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ORIGINAL ARTICLE

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Phase I and pharmacokinetic study of anhydrovinblastine every 3 weeks in patients with refractory solid tumors

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Abstract *Purpose*: Anhydrovinblastine (AVLB) is a novel semisynthetic vinca alkaloid. We conducted a phase I trial to determine the maximum tolerated dose (MTD), dose-limiting toxicities (DLT) and pharmacokinetics of AVLB given as a 1-h intravenous infusion once every 3 weeks in patients with advanced refractory solid tumors. *Patients and methods*: Entered into the study were 24 patients with normal bone marrow, hepatic and renal function, and of these 21 were evaluable. There were 12 males and 12 females with a median age of 60 years (range 27–75 years). Diagnoses were non-small-cell lung cancer (NSCLC) (11), colorectal cancer (5), soft tissue sarcoma (4), and miscellaneous (4). Patients had had a median of three prior chemotherapy regimens (range one to six). A total of 51 courses were administered at doses of 2.5, 5, 10, 16.5, 21, 25 and 30 mg/m^2 in one, three, one, three, six, six and one patient respectively. *Results*: Grade 2 infusional hypertension, anemia, and dizziness were noted at 16.5 mg/m^2. At 25 mg/m^2, two of six evaluable patients had DLT. DLT was grade 4 constipation, neutropenia and grade 3 nausea/vomiting. At 21 mg/m^2 one of six evaluable patients had DLT (grade 3 nausea/vomiting). This dose was the MTD. Stable disease was noted in one patient with metastatic sarcoma to the lungs and in three patients with metastatic NSCLC. The pharmacokinetics of AVLB were linear, and well characterized by a two-compartment model, with a mean clearance of 26.4 l/h per m^2 and median terminal half-life of 18 h. *Conclusions*: The recommended phase II dose is 21 mg/m^2. A phase II study in NSCLC is being initiated.

Keywords Phase I · Anhydrovinblastine · Advanced solid tumors

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Introduction

Anhydrovinblastine (AVLB) is a novel semisynthetic vinca alkaloid. It differs from vinblastine in having a 3′4′ double bond in the catharanthine moiety (Fig. 1), a property it shares with vinorelbine (Navelbine). AVLB is more active than vinblastine and vincristine against human tumor xenografts of H460 non-small-cell lung cancer (NSCLC) and of C4 cervical carcinoma in nude mice at equitoxic doses. The improved efficacy results from a combination of increased antitumor potency as well as the ability to administer increased doses of AVLB compared to vinorelbine. In rats, AVLB has a terminal half-life of about 8 h and a clearance of approximately 1.5 l/h. Toxicities in rats are reversible myelosuppression and gastrointestinal toxicity. The maximally tolerated dose (MTD) of a single dose in rats is 17.5 mg/m^2. In dogs, major toxicities are diarrhea and myelosuppression; nausea, vomiting and anorexia and weight loss are also seen. Transient renal dysfunction has been noted in a few dogs. The MTD is 40 mg/m^2. The MTD in animals is defined as the highest dose that produces reversible and tolerable toxicity.

Patients and methods

Eligibility

Patients with histologically documented, advanced solid malignancies refractory to conventional therapy or for whom no effective therapy existed were entered. Inclusion criteria included: age ≥18 years, an Eastern Cooperative Oncology Group performance

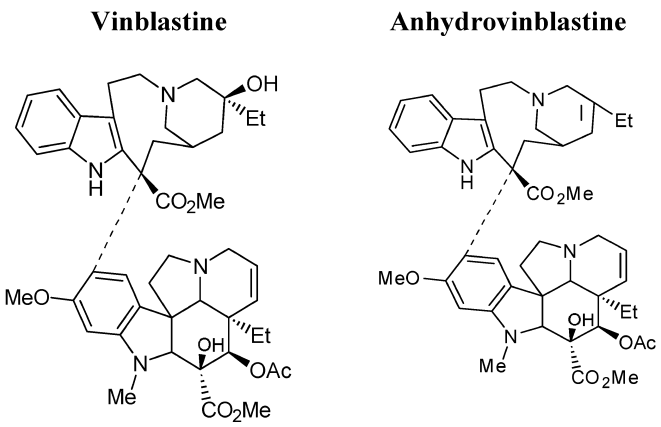

Fig. 1 Chemical structures of vinblastine and anhydrovinblastine

status of 0–2, and a life expectancy of ≥12 weeks; no chemotherapy or radiotherapy in the 4 weeks prior to entering the study (6 weeks for nitrosoureas, mitomycin C or radiotherapy to more than 20% of bone marrow); ANC ≥1500/μl, platelet count ≥100,000/μl, total serum bilirubin ≤ 1.3 mg/dl, AST and ALT ≤ 2.5 times the upper limit of the institutional normal, and serum creatinine ≤ 1.5 mg/dl or creatinine clearance ≥60 ml/min; no uncontrolled brain metastases or general medical problems, and no neurotoxicity from previous therapy greater than National Cancer Institute Common Toxicity Criteria (NCI CTC) grade 2. All patients gave written informed consent according to federal and institutional guidelines before treatment.

Dosage and drug administration

Prescient NeuroPharma of Vancouver, Canada, supplied the AVLB in single-dose vials. It was infused intravenously over 1 h in 250 ml 5% dextrose in water within 8 h of dilution. The drug was given every 3 weeks without premedication. The starting dose was 2.5 mg/m^2 (one-seventh of the MTD in the rat, the more sensitive of the species studied). Dose escalation was based on the continual reassessment method (CRM) modified by Faries [2] according to pre-established dose levels [1]. Toxicity was graded according to the NCI CTC version 2.0. One patient was treated at each non-toxic or minimally toxic dose level. If toxicity of grade 1 or more was seen, the cohort was expanded to three patients unless dose-limiting toxicity (DLT) was seen.

DLT was defined as: grade 4 neutropenia for more than 7 days, febrile neutropenia or grade 4 thrombocytopenia, grade 3 non-hematologic toxicity except for controllable nausea/vomiting or diarrhea. DLT was defined on the first cycle only for dose escalation to the next level. Cumulative toxicity was noted for all cycles. There was no intrapatient escalation. Patients who were not eligible and/or not evaluable for toxicity during the first cycle were replaced. Weekly evaluations were performed. No dose escalation was made before the 4-week evaluation of the first cycle of the last patient included at each dose level. The MTD (the highest dose at which not more than one in six patients showed DLT) was determined in the standard way [6].

Pretreatment and follow-up studies

History, physical examination, and routine laboratory evaluation were performed before treatment and weekly during treatment. Laboratory evaluation included CBC, chemistry, and urinalysis.

Pretreatment studies also included a chest radiograph and radiologic studies to evaluate all sites of disease. The imaging studies were repeated every other course. Patients were able to continue treatment in the absence of progressive disease, defined as a 25% increase in the size of at least one bidimensionally or unidimensionally measurable lesion over baseline, or the appearance of a new lesion.

Plasma sampling and assay

AVLB was administered intravenously over 1 h. Blood (7 ml) for pharmacokinetics (PK) was collected before, at 0.25, 0.5 and 1 h during infusion, and at 0.25, 0.5, 1, 2, 4, 6, 8, 10, 12, 24, 48 and 72 h following the end of infusion. Samples were immediately centrifuged, and the plasma harvested and stored frozen at −20°C until assayed. Samples were assayed by a validated liquid chromatography/mass spectrometry (LC/MS) assay. The instrumental set-up included a Hewlett Packard Series II 1090 HPLC and Insersil column ODS 2, a Fisons VG Quattro 1B mass spectrometer no. 5763 in atmospheric pressure chemical ionization (APCI) mode, and a Pierce "reacti-Therm" module evaporator. The assay was linear over the range 10–2000 ng/ml, with a lower limit of quantitation of 10 ng/ml, and a minimum RSQ of 0.99987. The interday %RSD of quality control samples ranged from 2.1% to 10.4%. Vincristine was used as the internal standard, and AVLB had a retention time of approximately 10 min. All samples were assayed in duplicate and in random order.

Pharmacodynamics

The relationships between AVLB PK and both gastrointestinal and hematologic toxicities were evaluated. Nausea/vomiting and constipation were combined into one category for analysis, and hematologic toxicities were divided into either leukopenia/neutropenia or anemia/thrombocytopenia. Only cycle-1 toxicities were evaluated, with graded toxicities considered as categorical variables, and AUC, C_{max}, and dose considered as continuous variables. Recursive partitioning (Tree-based modeling, SYSTAT 10) was used to identify significant breakpoints between the prevalence of toxicity and PK parameters. Nonparametric procedures (Kruskal-Wallis or Mann-Whitney) were utilized to test for statistically significant differences between groups.

Results

General

A total of 24 patients were treated with 51 courses of AVLB through seven dose levels. Three patients were not evaluable (one brain metastases, one early disease-related death, one withdrawal after an acute drug reaction). All patients had received prior chemotherapy, including 13 who had previously received a taxane, 3 who had received a vinca and 13 who had received radiation and chemotherapy. The median number of prior chemotherapy regimens was three (range one to six courses).

The starting dose was 2.5 mg/m^2. Three patients were enrolled at 5 mg/m^2 because the first had grade 2 toxicity. Five patients were enrolled at 16.5 mg/m^2 (two unevaluable). Grade 2 toxicities including infusional hypertension, anemia and dizziness were noted. Six patients were entered at 25 mg/m^2. DLT, requiring hospitalization, included grade 4 constipation and grade 3 nausea/vomiting was noted in two patients. This dose level exceeded the MTD. Since no severe toxicities were

seen at 16.5 mg/m^2 and the increment to 25 mg/m^2 represented a 50% increase, six evaluable patients were entered at 21 mg/m^2; one of the six had DLT (grade 3 nausea/vomiting). One patient enrolled at 30 mg/m^2 before it was recognized that the grade 3 nausea/vomiting at 25 mg/m^2 was drug related, had grade 3 leukopenia and neutropenia and grade 1 anemia.

Hematologic toxicity

Four patients treated at dose levels 21 and 25 mg/m^2 showed grade 3 (three patients) and grade 4 (one patient) neutropenia. The duration of the grade 4 neutropenia was 2 days; this patient also had grade 3 anemia. The onset of neutropenia was typically delayed; the median time to nadir was 14 days (range 2–22 days). There were no treatment delays secondary to neutropenia. The nadir neutrophil platelet counts are given in Table 1.

Nonhematologic toxicity

The most common non-hematologic effects of AVLB were dose-limiting nausea/vomiting and constipation (Table 2). Of the 21 evaluable patients, 13 (61%) had grade 1–2 nausea/vomiting. At 25 mg/m^2, two patients had DLT. Both had grade 3 nausea/vomiting uncontrolled by outpatient antiemetics such as prochlorperazine, and one also had grade 4 constipation (paralytic ileus) and grade 4 hematologic toxicity (febrile neutropenia). At 21 mg/m^2, one patient had DLT (nausea/vomiting).

Cumulative toxicity

Two patients received more than two cycles of AVLB. One, who received 14 cycles at 25 mg/m,^{2} exhibited transient grade 3 leukopenia and neutropenia with cycles 7 and 10, and also grade 3 nausea/vomiting and dehydration with cycle 8.

Antitumor activity

Four patients (one sarcoma, three NSCLC) had stable disease when evaluated after two courses of AVLB. One (NSCLC) had stable disease through 14 cycles and at the time of this report continued to show no evidence of progression. The median time to progression was 102 days (range 87–639 + days).

Pharmacokinetics

Plasma concentration data for AVLB were available in 20 patients. C_{max} ranged from 28.2 ng/ml at 2.5 mg/m^2 to 571 ng/ml at the 30 mg/m^2. The data fitted a two-compartment PK model, with a median (range) r^2 of 0.89 (0.78–0.96). The median $t_{1/2\alpha}$ and $t_{1/2\beta}$ were 0.17 and 17.6 h. The mean clearance (CV%) and volume of distribution (CV%) of AVLB were 26.4 l/h per m^2 (49%) and 451 l/m^2 (34%), respectively. A minority of subjects demonstrated evidence of a third elimination phase which could not be characterized.

AVLB exhibited linear PK over the range of doses studied, with no significant change in clearance with

Table 1 Hematologic toxicity of AVLB (cycle 1 only). One patient had a platelet count of 98×10^9/l at 30 mg/m^2; this was the only thrombocytopenia seen

Dose (mg/m^2)	Number of patients/courses	ANC nadir (μl)		Number of patients with neutropenia	
		Median	Range	Grade 3	Grade 4
2.5	1/1	4.70	–	0	0
5.0	3/6	5.97	4.57–8.14	0	0
10.0	1/4	5.97	–	0	0
16.5	3/6	2.44	2.09–3.11	0	0
21.0	6/10	2.90	0.97–5.68	1	0
25.0	6/23	1.03	0.25–4.13	1	1[a]
30.0	1/2	0.96	–	1	0

[a]The neutropenia lasted 2 days

Table 2 Nonhematologic toxicities of AVLB (cycle 1only). At doses of 2.5 to 10 mg/m^2, five patients received 11 courses; one grade 2 nausea/vomiting was seen

Dose (mg/m^2)	No. of patients/ courses	Constipation		Nausea/vomiting		Tumor pain		Neurotoxicity	Arthralgia/ myalgia	Hypertension	
		Grade 1/2	Grade 3/4	Grade 1/2	Grade 3/4	Grade 1/2	Grade 3/4	Grade 1/2	Grade 1/2	Grade 1/2	Grade 3/4
16.5	3/6	0	0	2	0	0	0	0	0	3	0
21	6/10	3	0	3	1	0	1	3[a]	2	0	0
25	6/23	3	1	2	1	1	1	0	2	1	1
30	1/2	0	0	0	–	0	0	0	0	0	0

[a]Peripheral neuropathy

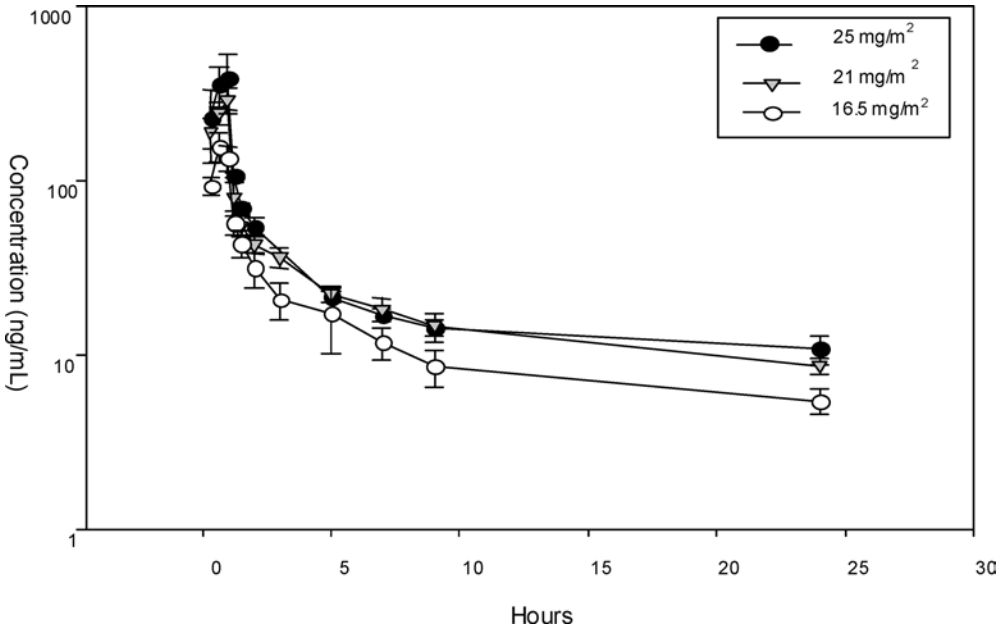

Fig. 2 AVLB concentration–time profiles. The data are presented as means ± SE

increasing dose ($P > 0.05$, Kruskal-Wallis) (Fig. 2). Similarly, the AUC increased linearly with dose (r^2 0.82, $P < 0.05$ by linear regression). A similar linear relationship was observed between C_{max} and dose.

Pharmacodynamics

The relationships between cycle-1 toxicities and AUC, C_{max}, and dose were evaluated. C_{max} was a better predictor of AVLB toxicity than either dose or AUC. C_{max} was associated with both the occurrence of gastrointestinal toxicity and neutropenia ($P < 0.05$). Recursive partitioning identified significant C_{max} breakpoints of approximately 250 ng/ml for both toxicities. Four of the eight patients with AVLB C_{max} > 250 ng/ml exhibited significant gastrointestinal toxicity (one grade 2, two grade 3, one grade 4), in contrast to none of 12 patients with C_{max} < 250 ng/ml ($P < 0.05$). Similarly, four of eight patients with a C_{max} > 250 ng/ml had cycle-1 neutropenia (three grade 3, one grade 4), in contrast to none of 12 patients with a C_{max} < 250 ng/ml ($P < 0.05$).

Discussion

AVLB is a novel vinca alkaloid, which can safely be administered every 3 weeks at a dose of 21 mg/m^2. The DLT is nausea/vomiting, which could be early or late. The prophylactic use of 5HT3 antagonists should be considered in future trials. The exacerbation of constipation by coadministration of narcotics indicates the need for caution when this combination is given. The prophylactic use of laxatives should be considered in patients on narcotics who receive AVLB. The PK of AVLB are linear at doses of 2.5 to 30 mg/m^2, and are well described by a two-compartment model. The human PK appear similar to those of vinblastine, which has a terminal elimination half-life of approximately 20–25 h [2, 3, 4], and a clearance of approximately 33 l/h per m^2 following bolus dosing [5]. Because our data show that toxicity was best correlated with C_{max} an alternate weekly dosing schedule is being investigated in a separate phase I study. A phase II study of AVLB in NSCLC is being initiated.

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