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Research Article

Single-Agent Oral Vinorelbine in the Treatment of Pediatric Progressive Optic Pathway Glioma: A Single Institutional Experience

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ABSTRACT

Purpose: The vinca alkaloids' activity against pediatric low-grade glioma (PLGG) is well established. The goal of the present study is to describe our experience with oral vinorelbine in patients with progressive optic pathway glioma (OPG), not only regarding the clinical response, but also the cost benefit using an oral medication. Methods: Patients under 21 years of age with unresectable and/or progressive OPG were eligible. Oral vinorelbine was administered at a dose of 90mg/m^2 daily on days 0, 8 and 22, in a scheme of 4 weekly cycles for a total of 18 cycles (54 doses).

Results: From 2013 to 2018, sixteen patients were enrolled onto the study, with a median age of 9,1 years (range 4,6-17,8y). The most common histology was pilocytic astrocytoma (88,8%). Best response to chemotherapy was reviewed with a response rate (complete, partial, or minor response) of 30% for the patients treated exclusively with the oral drug. Five-year event-free survival (EFS) rate was 43.4%. Six patients had to change to intravenous vinorelbine due to gastrointestinal toxicity, vomiting grade III. None of the patients showed neurotoxicity. The total cost including drug acquisition, administration and toxicity management was lower with the oral formulation comparing to IV one.

Conclusion: Single-agent oral vinorelbine seems to have some clinical activity in the management of recurrent or refractory pediatric OPG, being an interesting and cost-effective option, minding that gastrointestinal toxicity may be limiting and a combination of antiemetics should be considered in this treatment regimen.

Introduction

Low grade gliomas (LGG) are the most frequent pediatric brain tumors, rated based on their histological features according to the World Health Organization (WHO) criteria as grades I and II tumors [1-5]. Optic pathway/hypothalamic gliomas (OPG) account for 2% of all gliomas with, approximately 75% of these tumors diagnosed during the first decade of life, mostly (60%) before the age of 5 years [6, 7]. These tumors can affect several anatomic regions along the optic pathway and the size/extent of the tumor influences the clinical presentation [6, 7]. Surgical excision remains the mainstay of treatment. Patients with unresectable tumors, especially because of their location, usually need adjuvant therapy [1-5]. Radiotherapy and several chemotherapy regimens have shown some activity against unresectable pediatric LGG (PULGG), but due to excellent overall survival and some indolent nature, most of these cases should be considered as a chronic disease, with rising concerns about morbidity and treatment late effects [1-5, 8].

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Vinca alkaloids-based therapies such as vinblastine and vincristine have been used in PULGG with reported disease control, and so has intravenous vinorelbine, a semi-synthetic vinca alkaloid published by our institution [9-12]. The goal of the present study is to describe our experience with oral vinorelbine in patients with OPG, not only regarding the clinical response, but also the cost benefit using an oral medication in a group of patients with such a chronic disease.

Patients and Methods

A single-institutional prospective cohort of 16 patients diagnosed with OPG was treated at IOP/GRAACC/Federal University of São Paulo (UNIFESP) between 2013 and 2018. The data were collected and analysed in January 2021.

I Eligibility Criteria

The following criteria were required for enrolment in the study: i) 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. ii) Patients with recurrent/refractory tumors, recurrence defined as progression following completion of previous treatment and refractoriness as progression during chemotherapy; iii) under 21 years of age when originally diagnosed; iv) Histologic confirmation at diagnosis was recommended. However, histology was not mandatory for patients with intrinsic chiasmatic tumors and OPG associated with NF1; v) Patients with evidence of dissemination were eligible for the study; vi) Recurrent/refractory patients had to have evidence of radiographic progression (i.e., 25% enlargement on magnetic resonance imaging (MRI), and/or clinical deterioration such as impairment of visual acuity; vii) interval of at least 4 weeks from previous treatment; viii) Corticosteroids were allowed to control progressive symptoms, if necessary. Patients had to be on a stable or decreasing dose for at least 1 week prior to enrolment; ix) adequate hematologic, renal and hepatic functions; x) 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.

II Treatment

Oral vinorelbine was administered at a dose of 90mg/m^2 daily on days 0, 8 and 22, in a scheme of 4 weekly cycles for a total of 18 cycles (54 doses). Therapy was ceased on completion of the targeted cycles or on evidence of disease progression. For patients over 15 years of age the original dose was reduced to 80mg/m^2. Before each cycle, the absolute neutrophil count was supposed to be 500/mm^3, platelet count 100.000/mm^3, creatinine level < 1.5 mg/dL and transaminases < 1.59, the normal institutional 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. Adverse events were categorized according to Common Terminology Criteria for Adverse Events Version 4.0. 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. The same criteria were applied in case of grade III/IV gastrointestinal toxicity and if the symptoms persisted despite the dose reduction, switching to vinorelbine IV was considered.

III 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. Visual assessment was performed by visual evoked potential scans or visual field campimetry at the time of inclusion, during and after treatment if available. MRI assessments were performed after the 4th, 8t^h, 12th and 18th cycles and every 4 months after the treatment. Tumor measurements were assessed by two physicians (FAS and AMC) 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. Response was graded using the revised RECIST criteria (response evaluation criteria in solid tumors). Complete response (CR) was defined as no radiological evidence of tumor; Partial response (PR) as 50% reduction in the product of the two greatest tumor diameters; Minor Response (MR) as 25-50% reduction; Stable disease (SD) as 25% decrease, and Progressive disease (PD), 25% increase in the tumor size. Objective response (OR) was defined as CR, PR or MR with stable or improved clinical findings. In addition, and regardless of radiological changes, children who showed visual deterioration on two consecutive visual assessments were deemed to have PD.

IV Statistical Analysis

Database and medical records review identified patient's age, associated syndromes, primary site, pathology, BRAF mutation/fusion status when available, treatment history and follow-up. The primary endpoint of the trial was response rate to single-agent oral vinorelbine and the secondary endpoints were the 3 and 5-year progression free and overall survival, safety and duration of response. A two-stage design was used for patient accrual based on the occurrence of OR. Initially, ten patients were to be accrued. If < 2 patients responded to vinorelbine, the study would be discontinued due to lack of efficacy. If > 3 patients responded, ten additional patients would be enrolled and treated (Simon's optimal two stage design). With adjustment for potential incomplete data, the required initial sample size was 23 patients. The study would also be discontinued due to prohibitive toxicity.

Event free survival (EFS) was defined as the time in months to first disease progression, disease recurrence or disease related-death from date of entrance into the study. Overall survival (OS) was defined as the time elapsed from date of entrance into the study to the time of death due to all causes or the last follow-up visit. Survival times (OS and EFS) were calculated using Kaplan-Meier method. The evaluation of cost benefit occurred comparing the two studies with vinorelbine performed in our institution, observing the costs related to the treatment and the patient's quality of life. The review was conducted with institutional ethics approval, including provision of informed consent and assent.

V Cost Analysis

To evaluate the comparative cost effectiveness of oral vinorelbine, the commonly accepted dose regimens for each agent were established,

costs of drug acquisition, administration as well as the toxicity management. The costs of chemotherapy delivery in hospital (in-patient) and ambulatory care and possible complications were estimated from the perspective of the Brazilian Unified Health System (Sistema Único de Saúde -SUS). The refund cost of the healthcare system for chemotherapy varies according to the line of treatment, estimated, for the first to fourth line, in R$ 1,700.00 ($314.81), R$ 1,400.00 ($259.25), R$ 800.00 ($148.14) and R$ 427.50 ($79.16) respectively.

Results

I Patients' Characteristics

Sixteen patients with OPG were treated with oral vinorelbine at the IOP-GRAACC-UNIFESP over the five-year period from 2013 to 2018. Patients' characteristics are summarized in (Table 1).

Table 1: Patients' characteristics.

Age (months)	Sex	Syndrome	Local	Metastasis	Surgery	Pathology	Prior Treatment	Oral Vinorelbine Cycles	Evaluation	Toxicity
56	F	No	Optic	No	Partial Resection	PA GI	No	4	SD	GI
72	M	Russel	Optic	No	Partial Resection	PA GI	Yes (Four lines)	18	SD	No
77	M	No	Optic	No	Partial Resection	PA GI	Yes (One line)	18	PR	No
90	F	No	Optic	No	Biopsy	PA GI	No	8	PD	GI
96	F	No	Optic	No	Biopsy	PA GI	No	4	PD	No
102	M	No	Optic	No	Partial Resection	A GII	No	12	SD	GI
104	M	No	Optic	No	Biopsy	Inconclusive	No	4	MR	GI
107	F	NF1	Optic	No	No	-	No	4	PD	GI
111	F	No	Optic	No	No	-	No	18	MR	No
127	M	NF1	Optic	No	No	-	No	4	PR	GI
136	M	No	Optic	No	Partial Resection	PA GI	No	18	SD	No
150	F	No	Optic	No	No	-	No	18	PD	No
158	M	No	Optic	No	Biopsy	PA GI	No	4	PR	GI
177	M	No	Optic	No	Partial Resection	PA GI	Yes (Two lines)	18	SD	GI
180	F	No	Optic	No	No	-	Yes (One line)	18	PR	GI
213	F	NF1	Optic	No	No	-	Yes (Two lines)	18	SD	GI

A GII: astrocytoma grade II; F: female; GI: gastrointestinal; M: male; MR: minor response; NF1: neurofibromatosis type 1; PA GI: pilocytic astrocytoma grade I; PD: progression disease; PR: partial response; SD: stable disease.

The median age of the oral vinorelbine cohort was 9.1 years (range 4.6-17,8y), 50% were male and 18.7% met diagnostic criteria for neurofibromatosis type 1 (NF-1). Only one patient was diagnosed with diencephalic syndrome. Other clinical presentations included five patients (31.2%) with visual acuity deterioration, eight (50%) with increased intracranial pressure and four (25%) with endocrine dysfunctions - early puberty. Histologic diagnosis was made in nine patients. The most common histology was pilocytic astrocytoma grade I (88.8%). One patient had astrocytoma grade II and in one case the biopsy was inconclusive. None of the patients had metastatic disease at the time of initiation of the therapy.

Eligibility criteria were met for all patients: thirteen patients on observation were included due to visual deterioration or radiographic progression; Five of these had been previously submitted to surgery, three partial resections and two biopsies. Three had been submitted to surgery (partial resection) and prior chemotherapy and two had been submitted to chemo without any surgical intervention before. Three were treatment naïve on observation only. Three other patients had visual deterioration or large tumors that were considered for immediate treatment at the diagnosis, two of them were submitted to biopsy procedure. In summary, ten patients had undergone some surgery intervention before (4 biopsies and 6 partial resection) and five patients had received prior chemotherapies (range 0-4). None of them had received radiotherapy as prior treatment.

II Treatment Outcomes and Toxicities

All 16 patients were assessable for response. Considering the patients exclusively treated with the oral drug, the best response observed was two PR and one MR, for an overall rate (OR) of 30% (95 % CI 43–81%). Four patients (40%) showed SD. The response rate during oral administration for the patients that, due to toxicity, changed to the intravenous vinorelbine, was one MR and two PR (50%). Two patients showed SD (33.3%). Three patients showed progressive disease during therapy with the oral formulation. Two of them had both radiological and visual PD after four (#5) and eight cycles (#4). The other patient (#12) showed visual deterioration after eighteen cycles due to the cystic component and was submitted to neurosurgery. Four patients developed PD following completion of therapy with 20, 28, 30 and 58-month disease free survival. Of the patients that had changed to IV formulation due to toxicity, one case with NF1 progressed during therapy despite the change to intravenous vinorelbine, with no radiological changes but visual deterioration (#8) and the other progressed after the end of therapy, achieving a 39-month EFS (#7). Of the fourteen patients who had baseline visual assessment (three visual evoked potential scans, eight visual field campimetry and three both methods), eight were stable and two showed improvements. Four showed visual impairment, two with radiological progressive disease, one with no radiological changes and the other due to cystic component as described above.

One patient (#16) lost follow up after 20 months with stable disease and one patient (#4) died due to surgical complications after PD. Of the patients that had an underlying diagnosis of NF1, all of them had GI toxicity and two of three had to change chemo to intravenous vinorelbine, with stable disease, after four cycles due to intolerance and one PD (#8) as previously described. The patient with Diencephalic Syndrome had SD during the eighteen cycles and achieved a 28-month EFS. As he became older, he also developed hypothalamic obesity. Of ten patients who underwent surgery at diagnosis, only two samples were analysed for BRAF mutation (#2,11), both with the BRAF-KIAA 1549 fusion. They achieved SD during the 18 cycles but had PD after therapy with 20 and 28-month EFS, respectively.

No patients had admissions for febrile neutropenia and only one experienced one delay in starting a chemotherapy cycle due to neutropenia with no need for dose reduction. Ten patients showed gastrointestinal toxicity, all of them with grade I/II nausea, four patients also reported grade I diarrhea and one grade II diarrhea in, at least, one cycle of the treatment. Six of them discontinued the oral regimen due to grade III vomiting, switching to intravenous vinorelbine (2SD, 1MR, 2PR, 1PD). Of these, excluding the patient that progressed during therapy, four (#1,6,10,13) achieved stable disease after the end of therapy and one (#7) progressed with a 39-month disease free survival. None of the patients showed neurotoxicity. Patients were followed up until January 2021 with a mean follow-up of 51.5 months (range 8-92). Patients who had changed to IV vinorelbine were considered censored at date of last follow-up. Mean time to progression was 21 months (range 4-58 months) and Kaplan-Meier analysis showed a 3-year EFS of 57.8%, a 5-year EFS of 43.4% and a 5-year OS of 93.8% (Figures 1A & 1B).

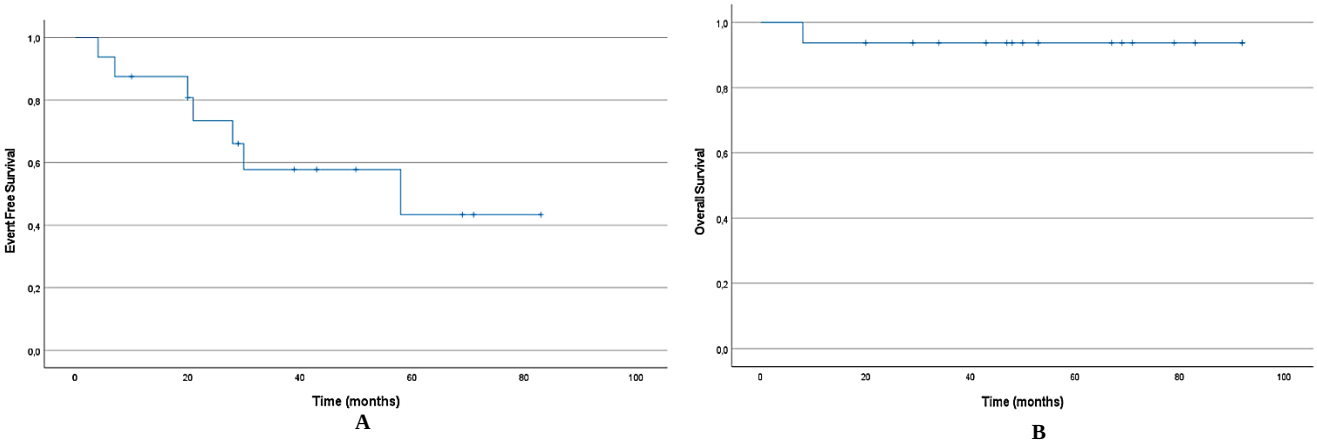

Figure 1: A) Event Free Survival and **B)** overall survival of all the 16 evaluable patients.

III Cost Analysis

The acquisition cost per cycle considering 30mg/m^2 D1-D8-D22 for intravenous vinorelbine and 90mg/m^2 D1-D8-D22 for the oral formulation estimated per 1m^2 in reais and dollar (5.40 reais) R$276.00 ($51) and R$1,485.00 ($275) respectively. The intravenous administration for the drug required a long-term central venous access device, two medical visits and three day-time-hospitalization whereas the oral one required one medical visit with a self-administered medication (with parents' supervision) at home, totalizing R$ 6,411.25 ($1,187.26) and R$12.47($2.30), respectively. Regarding febrile neutropenia both IV and oral showed low toxicity with few cases in the intravenous presentation. However, the oral route showed more grade III GI toxicity (vomiting), requiring hospital visit with need for intravenous antiemetics administration with an estimated cost of R$ 732.91 ($135.72).

Discussion

Here we report a five-year period overview of patients with PULGG (OPG) diagnosed and treated at the IOP-GRAACC-UNIFESP. The median age at diagnosis for this group of patients is around 6-8 years and grade I pilocytic astrocytoma (PA) is the most common histological subtype with similar results reported in our series [1, 5, 11]. They may be asymptomatic or may present with variable symptoms like visual acuity deterioration, visual field narrowing, strabismus, proptosis and nystagmus. Endocrine dysfunctions like early puberty and increased intracranial pressure with hydrocephalus may also occur [6, 7]. In our series, we had all these clinical presentations and also a patient with failure to thrive diagnosed with diencephalic syndrome.

Considering the growing concerns of therapy-related toxicities, especially radiotherapy in young children and patients with NF-1, chemotherapy protocols have had an increasingly important role in the treatment of progressive pediatric low-grade gliomas not amenable to complete resection [1-5, 9, 13-15]. In this context, we evaluated the feasibility and toxicity of the single-agent oral vinorelbine in the PULGG treatment. The vinca alkaloids activity against pediatric LGG is well established and the previous study of our institution had supported the use of single-agent vinorelbine, a semi-synthetic anticancer agent of the vinca alkaloid group, in the management of pediatric patients with LGG of the optic pathway with 63% of the patients showing objective response [9-12, 16, 17].

Vinorelbine differs from other vinca alkaloids in its chemical structure, effects on microtubules, and toxicity profile [18]. Its cytotoxic effect is mediated through inhibition of the polymerization of tubulin dimmers into microtubules, which results in the disruption of mitotic spindle formation instead of axonal neurons [18, 19]. Since this drug has an oral formulation and once the reliability of bioequivalent of intravenous and

oral forms is confirmed, concomitant or alternative use of oral chemotherapies represents a substantial interest for oncologist and patients because of its advantages, including easier administration, greater convenience for the patient and reduced need for hospitalization [19-21].

In this study, single-agent oral vinorelbine, despite the small number of patients, seems to have some clinical activity with a progression free survival which may be comparable to previous chemotherapy studies with other single agents in PLGG as vinblastine [9, 10, 13, 22]. Currently, the combination of vincristine/ carboplatin is still the most used first line option with a reported OR rate of 56% [11]. Considering that most children with PLGG may require several lines of chemotherapy and that similar outcomes have been observed between the successive chemotherapy regimens, the use of an oral presentation with low toxicity profile seems justifiable as reported in previous studies, showing comparable toxicity profiles of oral and intravenous vinorelbine [19-21, 23]. The well described hematologic and neurologic (abdominal pain and peripheral neuropathy) toxicities attributed to the vinca alkaloids were not observed in the present study, comparing with our previous one, in which intravenous vinorelbine showed hematologic as the most common toxicity with a few patients also experiencing neurotoxicity. It seems reasonable to consider a better toxicity profile with the oral form. However, the present group presented with gastrointestinal toxicity as the most common toxicity observed with need for discontinuation of the treatment regimen in some cases.

It is important to note that the oral form of vinorelbine is described as highly emetogenic and, according to the well documented ASCO guidelines, a two or three-drug antiemetic combination is recommended, including 5-HT3 receptor antagonist, dexamethasone and aprepitant or fosaprepitant [24]. The decision to use dexamethasone should take into account the adverse effects of these drug and, unfortunately, other medications such as aprepitant are not yet available in our public health system with an estimated cost of R$700.00 ($130.00) per dose, which seems prohibitive for use in a low-income country. Considering the steeply rising health care cost and the economic difficulties in low-income countries, it has become increasingly important that new drugs be also assessed for their cost-effectiveness and clinicians be able to understand and critically appraise these data [25-27]. Our series assessed the real cost of the institution regarding drug administration and toxicity profiles showing a real evaluation, comparing the intravenous and oral vinorelbine that should be considered at the moment of decision making.

The limitations of this analysis were the sample size, the impossibility to use a better antiemetic combination as previously described and lack of a correlative biology study. Over the past decade, an increasingly detailed understanding of the molecular and genetic characteristics of this group of tumors allowed the development of promising tumor-specific, molecularly targeted therapies, but until the use of these new drugs is widespread, especially in low-income countries, effective chemotherapy regimens with reasonable toxicity profiles and ease of administration will continue to play an important role in the management of children with ULGG [3-5].

Conclusion

Once PULGG shows excellent long-term survival, the treatment strategies should consider the chronicity of the disease and minimize therapy-related toxicities. Our study showed an interesting and cost-effective option against PLGG, minding that gastrointestinal toxicity may be limiting, especially in low-income countries, where more intensive antiemetics combinations are not yet available in public health system, and should be considered in this treatment regimen.

Ethical Statement

The study received ethical approval from the ethics committee of the University of São Paulo (UNIFESP) and carried out in accordance with the Code of Ethics the World Medical Association (Declaration of Helsinki). The parents signed the informed consent of the study.

Data Availability Statement

The data that support the findings of this study are available on reasonable request from the corresponding author.

Code Availability

None.

Funding

None.

Conflicts of Interest

None.

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