Cancer Chemother. Pharmacol. 5, 67–69 (1980)

Cancer Chemotherapy and Pharmacology

Phase I Evaluation of Divided-Dose Vinblastine Sulfate*

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Summary. *The known pharmacokinetics of vinblastine sulfate given by intermittent bolus dictate alternate dose schedules for prolonging the therapeutic levels. Herein, we have tested a divided dose schedule which shows out-patient feasibility, manageable toxicity, and encouraging responses.*

Introduction

Vinblastine sulfate has proven to be an active chemotherapeutic agent in a variety of human neoplasms [5]. The major mode of action of this drug is believed to be by binding to cell microtubules inhibiting spindle formation and thus producing metaphase arrest [2]. This cytotoxic activity takes place mainly in late S-phase [2]. Vinblastine sulfate when given by intravenous bolus disappears rapidly from serum with a second phase half-life ($T_{1/2}$) of 225 min [6]. Also, tissue levels are low at 48 h when compared to vincristine [3].

Phase specific agents are known to have increased therapeutic efficacy in tumors when exposure time to the active drug is prolonged [1]. This schedule dependency has been mainly exploited in leukemia [8]. In an attempt to enhance the schedule-dependent efficacy of vinblastine, a Phase I study of this agent given in divided doses to prolong serum and tissue levels was initiated.

Materials and Methods

Patient Eligibility. All patients with progressive, histologically documented neoplastic disease who had failed conventional therapy were evaluated for study. All patients had to meet the following criteria: expected survival greater than two weeks, white blood cell (WBC) count greater than 3500/mm^3, platelet count greater than 150,000/mm^3, serum total bilirubin less than 2.0 mg/dl, and absence of neurologic dysfunction. Informed consent was obtained from all patients.

Treatment. Vinblastine sulfate (Velban®, Eli Lilly and Company) was given as an intravenous bolus, using a modified Fibonacci escalation scheme [4], with the starting dose at $\times = 0.4$ mg/m^2. Doses were given as follows: Eight hours apart every two weeks:

Day 1 = 2×	Day 2 = ×
Day 1 p.m. = ×	Day 2 p.m. = ×

Results

A total of 16 patients were treated with 36 courses. Pertinent patient characteristics regarding tumor type and previous therapy are shown in Table 1. There were ten male and six female patients with a median age of 66 years with a range of 53–75. Only two patients in the study received no prior chemotherapy or radiation. We encountered no cases of nausea, vomiting, hair loss, or hepatitis. One patient, a 75-year-old white female with adenocarcinoma of the lung previously treated with M-AMSA had 1+ paresthesias and no other patient had neurologic toxicity. Thrombophlebitis and cellulitis occurred in one patient secondary to inadvertent subcutaneous administration.

No toxicity was observed until a dose of $\times = 1.0$ mg/m^2 (Total dose = 5 mg/m^2 over 48 h). Leukopenia was the dose limiting toxicity but was predictable with the nadir of granulocyte count occurring at a mean of 7.4 days with a range of 7 to 10 days. Recovery of nadir of granulocytes occurred at a mean of 14.9 days with a range of 10 to 20 days. The median nadir of granulocyte suppression at a dose of $\times = 1.2$ mg/m^2 was 900/mm^3 with a range of 210–3500/mm^3 (Table 2).

Only one patient achieved leukopenia at a lower dose of $\times = 1.0$ mg/m^2. Two patients were than

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* Supported in part by the Don Monti Memorial Foundation

0344-5704/80/0005/0067/$ 01.00

Table 1. Patient characteristics and response

Tumor type	Patients	Previous therapy		Evaluable for response	Responses
		Radiation therapy	Chemotherapy		
Lung	9	8	7	2	1 PR (4+months) 1 PROG
Breast	1	1	1	0	
Stomach	1	0	1	0	
Liposarcoma	2	1	1	1	1 PROG
Mesothelioma	1	1	1	1	1 PROG
Ovary	1	1	1	1	1 PR (2+months)
Renal cell	1	0	0	1	1 PROG
Total	16	12	12	6	2 PR

PR = partial response (duration)
PROG = Progression

Table 2. Myelosuppression

Dose (x=)	Patients	Total WBC nadir ($\times 10^3/mm^3$)		Granulocyte nadir ($\times mm^3$)		Platelet ($\times 10^3/mm^3$)	
		median	range	median	range	median	range
1 mg/m^2	3	6.7	2.6–8.8	4,190	1,300–5,280	258	200–350
1.2 mg/m^2	11	2.7	1.1–6.5	900	210–3,500	207	90–400
1.4 mg/m^2	3	3.5	1.0–5.1	1,500	450–3,450	146	90–200
1.6 mg/m^2	3	2.1	0.7–5.1	550	250–2,650	250	150–300
2 mg/m^2	2		1.5–2.4		750–1,440		187–333

hospitalized with treatment induced leukopenia and fever at the higher doses of $\times = 1.6\,mg/m^2$. Thrombocytopenia occurred in only three patients on days 5, 6, and 8 with recovery by day 15 in all patients. No cumulative toxicity was noted despite repeated treatments.

Response. Six patients were evaluable for response. Two patients with carcinoma of the lung (adenocarcinoma and large cell anaplastic), one with ovarian carcinoma, one with mesothelioma, one with liposarcoma, and one with hypernephroma. Partial response (as defined previously [9]) was seen in the patient with adenocarcinoma of the lung previously treated with radiation therapy only ongoing for over four months. A partial response was also seen in the patient with adenocarcinoma of the ovary previously treated with cyclophosphamide, methotrexate, and 5-fluorouracil and radiation therapy. The duration of the response was two months. Of the non-responding patients, two patients had no prior chemotherapy (the one with large cell anaplastic carcinoma and the one with renal cell adenocarcinoma). No patient received prior vinca alkaloids.

Discussion

Vinblastine sulfate is a phase specific agent with major cytotoxic activity occurring in late S-phase. Due to its marked schedule dependency, renewed interest in prolonging the therapeutic levels has recently occurred. Yap et al. using a 5-day continuous infusion have shown a partial response rate of 47% in heavily pretreated patients with breast cancer [10]. Major response occurred in four of eight patients who had previous vinca alkaloid therapy. However, this schedule is inconvenient for the patient because of the need for hospitalization and central venous catheterization. The schedule we have devised is intended to prolong therapeutic levels of vinblastine in an outpatient setting.

Leukopenia was dose limiting but predictable and manageable. Thrombocytopenia was rare and occasional thrombocytosis was seen. This platelet sparing effect of vinca alkaloids has been reported by others [7]. This may have added implications in future combination chemotherapy protocols. The responses seen in one patient with ovarian carcinoma and in one patient with adenocarcinoma of the lung have

encouraged us to undertake a phase II trial. Our starting dose recommendation is $\times = 1.2\ mg/m^2$ (total dose $6\ mg/m^2$) with necessary escalation in previously untreated patients.

Acknowledgements. We wish to thank Ms. Marie Sweeny and Ms. Celia Coffey for their secretarial assistance. Supported in part by Don Monti Memorial Foundation.

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Received March 10/Accepted June 23, 1980