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Phase II Evaluation of Intravenous Vinorelbine (Navelbine) in Recurrent or Refractory Pediatric Malignancies: A Children's Oncology Group Study^{7,8}

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Abstract

Background—A Phase II trial was developed to determine the efficacy and toxicity of intravenous vinorelbine, a semi-synthetic vinca alkaloid, in children, adolescent, and young adults with recurrent or refractory solid malignancies.

Procedures—Fifty patients were enrolled among 3 strata: soft tissue sarcomas (rhabdomyosarcoma, non-rhabdomyosarcoma, primitive neuroepithelial tumor) (20 patients); brain tumors (astrocytoma (4 patients), medulloblastoma (2 patients), other (16 patients)) (22 patients); neuroblastoma (8 patients). Vinorelbine was given weekly for 6 consecutive weeks during an 8 week interval. The response rate and toxicity profile was assessed.

Results—Among the first 35 patients treated at 33.75 mg/m²/dose, 25 experienced grade 3–4 neutropenia (75%). The dose was decreased to 30 mg/m²/dose in the remaining 15 patients. The median age was 10 years (range, 1–25). Four responses (1 complete, 3 partial) occurred within the soft tissue sarcoma strata (all with rhabdomyosarcoma) and 2 occurred in the brain tumor group (medulloblastoma and astrocytoma). The most common toxicities were hematological and neurological.

Conclusion—Vinorelbine at dose of 30 mg/m² can be safely administered to children with recurrent or refractory solid malignancies. The study design identified vinorelbine to be active in the sarcoma category, with a response rate of 36% (4/11) among rhabdomyosarcoma patients.

Keywords

Vinorelbine; sarcoma; rhabdomyosarcoma brain tumor; neuroblastoma

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Introduction

Vinca alkaloids are an important class of cell-cycle-dependent antimitotic agents used extensively for treatment of pediatric malignancies. Vinorelbine (Navelbine®, GlaxoSmithKline, and Research Triangle Park, NC) is one of several analogs of these parent compounds that have been synthesized to broaden their therapeutic activity and improve therapeutic index, and for the potential of oral administration (1,2). Vinorelbine is an active oncolytic agent both as a single agent and in combination therapy for breast and non-small-cell lung cancers (3-10). The primary toxicities demonstrated in adults were neutropenia and leucopenia; peripheral neuropathy and constipation were noted less frequently (9,10). A phase I trial of vinorelbine was completed within the Children's Cancer Group (11). In that trial, vinorelbine was given in a continuous weekly schedule. The MTD was 30 mg/m² and the dose-limiting toxicity was neutropenia. This report describes the Children's Oncology Group phase II trial evaluating vinorelbine as a single agent among pediatric and adolescent/young adult patients who had a recurrent soft tissue sarcoma (STS), neuroblastoma (NB) or primary brain tumor (CNS).

Methods

Patient Enrollment

Patients were enrolled between May 1998 and May 2002. In March 2001, the dose of vinorelbine was reduced to 30 mg/m² from 33.75 mg/m² because of excessive neutropenia observed in the first 35 patients. Patients were required to be ≤21 years of age when originally diagnosed with soft-tissue sarcoma (STS), CNS tumors or neuroblastoma (NB). Patients were required to have had 1) histological verification of the malignancy at original diagnosis (excluding brain stem tumors); 2) measurable disease and have relapsed or become refractory to conventional therapy; 3) a life expectancy of at least 2 months; 4) received no more than 2 prior chemotherapy regimens; 5) fully recovered from the toxic effects of any prior therapy; 6) adequate bone marrow, renal, liver, and central nervous system function. Informed consent was obtained from the patient and guardian in accordance with institutional policies and as approved by the U.S. Department of Health and Human Services.

Study Design

Patients were enrolled to one of 3 strata: 1) STS 2) NB and 3) CNS tumors. The STS stratum included patients with rhabdomyosarcoma (RMS) as well as those with nonrhabdomyosarcoma sarcomas. The CNS stratum was composed of 3 substrata: a) astrocytoma, b) medulloblastoma and 3) other CNS tumor diagnoses. In contrast to the Phase I dose schedule of continuous weekly therapy, a course of therapy in this study was defined as an eight week interval during which vinorelbine was administered as a weekly intravenous bolus for six consecutive weeks followed by a 2 week rest. Based on this change the Phase II starting dose was increased to 33.75 mg/m². Patients who maintain at least stable disease could receive a maximum of 10 courses in this study. Patients were not permitted to receive radiotherapy to symptomatic sites while receiving vinorelbine. Response assessments were performed after every course of therapy. Tumor measurements were based on computed tomography or magnetic resonance imaging evaluations. Minimum size of evaluable lesions was 1 cm². Bone marrow and bone lesions were evaluable sites and monitored in the appropriate patient group. The World Health Organization (WHO) criteria as outlined below were used to define response. (12) Patients who demonstrated objective evidence of response in the presence of grade 3 or 4 hematological toxicity or who had treatment delays beyond Day 63 (Week 9) from their prior course of treatment had their

subsequent dose of the agent decreased to 27 mg/m². Dose reductions below 27 mg/m² were done with the approval of the Study Chair.

Statistical Analysis

The primary analysis of the efficacy of vinorelbine required the assessment of the response rate to vinorelbine. All patients who completed at least 2 weeks of protocol therapy were considered evaluable for response.

Disease response was classified as: 1) Complete Response (CR) - Complete disappearance of all measurable and evaluable disease, with no new lesions, disease-related symptoms, or failure of normalization of markers and other abnormal lab values associated presence of the tumor; 2) Partial Response (PR) - Greater than or equal to 50% decrease under baseline in the sum of products of longest perpendicular diameters of all measurable lesions, with no progression of evaluable disease and no new lesions; 3) Stable Disease/No Response (SD) - Does not qualify for CR, PR, or progressive disease; and 4) Progressive Disease - Twenty-five percent increase or an increase of 10 cm² (which ever is smaller) in the sum of the products of the longest perpendicular diameters of all measurable lesions compared to smallest sum observed (over baseline if no decrease) using the same techniques as baseline, clear worsening of any evaluable disease, reappearance of any lesion that had disappeared, appearance of any new lesion/site, and/or failure to return for evaluation due to death or deteriorating condition (unless clearly unrelated to this cancer).

Statistical Plan

The study utilized a two stage design within each stratum. (13,14) Ten response-evaluable patients were to be enrolled in each stratum. If none of the first 10 patients demonstrated a CR or PR, the enrollment to the stratum was to be terminated with the conclusion that vinorelbine was not efficacious in the stratum. If six or more of the first 10 patients demonstrated a CR or PR, the enrollment to the stratum was to be terminated with the conclusion that vinorelbine was efficacious in the stratum. Otherwise enrollment was to be continued to a total of 20 response-evaluable patients, at which point enrollment was to be terminated for the stratum. If 3 or fewer patients demonstrated a CR or PR, vinorelbine was considered not efficacious in the stratum. If 4 or more patients demonstrated a CR or PR, vinorelbine was considered efficacious in the stratum. If vinorelbine was associated with a 10% response rate, it would be identified as ineffective with probability of 0.87. If vinorelbine was associated with a 30% response rate, it would be identified as effective with probability of 0.88.

This study utilized the NIH NCI Clinical Toxicity Criteria version 2.0 for toxicity and adverse event reporting. All toxicities were reviewed and relationship to study drug was defined. A final summary of all grade 3 and 4 toxicities were reported as a proportion of cases experiencing the toxicities divided by the number of cases evaluable for toxicity of the therapy. The proportion of cases developing toxicity by course of therapy was used to characterize the toxicities associated with each course of treatment.

The distributions of quantitative variables such as age at study entry and age at diagnosis were presented with median and range. The distributions of qualitative variables such as gender and race were presented with the number and percentage in each category. The SAS[®] statistical package (SAS institute, Cary, NC) and EPILOG statistical package (Epicenter Software, Pasadena, CA) were used for data analyses.

Results

Pretreatment and demographic characteristics of the fifty patients who were enrolled in this trial are presented in Table I. The study was closed to accrual after the STS stratum was complete. The median number of courses delivered among these 50 patients was one, ranging one to 10. Six patients had an objective response, including 1 complete response (CR) and 5 partial responses (PR). (Table II) Responses in all patients were achieved after the first course of therapy. Among 20 patients in the STS stratum, the responders (1 CR and 3 PR) occurred among 11 patients with RMS, for an overall response rate in RMS of 36% (4/11). Among these 4 responders, 3 had alveolar RMS (of 5 enrolled) and one had RMS not otherwise specified (NOS). No responses were observed among 3 patients with embryonal RMS. The primary involved site of the patient with CR was Head/Neck; the primary involved site for patients achieving a PR included upper extremity, lower extremity and thorax. The duration of response was 2 courses (CR, 2 PR) and 3 courses (1 PR). There were no responses among the 9 patients with non- RMS STS that included six patients with sarcoma NOS, two with synovial sarcoma and one with primitive neuroepithelial tumor. Overall, the median number of courses received for all 20 patients in the STS stratum was 2 (range 2 to 10). One of 2 patients with medulloblastoma achieved a PR and completed all 10 courses of therapy. One of 4 patients with astrocytoma achieved a PR which was sustained over 3 courses of therapy. There were no responses among the 16 patients enrolled in the other CNS substratum. There were also no responses among the 8 patients with NB.

Toxicities

The major toxicity demonstrated in this study was hematological. Among the first 35 participants who received vinorelbine at a dose of 33.75 mg/m², 25 experienced grade 3 or 4 neutropenia during the initial 2 courses of therapy (75%). Nine of these participants, including 5 with initial bone marrow involvement of disease, required delay in therapy and/or dose modification (26%). The protocol was amended at that time to reduce the starting dose of vinorelbine to 30 mg/m². After this change, ten of the subsequent 15 participants developed grade 3 or 4 neutropenia (67%); however, none of these participants required a dose delay or modification. Anemia was the second most common toxicity among participants (20%). Grade 3 sensory neuropathy occurred in four patients (8%). No deaths occurred among participants while enrolled on the study. Therapy was administered through central venous access in all patients. No cases of extravasation necrosis were reported. Two patients died of progressive disease within 30 days of terminating protocol therapy.

Discussion

Vinca alkaloids are among the most active groups of agents for childhood cancer therapy (15). The major clinical problems with these alkaloids are dose-limiting neurotoxicity, especially peripheral and autonomic neuropathies, risk of extravasation necrosis, and limited route of delivery (intravenous). Vinorelbine has been associated with less neurotoxicity and an established therapeutic activity against adult cancers, particularly breast carcinoma and non-small cell lung carcinoma (3-5) and the potential of oral administration (11). Of additional interest was that preclinical data suggested activity in pediatric brain tumors (16). Results from the Children's Cancer Group phase I trial of vinorelbine suggested that this agent may have activity in RMS and brain tumors (11). This information was the basis to evaluate vinorelbine further in a phase II trial among children and adolescents with recurrent malignancies.

Disease response was documented in this study among participants with recurrent RMS (4 cases), medulloblastoma and astrocytoma. Our observations regarding RMS are similar to the reports by Casanova et al (17,18) and Epelman et al (19). Our observation on the activity

of vinorelbine in patients with non-RMS is similar to observations noted among adult sarcoma patients (20). The sporadic responses in patients with CNS tumors noted in this trial were similar to results in our report of the Children's Oncology Group phase I trial (11) and in the report by Biassoni et al (21) regarding a patient with glioblastoma.

Of interest, vinorelbine-induced responses occurred among participants with RMS who had received vincristine previously suggesting that vinorelbine is a potentially effective agent in patients who develop refractoriness to vincristine. Unfortunately, data regarding cumulative vincristine dose exposure was not collected in this study. Drug resistance to tubulin-binding agents is felt to be mediated by several mechanisms that include: P-glycoprotein (ABCB1), an ATP binding cassette transport protein (22,23) RLIP76, a non-ATP binding cassette transport protein and alterations in the mitotic spindle checkpoint (24,25). However, specific factors associated with selective differences in resistance between vinorelbine and other tubulin binding agents are not known.

Among adult patients, the major dose limiting toxicity was neutropenia and the MTD was 30 mg/m²/dose (9,10). Unlike vincristine, peripheral neuropathy and constipation were less common side effects. In the Children's Oncology Group phase I study, as found among clinical trials in adults, neutropenia was the primary dose-limiting toxicity and the MTD was 30 mg/m². We attempted to use vinorelbine at a dose of 33.75 mg/m² in our current trial based on the modification of dose schedule to incorporate a 2 week rest interval after 6 weekly doses of vinorelbine. However, as noted herein, excessive episodes of neutropenia resulting in vinorelbine dose reductions occurred among the first 35 participants enrolled in our study. The study subsequently was amended to reduce the vinorelbine starting dose to 30 mg/m² and resulted in a significant reduction in treatment delays and dose modifications. The change in toxicity with the approximately 10% decrease in dose suggests a narrow dose-toxicity curve, the basis of which is unclear. Taking these observations into account, incorporation of vinorelbine in combination chemotherapy regimens must be approached cautiously due to the dose-related myelotoxicity documented here as well as in other trials among the pediatric population. (11,17,18).

In summary, vinorelbine at a dose of 30 mg/m² can be given safely in patients who have had prior chemotherapy and radiotherapy. Vinorelbine is demonstrably efficacious in the STS stratum, and particularly in RMS. The feasibility and efficacy of the combination of vinorelbine with daily low dose cyclophosphamide is being tested in the current ongoing European rhabdomyosarcoma protocol. The potential for oral administration of vinorelbine in pediatric cancers and the efficacy in CNS neoplasms remains to be defined.

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Table I**Demographic and Pretreatment Characteristics of Participants (N=50)**

Characteristic	
Age at Diagnosis (years)	
Median (Range)	8.5 (0-20)
Age at Study Entry (years)	
Median (Range)	10 (1-25)
Gender	
Male	24 (48%)
Female	26 (52%)
Race	
White	32 (64%)
Hispanic	10 (20%)
African American	6 (12%)
Native American	1 (2%)
Native Hawaiian	1 (2%)
Prior Hematopoietic Stem Cell Transplant	
Yes (Neuroblastoma(8), Glioblastoma(3), Sarcoma (2))	13 (26%)
No	35 (70%)
Not Reported	2 (4%)
Prior Radiation	
Yes	45 (90%)
No	5 (10%)
Bone Marrow Involvement	
Yes (Neuroblastoma (5))	5 (10%)
No	45 (90%)
Performance Status at Study Entry	
Asymptomatic and Fully Active	17 (34%)
Symptomatic, Fully Ambulatory, Restricted in Physically Strenuous Activity	20 (40%)
Symptomatic, Ambulatory, Capable of Self Care, More than 50% of Walking Hours Spent Out of Bed	12 (24%)
Not Reported	1 (2%)
Dose Level	
33.75 mg/m ²	35 (70%)
30 mg/m ²	15 (30%)

Table II

Response to Vinorelbine by Tumor Type

	Soft Tissue Sarcoma		CNS Tumor	Neuroblastoma	Total
	RMS	Non-RMS			
Complete Response	1	0	0	0	1 (2%)
Partial Response	3	0	2	0	5 (10%)
Stable Disease	6	3	3	3	15 (30%)
Progressive Disease	1	6	17	5	29 (58%)
Total	20		22	8	50

Abbreviations: RMS, RMS; Non-RMS, non-RMS