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Glutamic Acid Not Beneficial for the Prevention of Vincristine Neurotoxicity in Children with Cancer

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Abstract

Background—Vincristine causes known side effects of peripheral sensory, motor, autonomic and cranial neuropathies. No preventive interventions are known.

Procedure—We performed a randomized, placebo-controlled, double-blind trial of oral glutamic acid as a preventive agent in pediatric patients with cancer who would be receiving vincristine therapy for at least 9 consecutive weeks (Stratum 1= Wilms tumor and rhabdomyosarcoma) or 4 consecutive weeks in conjunction with steroids (Stratum 2=Acute lymphoblastic leukemia and Non-Hodgkin lymphoma). At designated time points, a scored neurologic exam using the Modified Balis Pediatric Scale of Peripheral Neuropathies was performed to document neurologic toxicity.

Results—Between 2007–12, 250 patients were enrolled (Stratum 1=50, Stratum 2=200). The glutamic acid treated group did not have a significantly lower percentage of neurotoxicity compared to placebo treated group either overall or within stratum or age subgroups. The only subgroup which was suggestive of treatment effect was for age. Patients 13 years or older showed a larger benefit in favor of glutamic acid ($p=0.055$) compared to patients less than 13 years ($p=1.00$). Constipation was the most frequently reported (14%) Grade II or higher neurotoxicity.

Conclusion—Vincristine-associated neurotoxicity in pediatric oncology remains a frequent complication of chemotherapy for multiple diagnoses with an approximate 30% of patients affected. Glutamic acid is not effective for prevention in pre-adolescents. There is a suggestion of benefit in patients 13 years or older, but the study was not designed to provide adequate power to test the treatment effect within this age group alone.

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Keywords

chemotherapy neurotoxicities; lymphoblastic leukemia/neurology; quality of life; support care; pediatric oncology

Introduction

Vincristine is a chemotherapeutic agent with a broad spectrum of clinical activity [1,2]. It is one of the most commonly used chemotherapeutic agents in the treatment of pediatric cancer and is used in the treatment of leukemias, lymphomas and most solid tumors of childhood. Its mechanism of action is related to its high affinity binding to microtubules in rapidly dividing cells resulting in a disruption of the mitotic spindle and arrest of cell division in metaphase [3]. The dose limiting toxicity seen with vincristine administration has been neurotoxicity, in particular a sensorimotor peripheral neuropathy due to microtubule dysfunction [4–7]. Peripheral neurons are especially sensitive to this microtubule dysfunction because of their dependence on axoplasmic flow. Interference with intracellular transport leads ultimately to axonal degeneration [8]. Neuron-specific tubulin isoforms, posttranslational microtubule modifications and the presence of associated proteins might also contribute to the specific neuronal sensitivity to vincristine [9–11].

Clinical manifestations result from peripheral sensory, motor, autonomic and cranial nerve involvement [12–14]. Common manifestations include symmetric loss of deep tendon reflexes, paresthesias and profound muscle weakness and subsequent muscle atrophy. It has also been associated with paralytic ileus, urinary retention, ptosis and cranial nerve palsies. No effective therapy for vincristine-induced neuropathy is known other than withdrawal of the drug with variable recovery of function seen.

Several adult trials backed by support from pre-clinical studies in a mouse model have suggested that glutamic acid administration may ameliorate the neurologic toxicity of vincristine without affecting its anti-tumor effects [12, 15–17]. There is no known mechanism for this potential beneficial effect. To determine if there is significant protection against neurotoxicity with the administration of glutamic acid, we performed a randomized, placebo-controlled, double-blind trial of oral glutamic acid in pediatric cancer patients who would be receiving vincristine therapy. In this study, we also wished to obtain and describe more specific data about the frequency and severity of neurologic side effects with vincristine use.

Methods

Patient Eligibility

Patients 3 years (y) of age, due to concerns of oral medication noncompliance and intolerance, and 21 years of age were eligible for either of two strata. Stratum 1 included newly-diagnosed patients with Wilms tumor or rhabdomyosarcoma (RMS) scheduled to receive at least 9 consecutive weeks of vincristine with the start of their chemotherapy. Stratum 2 included newly-diagnosed patients with acute lymphoblastic leukemia (ALL) or non-Hodgkin lymphoma (NHL) scheduled to receive at least 4 consecutive weeks of

vincristine with the start of chemotherapy accompanied by steroid therapy. Stratum 2 was separated due to concerns that steroid myopathy side effects might affect the neurologic exam. Patients using, or planning to use, itraconazole or scheduled laxatives or with neuromuscular disease, abnormal baseline neurologic exam, brain tumor, recent history of Guillian-Barre syndrome, or family history of Charcot-Marie-Tooth disease were ineligible.

Written informed consent was obtained from all patients prior to enrollment according to institutional review board guidelines. Participating institutions were from the SunCoast CCOP Research Base and/or the Children's Oncology Group.

Study design

Prior to the first dose of vincristine at week 1 of chemotherapy, enrolled patients were randomized to receive l-glutamic acid hydrochloride or placebo dosed three times daily starting anytime prior to first vincristine dose and continuing until 7 days following week 9 dose of vincristine (Stratum 1) or until 7 days following week 4 dose of vincristine (Stratum 2). L-glutamic acid was supplied as 250 mg capsules with dose administered as: 1 capsule for body surface area $<1\text{m}^2$ and 2 capsules for 1m^2 . The dose used approximated the surface area equivalency dosage found to be effective in the previous murine study and has also been well tolerated in previous trials [12, 15, 17–18]. Placebo was administered similarly based on body surface area. Capsules could be opened, for patients unable to swallow pills, and contents added to small amount of food without discernible difference. Standard scored neurologic examination was performed at baseline and at Week 5 of therapy for both strata. An additional neurologic examination was performed at Week 10 for patients in Stratum 1. For adherence monitoring, study logs were kept by the patient documenting each dose of study medication as well as symptoms. In addition, study personnel collected information regarding any missed, omitted or reduced doses of vincristine.

The primary endpoint was statistically analyzed using both the chi-square test and the Cochran-Mantel-Haenszel test adjusted for stratum. Subgroup analyses by stratum and age were conducted using logistic regression with independent factors of treatment, subgroup and the subgroup by treatment interaction. Within stratum comparisons were analyzed using Fisher's exact test. Adverse events were analyzed using Fisher's exact test. All reported p-values are two-sided. The planned sample size of 208 was based on an analysis pooled over both strata. The study was 80% powered to detect a 20% difference in the expected event rates.

Patient evaluation

At designated time points, a scored neurologic exam using language from the Modified Balis Pediatric Scale of Peripheral Neuropathies was performed to document neurologic toxicity (Table I)[19]. The examination documented incidence and grade of toxicity in the categories of sensory neuropathy, deep tendon reflex assessment, motor neuropathy, laryngeal nerve dysfunction, neuroconstipation, jaw pain and "other" using the NCI common Terminology Criteria for Adverse Events (CTCAE), Version 4.0. For monitoring of toxicity, the CTCAE v. 4 was also used to report any Adverse Events. A routine

chemistry panel was obtained at baseline, week 5 and week 10. Also, remission status was documented for patients in Stratum 2 at Day 29 bone marrow evaluation.

Results

Patient characteristics and Vincristine dosage

Between October 2007 and September 2012, 250 patients were enrolled. Clinical characteristics are presented in Table II. Fifty patients were enrolled in Stratum 1 while 200 were enrolled in Stratum 2, the great majority with ALL (Figure 1). No significant differences in characteristics were otherwise noted amongst any subsets.

The average daily dose of vincristine during the study is shown in Table III for the four different diagnoses. Some patients had missing data which explains the smaller sample sizes. The average daily dose is similar across drug and placebo for all four diagnoses. The actual dose of vincristine administered was compared to the planned dose. The percentage of patients who received a full dose was high (97% for placebo and 93% for glutamic acid) and not significantly different ($p=0.16$) between groups. In Stratum 1, the average number of vincristine doses received for older patients was 9.3 (SD=2.0) while for younger patients, the average number was 8.6 (SD=3.0). In Stratum 2, the average number of vincristine doses received for older patients was 4.6 (SD=1.1) while for younger patients, the average number was 4.6 (SD=1.0).

Neurotoxicity

All subjects with post baseline neurotoxicity scale data were included in the analysis. Neurotoxicity data grade 2 or higher was collected and compared overall and across subsets. The glutamic acid treated group did not have a significantly lower percentage of neurotoxicity compared to placebo treated group either overall or within stratum or age subgroups (Table IV). Subsets analyzed post-hoc included stratum, age (cutoff of less than 13y), gender, ethnicity, specific disease types, and individual neurotoxicity categories (i.e. sensory, motor, constipation, etc.). The only subgroup which was suggestive of treatment effect was for age (Table IV). Patients 13y or older showed a larger benefit in favor of glutamic acid (treatment difference in neurotoxicity rates of 0.28, $p=0.055$) compared to patients less than 13y (treatment difference in neurotoxicity rates less than 0.02, $p=1.00$). The lack of statistical significance between treatments in the older patients is partially due to the smaller sample size of this subgroup compared to the sample size of younger patients.

Neurotoxicity frequencies in each category of the modified Balis scale were calculated from collected data to further understand side effects noted in vincristine-treated patients. Reported grade 2 or higher neurotoxicities were seen as follows: constipation (14%), sensory changes (13%), motor changes (13%), jaw pain (3%), and laryngeal nerve dysfunction (1%).

Adverse Events

Grade 2 or greater toxicities were collected on all patients. No individual toxicity criterion was significantly different between study patients and placebo patients. The most common adverse events are recorded in Table V.

Bone marrow aspiration data was collected, at end of induction, on all ALL patients enrolled. The observed remission rates were 85% for placebo and 91% for glutamic acid. There was no statistical difference ($p=0.44$) between placebo and glutamic acid groups.

Discussion

In this randomized, double-blind, placebo-controlled study, we were unable to demonstrate any significant benefit to oral glutamic acid in reducing the neurotoxicities of vincristine chemotherapy, as measured by the Balis scales. We did not see evidence to support previous adult suggestions of toxicity reduction, pediatric pilot data suggesting neurotoxicity reduction nor evidence to buttress anecdotal reports of benefit in many children over many years of nonresearch use [12,15,17]. These previous studies relied on reflex loss and more subjective neuropathic measures as a major portion of outcome assessments. We specifically excluded reflexes, as they tend not to impact daily function, and instead relied on the more objective criteria of the Balis scale. This may explain our conflicting results.

It is of use to consider study limitations that may have led to a Type II error in which a true benefit was inadvertently not discerned. The dose of glutamic acid may have been insufficient to provide prevention. The two dose levels were somewhat arbitrary in that they were chosen based on previous murine and adult studies extrapolated to pediatric size-based dosing. However, insufficient dosing would contradict above anecdotal successes at the same dosing. In addition, statistical analysis on this study did not imply any greater suggestion of benefit in those receiving 500 mg versus 250 mg. Inadequate neurological examinations or a relative insensitivity of the Balis instrument to neuropathic signs could be other sources of error. The examinations were performed by non-neurologists and more sensitive measures of sensory neuropathy such as thresholds or nerve conduction studies were not included. However, oncology care providers as the primary examiners are very familiar with reporting per the CTCAE criteria, and determining minor subtleties in examination was not required. In fact, the study was designed in such a way as to simplify the neurologic evaluation through utilization of the modified Balis scale. Another confounding factor would be differential reporting by study evaluators on the exams with some including reported symptoms versus others only using measurable physical findings at the visit. Although this was not clearly defined in the protocol, this variable data collection is unlikely to affect the outcomes as vincristine toxicity is mostly cumulative during weekly administration with little transient symptoms, although jaw pain can be short-lived. Moreover, these brief effects were not the emphasized outcome we hoped to reduce.

We additionally considered whether glutamic acid was beneficial due to a reduction in outcomes that were not our primary objectives, either the minor Grade I neuro-symptoms or the worst Grade III/IV symptoms. However, these analyses (Supplemental Table I) did not lend any statistical support to this supposition either. Finally, the study was purposely

limited by collecting data in the first five or ten weeks of therapy only. It is certainly possible the cumulative nature of vincristine would have allowed a benefit to be seen over a much longer period of time. However, in Stratum 1, in those receiving ten straight weeks of vincristine, 50% of the neurotoxicity seen at Week 10 was already demonstrated by week 5 and would be unexpected by historical reports to increase much further than at that point, having already reached our expected 50% rate in the placebo group. Of note, at Week 10, there was no trend toward separation of the placebo and experimental arms that might suggest monitoring longer would reveal a difference.

The pre-specified primary analysis for the study indicates no significant difference between placebo and glutamic acid in preventing neurotoxicity. In the solid tumor stratum, the observed difference between groups was equal to the pre-specified treatment effect in the protocol; however, because of the small sample size and low power, the within strata treatment effect was not statistically significant. Subset analysis does not show statistical benefit across the randomization when looking at specific diseases types, patient gender, ethnicity, race or age. Age ≥ 13 years was the subset of most interest as a group since they historically are most likely to suffer the worst side effects from vincristine [20]. Although a suggestion of benefit was observed, it did not reach statistical significance ($p=0.055$). Benefit to this adolescent and young adult (AYA) group will remain an open question since the study was not designed to test the treatment effect within this age group with sufficient power. However, with no other subset showing any potential protection, further confirmatory evidence would be needed to validate this exploratory analysis which we acknowledge is limited to the initial phase of therapy and a predominantly younger population.

A secondary objective was to assess if glutamic acid was able to reduce the frequency of held doses of vincristine due to neurologic side effects. Over the course of the study, Children's Oncology Group protocol recommendations evolved to recommend holding vincristine only for the most severe effects due to the variable nature of recovery and value of the treatment. For this reason, we did not reach our estimated 30% held rate but instead only an average 5% dose reduction from planned. Nevertheless, despite the reduction in power to detect a difference, there was no trend toward the study group being held less often.

This research provided information on neurotoxicities in vincristine-containing pediatric cancer treatment that is not readily available in the literature. One report found a 3.6% significant peripheral neuropathy rate (Gr. III/IV) in a low-risk ALL cohort including 2.5% within the first 9 weeks [21]. The effects are much more extensive when bothersome Grade II effects are included. Constipation was most common, as might be expected. In fact, accrual to the study was slow initially due to a reluctance of providers to withhold prophylactic laxative use. However, we only found 14% of all patients experienced this complication so prophylaxis may not be indicated. Sensory and motor dysfunctions were also seen in a moderate number of patients while jaw pain and especially detectable laryngeal nerve dysfunction were quite rare. Our results did confirm the known decreased incidence of vincristine neuropathy in African-Americans. In this study, neurotoxicity was

seen in 12% vs. 33% in Caucasians. This finding has been partly accounted for by different expression of metabolic enzymes, i.e., increased CYP3A5 in African-Americans [20].

Of note, the glutamic acid group exhibited no significant differences in other side effects or toxicities and remission rates were statistically equivalent. At the time of the study development, the risk of impacting disease control was discussed, and there will always be concerns when a supportive care intervention is aimed at blocking only the negative side effects of treatment. Protection of tumor effect must be monitored and preserved.

Vincristine-associated neurotoxicity in pediatric oncology remains a frequent complication of chemotherapy for multiple diagnoses with an approximate 30% of patients affected. Glutamic acid is not effective in the pre-adolescent population for prevention, and alternative methods of supportive care will need to be investigated.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Figure 1.
CONSORT diagram

Table I

Neurologic Examination Form

Sensory Neuropathy:				
None	Paresthesias, pain or numbness that do not require treatment or interfere with extremity function.	<ul style="list-style-type: none"> Paresthesias, pain or numbness that are controlled by non-narcotic medications (without causing loss of function) <u>or</u> Paresthesias, pain or numbness that alter fine motor skills (buttoning shirt, coloring, writing or drawing, using eating utensils) without affecting ability to perform these tasks <u>or</u> Paresthesias, pain or numbness that alter gait. 	<ul style="list-style-type: none"> Paresthesias or pain that are controlled by narcotics <u>or</u> Paresthesias or pain that interfere with extremity function (gait, fine motor skills as outlined in motor neuropathy below) <u>or</u> Paresthesias or pain that interfere with quality of life (loss of sleep, ability to perform normal activities severely impaired). 	<ul style="list-style-type: none"> Complete loss of sensation <u>or</u> Pain that is not controlled by narcotics
Motor Neuropathy:				
None	Subjective weakness, but no deficits detected on neurological exam, other than abnormal deep tendon reflexes.	<ul style="list-style-type: none"> Weakness that alters fine motor skills (buttoning shirt, coloring, writing or drawing, using eating utensils) without affecting ability to perform these tasks <u>or</u> Weakness that alters gait. 	<ul style="list-style-type: none"> Unable to perform fine motor skills (buttoning shirt, coloring, writing or drawing, using eating utensils) <u>or</u> Unable to ambulate without assistance. 	Paralysis
Laryngeal Nerve:				
Normal	Asymptomatic; weakness on clinical exam/testing only	Symptomatic, but not interfering with ADL; intervention not indicated	Symptomatic; interfering with ADL; intervention indicated (e.g. thyroplasty)	Life Threatening: tracheostomy indicated
Constipation:				
Absent	Occasional / intermittent symptoms; occasional use of stool softeners, laxatives, dietary modification, or enema	Persistent symptoms with regular use of laxatives or enemas indicated	Symptoms interfering with ADL; manual evacuation indicated	Life Threatening consequences (e.g., obstruction, toxic megacolon)
Jaw Pain:				
None	Mild pain not interfering with function	Moderate pain; pain or analgesics interfering with function, but not interfering with ADL	Severe pain; pain or analgesics interfering with ADL	Disabling
Assessment of Deep Tendon Reflexes:				
		Normal	Decreased	Absent
	Upper extremity			
	Lower extremity			

Table II

Summary of Demographics and Other Patient Characteristics

Characteristic	Stratum 1 (N=50)		Stratum 2 (N=200)	
	Placebo*	Glutamic Acid	Placebo	Glutamic Acid
Diagnosis				
Wilms Tumor	10	13		
Rhabdomyosarcoma	14	13		
Acute Lymphoblastic Leukemia			87	92
Non-Hodgkin Lymphoma			11	9
Gender				
Female	11	12	42	34
Male	12	14	57	67
Ethnicity				
Hispanic/Latino	2	3	23	26
Not Hispanic/Latino	19	22	67	70
Unknown	2	1	9	5
Race				
White	15	20	74	78
African-American	4	5	10	10
Other or Mixed	1	1	6	5
Unknown	3	0	9	8
Age				
Mean (S.D.)	8.8 (5.5)	9.1 (5.6)	8.5 (4.8)	8.4 (4.7)
Body Surface Area (m ²)				
Mean (S.D.)	1.1 (0.5)	1.1 (0.5)	1.1 (0.5)	1.1 (0.5)
Study dosage				
250 mg	15	18	54	56
500 mg	8	7	45	45

* One subject was randomized to placebo but immediately discontinued and provided no baseline data except diagnosis.

Table III
Summary of Average Vincristine Dose, mg, received during the study (Mean (S.D.) N patients with data available)

	Diagnosis			
	Wilms Tumor	Rhabdomyosarcoma	ALL	NHL
Placebo	1.2 (0.4) 8	1.4 (0.5) 13	1.4 (0.4) 80	1.8 (0.3) 10
Glutamic Acid	1.2 (0.4) 8	1.6 (0.4) 11	1.5 (0.4) 78	1.5 (0.5) 8

ALL, Acute lymphoblastic leukemia; NHL, Non Hodgkin lymphoma

Table IV

Summary of Neurotoxicity Analyses by Stratum and by Age.

	Grade 2 Neurotoxicity		Fisher Exact	Logistic Regression p-values			
	Placebo	Glutamic Acid	p-value	Trt	Strata	Trt* Strata	
Stratum							
1*	9/19 (47.4%)	4/17 (23.5%)	0.177				
2**	25/88 (28.4%)	21/79 (26.6%)	0.863	0.145	0.419	0.227	
Age				Trt	Age	Trt* Age	
< 13	23/81 (28.4%)	22/75 (30.3%)	1.000				
13	11/26 (42.3%)	3/21 (14.3%)	0.055	0.077	0.722	0.058	
Primary Efficacy Analysis:			Chi-square				
All Patients/All Exposures			p-value				
	34/107 (31.8%)	25/96 (26.0%)	0.369				

Trt, Treatment;

* Wilms Tumor or rhabdomyosarcoma patients observed over 10 weeks;

** ALL or NHL patients observed over 5 weeks.

Table V

Adverse events with greater than 2% incidence in Glutamic Acid.

Event	Placebo (N=123)					Glutamic Acid (N=127)					p-value*	
	Grade					Grade						
	1	2	3	4	All	1	2	3	4	All		
Constipation	4	1			5 (4.1%)	2		1		3 (2.4%)	0.495	
Mucositis/Stomatitis NOS					0 (0.0%)	1		2		3 (2.4%)	0.247	
Nausea	1	3			4 (3.3%)	2		1		3 (2.4%)	0.719	
Vomiting	2	1			3 (2.4%)	5	3	1		9 (7.1%)	0.137	
Hyperbilirubinemia			1		1 (0.8%)	2		1		3 (2.4%)	0.622	
Neuropathy: sensory	2	1			3 (2.4%)			3		3 (2.4%)	1.000	
Seizure		1	1	1	3 (2.4%)				2	1	3 (2.4%)	1.000
Pain	2	1	1		4 (3.3%)	2	2	3		7 (5.5%)	0.540	

* Fisher exact test of cumulative incidence over all severity grades.