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ORIGINAL ARTICLE

Phase I trial of metronomic oral vinorelbine in patients with advanced cancer

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Abstract
Background Antitubulin agents exhibit antiangiogenic effects in vitro and in vivo. We evaluated the safety and feasibility of administering a metronomic schedule of oral vinorelbine designed to optimize its antiangiogenic effects.
Methods Patient with advanced cancer who had progressive disease after standard therapy received oral vinorelbine 3 times weekly (i.e., Monday, Wednesday, Friday) at the 6 dose levels ranging from 20 mg (1 week on, 1 week off) to 50 mg (3 weeks on, 1 week off) in cohorts of 3–6 patients at each dose level using a standard phase I design. Dose-limiting toxicity (DLT) during cycle 1 included: (1) neutrophil nadir $< 500/\mu L$ attributed to therapy, (2) platelet nadir $< 50{,}000/\mu L$ attributed to therapy, (3) grade 3–4 non-hematologic toxicity attributed to therapy, and (4) neutropenia associated with grade 2 fever (i.e., febrile neutropenia).
Results Nineteen patients received 50 cycles of therapy (range 1–11 cycles) at 6 dose levels. There were no dose-limiting toxic events. There were no consistent changes in serum TIE-2 or VCAM-1 levels, or urinary VEGF. One patient with renal cell carcinoma had stable disease for 9 months, and another patient with metastatic prostate cancer had a 70% decline in serum prostate-specific antigen, which lasted 4 months.
Conclusions Oral vinorelbine may be given using a metronomic schedule, 50 mg thrice weekly for three of 4 weeks, with minimal toxicity in patients with advanced cancer.

Keywords Metronomic · Oral · Vinorelbine · Advanced cancer

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Introduction

Vinorelbine is a semi-synthetic vinca alkaloid that interferes with microtubule assembly through its interaction with tubulin, thereby producing inhibition of mitosis at metaphase [1–3]. Vinorelbine has significant antitumor activity in a variety of cancers, including carcinoma of the lung, ovary, and breast, as well as Hodgkin's and non-Hodgkin's lymphoma and Kaposi's sarcoma [4–7]. It is most commonly given intravenously using a weekly or intermittent schedule.

Antitubulin agents are known to have antiangiogenic effects at doses below that required to induce cytotoxicity, including taxanes such as paclitaxel [8] and docetaxel [9], and vinca alkaloids such as vinblastine [10]. The use of these agents at low doses given more frequently, referred to as "metronomic" scheduling, optimizes the antiangiogenic effects of therapy [11, 12]. Some antitubulin agents such as paclitaxel are more effective when given using a weekly schedule in breast cancer [13, 14], suggesting that they may induce their clinical effects in part via their effect on inhibiting angiogenesis. However, similar findings have not been observed for paclitaxel in other diseases such as non-small-cell lung cancer [15] or for docetaxel in breast, prostate, or lung cancer [16–18], suggesting that the benefits of metronomic scheduling may be drug and disease specific.

Most studies evaluating metronomic scheduling of antitubulin agents have used weekly drug scheduling. Oral drug administration would facilitate more frequent dosing that may further optimize the antiangiogenic effects of therapy [11]. An oral formulation of vinorelbine is available, which has an oral bioavailability of 43% and a terminal half-life of approximately 29 h (±7.9 h), permitting more thrice weekly or every other day dosing [19, 20]. A phase I study of oral vinorelbine using a weekly schedule identified 80 mg/m^2/week as the recommended phase II dose, with neutropenia being dose limiting [20]. We hypothesized that a thrice weekly dosing schedule would more effectively inhibit tumor angiogenesis and initiated a phase I trial of oral vinorelbine in order to identify a dose that could be given at least thrice weekly for at least 3 consecutive weeks and the highest dose that could be administered using this schedule. We also measured angiogenic factors in the blood and urine before and during therapy, including serum vascular cell adhesion molecule (VCAM-1) [21] and the angiopoietin receptor TIE-2 [22], as well as urinary vascular endothelial growth factor (VEGF) [21–23].

Methods

Eligibility criteria

Inclusion criteria included histologically documented advanced carcinoma that was refractory to standard treatment or for whom no curative therapy was available, age of 18 years or older, Eastern Cooperative Oncology Group (ECOG) performance status 0, 1, or 2, and adequate hematologic (neutrophils $\geq$ 1000/μL and platelets $\geq$ 100,000/μL), renal (serum creatinine $<$ 1.5 mg/DL), and hepatic function (total bilirubin within normal limits and aspirate transaminase level $\leq$ 3-fold the upper limits of normal). Patients were required to be willing and able to attend clinic 3 times weekly for directly observed administration of oral vinorelbine. Patients with functional or mechanical gastrointestinal obstruction or chronic nausea/vomiting that would make it difficult to comply with oral drug administration were not eligible.

Regulatory review

The protocol was reviewed and approved by the institutional review board (IRB) at Montefiore Medical Center, Bronx, New York. All patients provided written consent approved by the Montefiore Medical Center Institutional Review Board.

Drug administration

Oral vinorelbine was provided by Glaxo Smith Kline, Inc. and was formulated in capsules of 10 or 20 mg. Cohorts of 3–6 patients received oral vinorelbine 20 mg thrice weekly (e.g., Monday, Wednesday, Friday; or Tuesday, Thursday, Saturday) for progressively increasing durations of therapy, first for 1 week (followed by a 1-week rest period—dose level A), then for 2 weeks (followed by a 1-week rest period—dose level B), followed by 3 weeks (followed by a 1-week rest period—dose level C). Upon reaching the 3 consecutive week dose levels, the vinorelbine dose was increased to 30 mg (dose level D), 40 mg (dose level E), and 50 mg (dose level F) thrice weekly using the 3-week-on/ 1-week-off schedule. Treatment was repeated after the rest period was completed if the subject recovered from all toxicity. Each vinorelbine dose was administered in the oncology clinic in the presence of the nursing staff, and the dose and time of administration were recorded in the medical record. No preventive antiemetics were given. All vinorelbine doses were given with water (6–8 oz) within 30 min of a meal (i.e., usually after breakfast or lunch). The prescribed number of capsules was all taken at the same time. During the course of the study after dose escalation to all 6 planned dose levels had occurred, the drug rights were purchased by Pierre Fabry Medicament, after which time additional drug supplies were not available and the study was terminated.

Dose escalation schema

A standard phase I escalation design was used, with patients evaluated in cohort of 3–6 patients at each dose level with escalation to the next dose level if 0 of 3 or 1 of 6 patients had a dose-limiting toxicity (DLT) during cycle 1 [24]. A cycle was defined as the first 4 weeks of therapy (including the

on-treatment and off-treatment period). The definition of DLT during cycle 1 included: (1) neutrophil nadir < 500/μL attributed to therapy, (2) platelet nadir < 50,000/μL attributed to therapy, (3) grade 3–4 non-hematologic toxicity attributed to therapy, and (4) neutropenia associated with grade 2 fever (i.e., febrile neutropenia). Adverse events were graded according to National Cancer Institute Common Terminology Criteria for Adverse Events, version 2.0. Patients remained on study until disease progression, unacceptable toxicities, or withdrawal of consent occurred.

Dose adjustments

Each 7- to 21-day course of therapy was held if there was grade 3–4 non-hematologic toxicity, grade 4 neutropenia (neutrophils < 500/μL), grade 3–4 neutropenia (neutrophils < 1,000/μL) associated with grade 2 fever (i.e., febrile neutropenia), grade 3–4 thrombocytopenia (platelets < 50,000/μL), grade 2 neurotoxicity, or grade 2 toxicity that in the judgment of the treating physician was poorly tolerated by the patient. The dose was reduced in subsequent cycles by one dose level if patient had recovered from toxicity and the previous treatment course was held due to toxicity, or if any of the events occurred between treatment courses.

Study procedures

A complete blood count, serum chemistry, and liver function tests were evaluated at baseline, weekly for 4 weeks, and then prior to the next cycle thereafter. Patients were evaluated for response by using standard Response Evaluation Criteria in Solid Tumors (RECIST) at baseline and every 12 weeks [25]. Serum and urine samples were collected at baseline and for four consecutive weeks during the first cycle of therapy. Serum was obtained from a serum separator or standard red top tube, allowed to clot on ice for 30 min, and then separated by centrifugation at 3,000 × *g* for 30 min. Serum was cryopreserved at −20°C in 1 ml aliquots for later analysis; at least three aliquots were preserved for each patient at each time point. Serum VCAM-1, serum TIE-2, and urine VEGF (not correct for urine creatinine) were measured in duplicate using commercially available enzyme-linked immunosorbent assays (R & D Systems and Oncogene Research Products). All samples with a coefficient of variation >10% were repeated. The assays have the following limits of detection: VCAM-1—<0.6 ng/mL, TIE-2—<0.014 ng/ml, and VEGF—<9 pg/ml. Descriptive statistics was employed to summarize data. We also performed an exploratory analysis in order to determine whether oral vinorelbine affected blood or urine levels of selected putative surrogate markers for angiogenesis.

Results

Patient characteristics

Nineteen patients were treated between October 2002 and May 2004. The characteristics of the 19 treated patients are shown in Table 1. The median age was 65 years (range 44–79 years). The most common cancer types included carcinoma of the prostate ($N = 6$), breast ($N = 4$), lung ($N = 3$), endometrium ($N = 3$), kidney ($N = 2$), and cervix ($N = 1$).

Results of dose escalation and overall toxicity

The dose escalation schema and results of dose escalation are shown in Table 2. Nineteen patients received 50 cycles of therapy (range 1–11 cycles) at 6 dose levels. One patient treated at dose level 3 was not evaluable for the evaluation of DLT. There were no DLT episodes occurring in cycle 1 in any patient at any dose level. Reasons for discontinuation of therapy included progressive disease in 17 (89%); one patient was not evaluable because he was unable to complete a full course of therapy, and another patient was removed from study by the treating physician. Further dose escalation was not possible due to cessation of the drug supply by the drug manufacturer.

Effect of vinorelbine on serum TIE-2, serum VCAM-1, and urine VEGF

Seventeen patients had serial measurement of serum TIE-2, serum VCAM-1, and urinary VEGF before treatment and weekly for 4 consecutive weeks. There were no consistent changes in levels of marker during therapy (Fig. 1a–c) and no statistically significant difference when comparing

Table 1 Patient characteristics

Median age (range)	65 (range 44–79 years)
Gender: female/male	10/9
ECOG performance status 0/1	8/11
Primary tumor site	
Prostate	6
Breast	4
Lung	3
Endometrial	3
Renal	2
Cervical	1
Median number of prior chemotherapy regimens	2 (1–4)

Table 2 Dose levels and results of dose escalation

Dose level	Vinorelbine dose (mg)	Schedule (weeks on/off)	No. of patients treated/evaluable	No. of DLT	No. of cycles
A	20	1 on/1 off	3/3	0	4 (range 1–2)
B	20	2 on/1 off	3/3	0	17 (range 2–11)
C	20	3 on/1 off	4/3	0	6 (range 1–3)
D	30	3 on/1 off	3/3	0	12 (range 3–6)
E	40	3 on/1 off	3/3	0	6 (range 1–3)
F	50	3 on/1 off	3/3	0	5 (range 1–2)

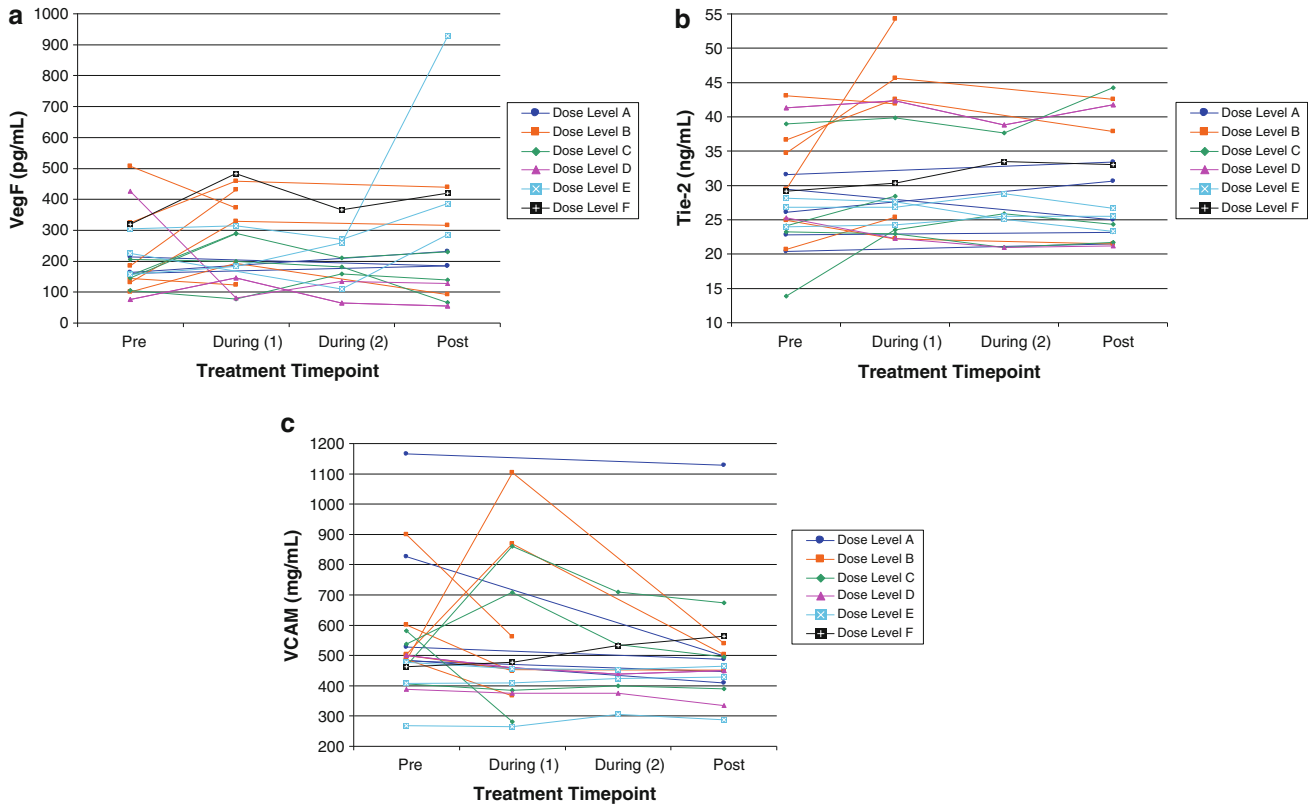

Fig. 1 **a** Measurement of urinary VEGF before and during the first 4 weeks of therapy. **b** Measurement of serum TIE-2 before and during the first 4 weeks of therapy. **c** Measurement of serum VCAM-1 before and during the first 4 weeks of therapy

pre- versus during- versus post-treatment levels any factor evaluated.

Adverse events

Adverse events are summarized in Table 3. The most common adverse events occurring in 10% or more of patients included nausea (37%), fatigue (32%), abdominal or epigastric pain (21%), anorexia (21%), diarrhea (10%), constipation (10%), and chills (10%), most of which were grade 1. There were no grade 4 events and only 4 grade 3 events including neutropenia ($N = 1$), fatigue ($N = 1$), and dyspnea ($N = 1$), the latter of which was likely disease related.

Antitumor activity

One patient with renal cell carcinoma had stable disease for 9 months. Another patient with prostate cancer had a greater than 50% decline in serum prostate-specific antigen (PSA) response that lasted 4 months.

Discussion

We evaluated a metronomic schedule of oral vinorelbine in 19 patients with advanced cancer who received dose ranging from 20 to 50 mg given 3 times weekly (e.g., Monday, Wednesday, Friday) and for up to 3 consecutive weeks.

Table 3 Treatment-associated adverse events

Toxicity	Grade 1	Grade 2	Grade 3
Neutropenia	0	0	1 (5%)
Palpitations	1 (5%)	0	0
Fatigue	6 (32%)	0	1 (5%)
Rigors, chills	2 (10%)	0	0
Diaphoresis	1 (5%)	0	0
Vomiting	1 (5%)	0	0
Anorexia	3 (16%)	1 (5%)	0
Constipation	2 (10%)	0	0
Diarrhea	2 (10%)	0	0
Nausea	6 (32%)	1 (5%)	0
Flatulence	1 (5%)	0	0
Epistaxis	1 (5%)	0	0
Hypocalcemia	1 (5%)	0	0
Motor neuropathy	1 (5%)	0	0
Abdominal pain	1 (5%)	2 (10%)	0
Arthralgia	1 (5%)	0	0
Chest pain	0	1 (5%)	0
Headache	0	1 (5%)	0
Myalgia	1 (5%)	0	0
Epigastric pain	0	1 (5%)	0
Dyspnea	1 (5%)	0	1 (5%)

No patient exhibited dose-limiting toxicity during the first 4 weeks, and a dose of 50 mg given for 3 of 4 weeks was determined to be feasible and associated with minimal toxicity. Therefore, a cumulative weekly dose of 150 mg was well tolerated. The study was terminated due to cessation of the drug supply. It is known that oral vinorelbine is approximately 43% bioavailable when given orally, indicating that a cumulative weekly oral dose of 150 mg is equivalent to a weekly parenteral dose of 65 mg, or about 38 mg/m^2 for an individual of average size (body surface area 1.7 m^2). Therefore, oral thrice weekly delivery results in comparable delivery to weekly parenteral dosing but produces more protracted exposure to lower drug concentrations.

Briasoulis and colleagues reported a phase I trial of oral vinorelbine using a thrice weekly schedule with nearly identical findings as our trial [26]. Sixty-two patients with advanced cancer were treated at six dose levels from 20 to 70 mg 3 times weekly for a median of approximately 12 weeks. Unacceptable toxicity consisting of neutropenia was observed at dose levels of 60–70 mg. The recommended phase II dose was 50 mg using the thrice weekly schedule on a continuous basis without scheduled treatment. Antitumor activity or disease stabilization was also observed, and three responding patients with renal cell carcinoma, medullary thyroid carcinoma, and Kaposi's sarcoma received continuous therapy for over 3 years without prohibitive toxicity. Therefore, the results of these two trials are concordant in identifying a dose and schedule of 50 mg thrice weekly as being associated with an acceptable toxicity profile and feasible to administer for at least 3 consecutive weeks or longer. Steady-state concentrations of vinorelbine and its active metabolite ranged from 0.5 to 1.5 ng/mL, concentrations known to inhibit angiogenesis with vinblastine, a structurally similar vinca alkaloid [10].

Addeo et al. treated 34 elderly metastatic breast cancer patients with metronomic oral vinorelbine in the frontline setting. Patients received oral vinorelbine at 70 mg/m^2 fractionated on days 1, 3, and 5 for 3 weeks on and 1 week off. The oral vinorelbine was well tolerated and demonstrated promising activity, two patients achieved a complete response (6%) and 11 achieved a partial response (32%). The favorable toxicity profile indicates that it may be possible to combine vinorelbine with other biological and cytotoxic agents.

We also performed an exploratory analysis to determine whether oral vinorelbine influences potential surrogate markers of angiogenesis, including serum TIE-2, serum VCAM-1, and urinary VEGF. TIE-2 (also known as Tek) is a novel endothelium-specific receptor tyrosine kinase that has been shown to be widely expressed in the quiescent vasculature of adult tissues [27]. Disruption of TIE-2 function in transgenic mice results in embryonic lethality due to a reduction in endothelial cell number and morphogenesis, which results in defects in vascular development [28]. Increased urine VEGF levels have been reported to correlate with progressive disease in patients treated with the antiangiogenic agent thalidomide [29]. VCAM-1 has an important proangiogenic role in metastasis [30]. We found no consistent changes in blood or urine levels during therapy. On the other hand, two patients did exhibit evidence of antitumor activity, including one patient with renal cell carcinoma who exhibited prolonged period of disease stabilization after progression and one patient with prostate cancer who had a transient decline in serum PSA.

In summary, this study demonstrates that oral administration of oral vinorelbine at a dose of 50 mg thrice weekly is safe with minimal toxicity and is consistent with a previous trial evaluating the same dose and schedule. Further evaluation of this metronomic dosing strategy alone or in combination with other agents is warranted.

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