with a response rate up to 36 % for single agents and 78 % for combinations (see Table 2). Currently, the combination of vincristine and carboplatin is the most used first line option, although this combination did not show significant advantage over the TPCV regimen (thioguanine, procarbazine, lomustine and vincristine) in a large randomised study conducted by the Children's Oncology Group (COG) [8, 9, 29].

Promising results were reported in a phase II study using the single agent vinblastine, a vinca alkaloid that has traditionally be used in the management of some solid tumors as in Hodgkin's disease [18]. Vinorelbine being a semi-synthetic vinca alkaloid, it was logical to test its activity against pediatric LGG. This agent has a broad-spectrum activity with low level of toxicity. It has demonstrated efficacy as a single agent and in combination therapy against some adult tumors and more recently against pediatric sarcomas, with a response rate between 36–58 % in phase II studies conducted by COG and the Istituto Nazionale Tumori [20, 30]. The COG study enrolled 22 patients with CNS tumors: with two responses, one recurrent medulloblastoma patient with PR sustained over a period of 80 weeks and one astrocytoma patient with PR that lasted for 24 weeks. In addition, three CNS tumor patients had SD (diagnosis not provided). Reports of SD in CNS tumor patients were also noted in a COG phase I study, with tumor control in three patients-astrocytoma, meningioma and ependymoma, respectively [22]. A

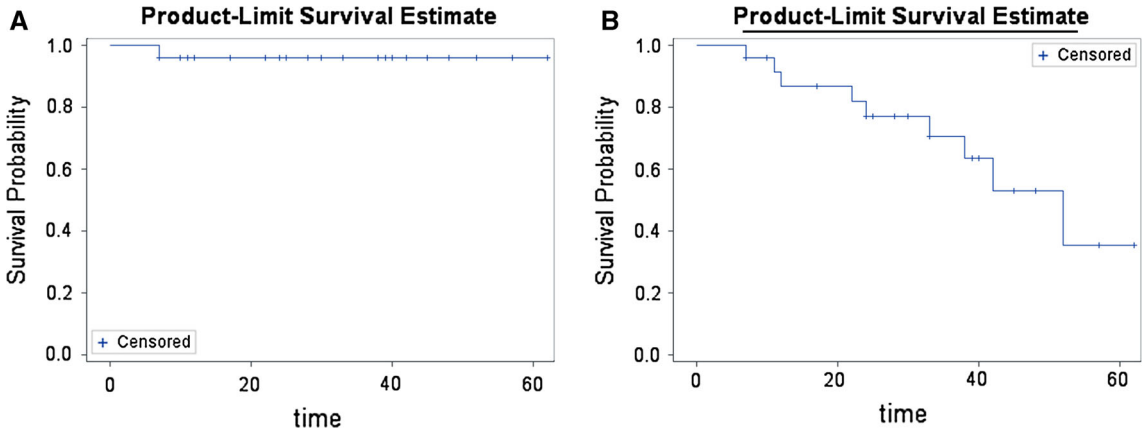

Fig. 3 **a** Overall survival and **b** progression free survival of the 22 evaluable patients

Table 2 EFS and OR with chemotherapy in clinical trials for children with progressive unresectable LGG

Single agent/regimen	No. of patients	OR	EFS (%)	Reference
Vincristine	10 (1 LGG)	1	NA	[19]
Vinblastine	51	18 (36 %)	42 at 5 years	[18]
Carboplatin	81	23 (29 %)	64 at 3 years	[11]
Temozolomide	30	3 (11 %)	31 at 4 years	[15]
Vincristine–Carboplatin (1st line)	78	44 (56 %)	68 at 3 years	[9]
TPCV	42	15 (36 %)	45 at 3 years	[10]
Etoposide–Cisplatin	34	24 (70 %)	78 at 3 years	[12]
Bevacizumab-irinotecan	10	07 (78 %)	NA	[16]
Vinorelbine	22	14 (63 %) (95 % CI 43–81 %)	64 at 3 years/37 at 5 years	Present study

EFS event free survival, *OR* objective response, *LGG* low-grade glioma, *NA* not available, *TPCV* thioguanine, procarbazine, lomustine and vincristine

sustained response was also described by Biassoni et al. in pediatric patient with recurrent glioblastoma [31]. Outside these early clinical trials and anecdotal reports, vinorelbine has not been studied against a large spectrum of CNS tumors. In particularly, there has been no trial of vinorelbine in pediatric LGG. Matthew et al. evaluated the activity of vinorelbine against xenografts derived from adult and pediatric CNS malignancies. In this experiment, vinorelbine demonstrated activity against several human glioma xenografts [22].

Our experience confirms previous reports from Rosenstock and Bouffet et al., suggesting that vinca alkaloids have an activity against paediatric LGG [18, 19]. The response rate observed in the current study is excellent, with 63 % of the patients showing OR. The projected 5-year PFS is in keeping with the results of other chemotherapy studies, summarized in Table 2. These results are interesting as there is increasing evidence that progressive unresectable LGG often have a growth potential that requires several lines of treatment [32]. The efficacy/toxicity profile of vinorelbine is without any doubt another advantage, as the repeated use of different chemotherapy agents exposes patients to a risk of cumulative toxicity, including hearing loss and bone marrow failure [9, 12]. There is no recognized long term or cumulative toxicity associated with prolonged use of vinorelbine. This makes this agent an appealing option in the armamentum of drugs to treat paediatric LGG. However, in our experience, two infants developed severe neutropenia. Increased haematological toxicity in infants has not been reported in previous studies of vinorelbine. Future trials should pay attention to this group of patients in order to provide more information on the potential relationship between age and toxicity. Whether vinorelbine acts as a cell cycle-dependent antimitotic agent or through an anti-angiogenic mechanism is unknown. In the absence of available animal models of LGG, the understanding of the activity of antineoplastic agents, in particular vinca alkaloids, in this tumor is only speculative. The results of this study confirm the important role of vinca alkaloids in the management of pediatric LGGs, as both vinblastine and vinorelbine have shown promising activity and a low toxicity profile. Although the response rate observed with

vinorelbine appears superior compared to that observed in the recent phase II of vinblastine (63 vs. 35 %), the 5-year progression free survival in the two studies is comparable. At this time no conclusions concerning the superiority of either of these therapeutic options can be made. However, since vinorelbine has an oral formulation, this offers the prospect to consider an oral agent for the management of this condition, with inherent benefits in terms of quality of life [23].

The limitation of this trial is the small size sample of the patient population. However, they represent an unselected group of consecutive patients seen in a large single institution. The lack of correlative biology study is another limitation. The recent description of the BRAF-KIAA 1549 fusion and its potential role in predicting the behavior of paediatric LGG may help in the treatment decision and may contribute to an interpretation of the chemotherapy trials [33]. However, in the present trial, the shortage histology material did not allow such correlative study. Finally, the young age of many participants in this trial precluded a systematic and thorough assessment of visual changes during the period of treatment. Such limitation is not unique to our trial, as none of the paediatric OPG clinical trials conducted lately has used a standardized visual acuity testing protocol to measure the visual benefit of chemotherapy in children with OPG [34–36]. There is an urgent need to develop international studies with clear ophthalmologic endpoints to overcome the lack of knowledge on visual outcome in OPG patients.

In conclusion, this phase II study showed interesting efficacy of another vinca alkaloid as single agent for the treatment of progressive unresectable LGG and particularly OPG, with low toxicity and excellent quality of life. Future studies should consider oral vinorelbine as a potential option for children with LGG.

Conflict of interest The authors declare that they have no conflict of interest.

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