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Vindesine: Phase II Evaluation in Colon Cancer and Description of its Platelet Stimulating Activity

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Summary. *Fifteen previously treated patients with measurable metastatic colon carcinoma were entered into a phase II study of vindesine, 3 mg/m²/week IV. Fourteen patients were evaluable for response. No objective tumor response was observed; however, seven patients experienced stable disease lasting 9, 10, 13, 15, 16, 19, and 26 weeks. Neurologic toxicity was the most common nonhematologic side-effect noted, manifesting as abdominal pain, constipation, paralytic ileus, or paresthesias. Leukopenia was observed in 16% of the 104 weekly courses. Nine patients had a 50% increase of their platelet counts above their pretreatment platelet counts; six patients had a doubling of their pretreatment platelet counts. Mean platelet counts revealed a linear increase with successive treatments during the initial 8 weeks of therapy. Serial CEA determinations demonstrated a parallel relationship with clinical progression in six of seven patients.*

Introduction

The commercially available vinca alkaloids, vincristine and vinblastine, have demonstrated clinical efficacy in a variety of neoplasms [12, 13]. Because of the clinical activities of these vinca alkaloids it was anticipated that vindesine (desacetyl vinblastine amide sulfate), a recently developed semi-synthetic analog of vinblastine, would extend the clinical spectrum of the vinca alkaloids. Vindesine has demonstrated activity in phase I and II trials in bronchogenic carcinoma [19], breast cancer [24, 25], melanoma [22], childhood acute lymphoid leukemia [17, 20], lymphoma [18], and blastic transformation of chronic granulocytic leukemia [17].

Because of the lack of effective chemotherapy for metastatic colon cancer, an active interest in identifying new therapeutic agents has led to this investigation of vindesine in metastatic adenocarcinoma of the colon. We report the disappointing results of our phase II trial of vindesine in advanced measurable colon carcinoma in previously treated patients. Analysis of the platelet counts of these patients demonstrated the thrombocyte-stimulating property of the drug. Serial carcinoembryonic antigen (CEA) determinations proved to be sensitive indicators of clinical progression.

Materials and Methods

Fiteen patients with biopsy-proven metastatic adenocarcinoma of the colon were entered into the study; no patient had rectal carcinoma. Of these patients, 14 were evaluable for follow-up; the remaining patient received only one dose of vindesine, died an early death, and is included in the toxicity evaluation only. Three patients had previously received chemotherapy regimens including vincristine; eleven had received 5-fluorouracil-containing combinations. Four patients had received two or more previous chemotherapy regimens.

Performance status was measured by Eastern Cooperative Oncology Group (ECOG) criteria, with four patients in the performance status (PS) 0–1 category, nine in PS 2, and two in PS 3. Twelve men and three women with a mean age of 60.7 years (range 35–73 years) were studied. Each patient had an expected longevity greater than 6 weeks, measurable disease, leukocyte count greater than 4,000/mm³, platelet count greater than 100,000/mm³, hematocrit greater than 30%, and no evidence of renal or hepatic impairment. Of the 14 evaluable patients in this study, 13 had leukocyte counts less than 10,000/mm³, 13 had alkaline phosphatase values less than 300 IU/l and 8 had normal LDH values [15].

Vindesine was supplied in sterile vials containing 10 mg lyophilized powder and was dissolved in sodium chloride immediately before injection. The treatment schedule was 3 mg/m² weekly by rapid IV injection.

Each patient was seen weekly and evaluated for response and toxicity. Dose modifications were based on hematologic toxicity, with 50% reduction of the dose for a leukocyte count of 3,000–5,000/mm³ and/or a platelet count of 75,000–100,000/mm³ and discontinuation of the drug until hematologic recovery for a leukocyte count less than 3,000/mm³ and/or a platelet count less than 75,000/mm³.

For mild neurologic toxicity (mild paresthesias, mild constipation, weakness) the dose was not changed. However, for more severe toxicity (severe paresthesias, abdominal pain, severe constipation, somnolence) treatment was delayed until recovery, with treatment resumption at a 25% dose reduction. Parameters followed weekly included history, performance status, neurologic and physical examinations, leukocyte count, hemoglobin, hematocrit, and platelet count. Creatinine, BUN, electrolytes, alkaline phosphatase, bilirubin, SGOT, SGPT, urinalysis, CPK, and coagulation profile were obtained every 3 weeks. CEA determinations, liver scan, chest x-ray, and any other appropriate tests were obtained at 3-month intervals or earlier upon clinical suggestion of response or progression.

Patients were evaluable if they received more than two weekly doses of vindesine. Complete response (CR) was defined as the disappearance of all measurable disease for 1 month or longer. Partial response (PR) was defined as a 50% decrease of all measurable disease for 1 month. Patients who

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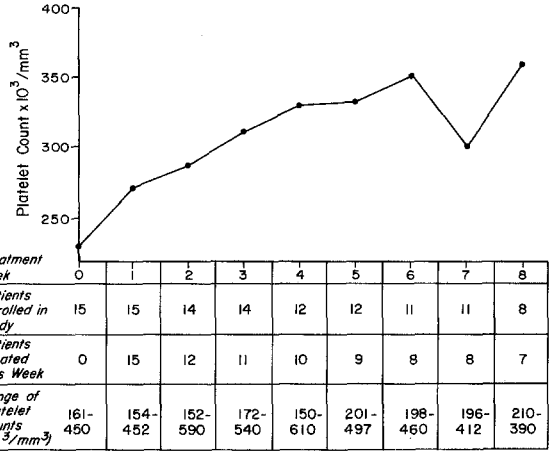
Table 1. Grade of toxicity (total cycles, 104; total patients 15)

Type of toxicity	0 (None)	1 (Mild)	2 (Moderate)	3 (Severe)	4 (Life-threatening)	Total
Hematologic[a]						
1. Leukopenia	> 4,500	3,000–4499	2,000–2999	1,000–1,999	< 1,000	
(cells/mm^3)	87	5	9	2	1	17
2. Thrombocytopenia	≥ 130,000	90,000–129,000	50,000–89,000	25,000–49,000	< 25,000	
(platelets/mm^3)	104	0	0	0	0	0
Neurologic[b]						
1. Abdominal pain		3	3			6
2. Constipation		3	1			4
3. Paralytic ileus				1		1
4. Peripheral neuropathy		3	2			5
5. Hallucinations				1		1
Gastrointestinal[b]						
1. Nausea and vomiting			2			2
Miscellaneous[b]						
1. Alopecia		4				4
2. Phlebitis		2				2
3. Generalized debilitation		2				2

[a] Number of *weekly cycles* in which toxicity was observed
[b] Number of *patients* in whom toxicity was observed



Treatment Week	0	1	2	3	4	5	6	7	8
Patients Enrolled in Study	15	15	14	14	12	12	11	11	8
Patients Treated This Week	0	15	12	11	10	9	8	8	7
Range of Platelet Counts (10^3/mm^3)	161-450	154-452	152-590	172-540	150-610	201-497	198-460	196-412	210-390

Fig. 1. Mean platelet counts. Mean platelet counts display a progressive increase during the first 8 weeks of therapy

displayed less than a 25% increase or decrease in measurable disease for at least 8 weeks without appearance of new lesions were classified as having stable disease.

Results

A total of 104 doses was administered to the 14 evaluable patients. Each patient received a mean of 7.4 weekly courses (median 5.5, range 3–17). None of the patients met the criteria for either CR or PR. Stable disease was encountered in seven patients receiving 5, 8, 10, 10, 12, 15, and 17 doses of vindesine with a duration of stable disease of 9, 13, 10, 15, 16, 19, and 26 weeks, respectively. Median survival of the 14 evaluable patients from the first dose of vindesine was 123 days (mean 160.4 days, range 30–453 days); for the seven stable disease patients, median survival was 256 days (mean 232.4 days, range 69–453 days).

Measurable disease included multiple pulmonary parenchymal nodules only in three patients; hepatomegaly greater than 5 cm below the costal margin or a defect on radionuclide scan greater than 5 cm in seven patients; hepatic involvement (as above) and pulmonary nodules, one patient; measurable hepatic involvement and lytic bone lesions, two patients; nonmeasurable hepatic involvement with palpable abdominal mass, one patient.

The toxicities are presented in Table 1. Neurologic toxicity was the most common nonhematologic side-effect observed, manifesting as abdominal pain in six patients, constipation in four patients, paralytic ileus in one patient, and peripheral neuropathy in five patients. Hallucinations were encountered in a single patient and could not be attributed to metastatic CNS lesions, other drugs, or metabolic derangements; symptoms resolved upon discontinuation of the drug and no brain metastases were detected in this patient at autopsy.

Leukopenia was observed in 17 cycles (16.3%) of the 104 evaluable weekly courses. Only one patient had severe leukopenia defined as a leukocyte count less than 1,000/mm^3. No sepsis-related hospitalizations or deaths were recorded. Thrombocytopenia associated with a platelet count less than 100,000/m^3 was not noted.

An increase of greater than 25% above the baseline platelet count was noted in 12 patients during 59 individual weekly cycles. Of these patients, 9 had a greater than 50% elevation of their platelet counts observed during 47 individual weekly cycles. Six patients (during 20 weekly cycles) had doubling of their pretreatment platelet counts.

Figure 1 depicts mean weekly platelet counts and illustrates a linear increase of the mean platelet count from week 1 through week 8. In the subsequent weeks (9–19) the mean platelet count consistently remained elevated, ranging from 321,000 to 438,000/mm^3 (means); however, the number of patients continuing in the study at this point was small, precluding a definitive comment on this trend. In four patients whose treatment was interrupted, the maximum platelet elevation occurred 2–3 weeks after a single injection of vindesine.

Table 2. Vindesine in colorectal carcinoma: Cumulative response rates

Institution	Evaluable patients	CR	PR
Rush-Presbyterian-St. Luke's	14	0	0
MD Anderson [4, 5, 26]	36	1	1
Memorial Sloan-Kettering [8, 27]	25	0	0
Thomas Jefferson [25]	6	0	2
Totals	81	1	3
		4/81 = 5%	

CEA was elevated in the 14 evaluable patients, with a median initial CEA value of 530 ng/ml (mean 1,461 ng/ml, range 18–4,750 ng/ml). CEA values less than 2.5 ng/ml are considered normal in our laboratory. In seven of the 14 patients CEA levels were measured again during the study. A parallel relationship between serial CEAs and clinical assessment of tumor response was observed in six of these patients. For this group median pretreatment CEA was 530 ng/ml (mean 1,858 ng/ml, range 13.8–9,100 ng/ml) and median CEA determination at assessment of treatment failure was 832 ng/ml (mean 3,489 ng/ml, range 56–17,200 ng/ml). Percentage increases of CEA values from pretreatment value to detection of clinical progression were 16, 35, 89, 132, 167, and 300. CEA elevations predicted clinical progression in three cases at 3, 4, and 17 weeks prior to objective clinical confirmation.

Discussion

Vindesine (desacetyl vinblastine amide sulfate) has demonstrated activity in phase II studies in bronchogenic carcinoma [19], breast cancer [24, 25], childhood acute leukemia [17, 20], melanoma [22], lymphoma [18], and blastic transformation of chronic granulocytic leukemia [17].

The data concerning previous phase II studies of vindesine in colorectal adenocarcinoma are tabulated in Table 2. The reports from the MD Anderson Hospital [4, 5, 26] cite 1 CR and 2 PRs among 36 patients studied. Forty additional patients [8, 25, 27], including those from the present study, also reveal little activity (2 PRs, 1 minor response) for vindesine in colorectal carcinoma. The combined response rate for all studies is only 5%.

In addition to performance status [7], prognostic factors including site(s) of metastases, initial leukocyte count, and lactic dehydrogenase (LDH) and alkaline phosphatase levels have been demonstrated to be predictors of survival in metastatic colon carcinoma [15]. Patients exclusively with pulmonary metastases have been shown to survive longer than individuals solely with liver metastases; patients with both liver and lung involvement have an intermediate survival. Although only one patient in our study had exclusively pulmonary metastases, six of the remaining 13 patients had both liver and pulmonary involvement. Additionally, patients with leukocyte counts less than 10,000/mm^3, alkaline phosphatase values less than 300 IU/l, and normal LDH values are three groups with longer survivals [15].

Toxicities in this study are similar to those observed in previous reports [3, 5, 10]; neuropathy is the most frequent dose-limiting non-hematologic side-effect and this presented most commonly in our series as abdominal pain. Previous treatment with vincristine did not select a population at increased risk for this side-effect. The mean age of our patients was 60.7 years, perhaps predisposing them to the vinca alkaloid-associated neuropathy more commonly encountered in the older age group. Leukopenia was observed in 16% of our cycles, but there were no sepsis-related hospitalizations or deaths. Thrombocytopoenia ($< 10^5$/mm^3) was not observed.

Both vincristine and vinblastine have been known to increase platelet counts [2, 14, 16]. This observation has been extended to individuals receiving vindesine [3, 4, 8, 9]. The present study demonstrated platelet counts to be increased by 50% above baseline following 45% of the individual weekly courses. Six of the 14 patients had doubling of their platelet counts during vindesine treatment.

Phase I and II studies in other disease sites corroborate this platelet-elevating property by showing a mean 20% increase in platelet counts [10] and an increase of more than 50,000–100,000/mm^3 in 22%–27% of patients treated [3]. The thrombocyte-stimulating property of vindesine may be more pronounced than that of other vinca alkaloids [21]. It is conceivable that this effect can be exploited in the treatment of refractory immune thrombocytopenias.

The ability of vindesine to elevate platelet counts makes this drug an attractive agent for use in combination chemotherapy programs employing agents which suppress thrombocytopoiesis. With weekly injections, a progressive linear increase of the mean platelet count was observed during the first 8 weeks. Characterization of this effect thereafter is difficult due to the limited number of patients remaining in our study; however, the platelet counts of the remaining patients consistently were elevated by 25%–50% above their pretreatment values, ranging from 321,000 to 438,000/mm^3 (means).

When the weekly injection schedule was interrupted in four patients, this linear increase of the platelet count was not observed. Rather, the maximum elevation of the platelet count occurred 2–3 weeks after the injection, declining rapidly over the next week to the pretreatment baseline level.

Serial CEAs have been analyzed in relation to clinical progression of colon cancer [1, 6, 23]. An increase greater than 25% is considered significant when the initial CEA is greater than 10 ng/ml [23]. A comparison of CEA measurements performed in our patients demonstrates a mean increase of 110% from pretreatment values to those at the time of clinical determination of progression. In three patients, increasing CEAs predicted progression before clinical detection by 3, 4, and 17 weeks. Generally, therefore, serial CEA determinations provide sensitive evidence of tumor progression. We are unable to comment on the course of serial CEA determinations in objectively responding patients, since there were none in this study.

The failure to demonstrate any response in our 14 patients with measurable colon carcinoma and the results of other phase II studies in colorectal carcinoma [4, 5, 8, 25–27], with a combined total response rate of only 5%, indicate little activity of this new vinca alkaloid in previously treated colon cancer patients. Studies of vindesine in previously untreated patients or with continuous infusions of this rapidly cleared drug [11] may provide more encouraging results. Nevertheless, the ability of the drug to elevate platelet counts requires further elucidation, since this effect may have potential application in thrombocytopenic states and in combination chemotherapy.

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