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Short Communication

Vindesine A Review of Phase-II Trials*

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Summary. *Vindesine is a new vinca alkaloid with broad-spectrum antineoplastic activity in experimental tumor models. Phase-I studies have shown that a weekly dosage regimen of 3–4 mg/m² IV produces manageable toxicity, with leukopenia and peripheral neuropathy being dose-limiting. Two hundred seventy-five patients have been enlisted in Phase-II trials at the Memorial Sloan-Kettering Cancer Center. Major objective responses (complete and partial remissions) were seen in bronchogenic carcinomas, melanoma, testicular carcinoma, esophageal carcinoma, acute lymphocytic leukemia, malignant lymphoma (Hodgkin's and non-Hodgkin's) and Wilms' tumor. Patients with hematologic and germ cell neoplasms were treated on a daily administration schedule (1.0–1.3 mg/m² IV for 5–7 days). Vindesine was well tolerated, with less than 5% of patients having a WBC nadir of <1000 cells/mm³ and with a platelet-sparing effect noted. Dose-related peripheral neuropathy occurred frequently and was generally mild to moderate in degree. Vindesine appears to be an active agent whose role will be further defined by completion of ongoing trials.*

Introduction

Vindesine (desacetyl vinblastine amide sulfate) is a semisynthetic vinca alkaloid that is currently undergoing phase-II testing at several cancer centers. Preclinical studies revealed a broad range of activity in murine hematologic and solid tumors, with a spectrum more similar to vincristine than to vinblastine [4]. An IV dosage of 3–4 mg/m² every 1–2 weeks by rapid IV injection was found to produce manageable toxicity in most phase-I trials; myelosuppression, peripheral neuropathy, alopecia, and phlebitis being the most commonly observed reactions [1, 3, 4]. A daily administration schedule of 1.0–1.3 mg/m² for 5–7 days was investigated when pharmacokinetic studies revealed a terminal half-life of 24.3 h for vindesine, which is shorter than those observed for vinblastine and vincristine (28.8 and 144 h, respectively) [4, 11].

In early clinical studies, objective responses have been reported in acute leukemia; Hodgkin's and non-Hodgkin's lymphomas; malignant melanoma; carcinomas of the kidney, lung, and testis; and several pediatric malignancies, including Ewing's sarcoma, Wilms' tumor, and histiocytosis [1, 3, 4, 5, 7, 8, 9, 11, 13]. During the past 2 years more than 275 patients have been entered into phase-II trials in a wide variety of neoplasms at the Memorial Hospital. This report deals with the progress of these trials, including the toxicity and therapeutic results observed with daily and weekly administration schedules.

Materials and Methods

Patients with histologic evidence of advanced malignancy and objectively measurable disease were eligible for inclusion in this study. Each patient had a performance status ≥ 50 (Karnofsky scale), an estimated survival of at least 8 weeks, and no other chemotherapy for at least 4 weeks prior to starting vindesine.

Vindesine was supplied in sterile vials containing 10 mg lyophilized powder and was dissolved in 10 ml sterile diluent (sodium chloride, 9 mg/ml; benzyl alcohol, 0.009 ml/ml) to give a concentration of 1.0 mg/ml. The drug was administered on two schedules: a) weekly, at 3 mg/m² with escalation to 4 mg/m² in the absence of myelosuppression; and (b) daily, at 1.0–1.3 mg/m² for 5–7 days, which was repeated every 3–4 weeks. The majority of patients were treated on the weekly schedule; however, those with tumors with high growth fractions (germ cell and hematologic neoplasms) received vindesine daily by rapid IV injection.

Therapeutic response categories were defined as: complete remission (CR), disappearance of all disease for 1 month or longer; partial remission (PR), over 50% decrease of all measurable disease for 1 month or longer; and minor response (MR), objective (>25%) tumor decrease, but less than that required for a PR.

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Table 1. Toxicity of vindesine in 61 patients with renal and lung carcinoma

Toxic effect	Number of patients	Percent
Leukocyte nadir (cells/mm^3)		
≧4000	13	21
3000–3999	16	27
2000–2999	20	33
1000–1999	10	16
<1000	2	3
Platelet nadir (platelets/mm^3)		
≧150,000	50	82
125,000–149,000	6	10
100,000–124,000	3	5
<100,000	2	3
Constipation	52	85
Alopecia	37	61
Fever	31	51
Nausea or Vomiting	8	13
Phlebitis	8	13
Diarrhea	3	5
Injection site tissue necrosis	3	5

Table 2. Phase-II trials of vindesine in adult solid tumors

	Entered	Adequate	CR	PR	MR
Lung cancer					
Non-small-cell	50	44	0	10	7
Small-cell	8	7	2	1	2
Renal cell carcinoma	22	17	0	0	2
Melanoma	20	19	0	2	3
Breast carcinoma	14	13	0	0	3
Testicular carcinoma	13	12	0	2	3
Esophageal carcinoma	12	11	0	1	1
Ovarian carcinoma	10	8	0	0	1
Head and neck epidermoid ca	9	7	0	0	2
Soft tissue sarcoma	9	7	0	0	2
Unknown primary carcinoma	8	8	0	2	1
Mesothelioma	5	5	0	0	1
Choriocarcinoma (women)	2	2	0	0	1
Endometrial adenocarcinoma	2	2	0	0	0
	184	162	2	18	27

Results

Toxicity

Renal and non-small-cell lung carcinoma are the subjects of our most extensive disease-oriented trials; toxicity data for these studies will be discussed in depth in that these patients are felt to be representative of the weekly vindesine treatment group as a whole. Table 1 reveals that leukopenia was the most common manifestation of marrow toxicity (median WBC nadir: 2,900; range 500–6,800 cell/mm^3), although less than 20% of patients had leukocyte counts below 2,000. Thrombocytopenia occurred infrequently, with fewer than 10% of patients experiencing a platelet count of less than 125,000 (median nadir: 260×10^3; range $91-488 \times 10^3$ platelets/mm^3). As with the other vinca alkaloids [10], platelet sparing and thrombocytosis were noted in this study; there was a mean 20% increase in platelet counts in patients who received the full dosage of vindesine, while a mean 40% decrease of leukocytes occurred in the same patients.

Neurotoxicity occurred in all patients; this was generally mild to moderate and was manifested as peripheral neuropathy. The degree of neurotoxicity was dose-related; patients who had marked symptoms (muscle weakness and decrease in manual dexterity which interfered with normal functioning) received a median of 30% more vindesine than patients with moderate toxicity (prolonged dysesthesias and muscle weakness not interfering with normal activity), and a median of 140% more drug than those with mild complaints. Other toxic effects of vindesine are presented in Table 1, which shows that the majority of patients experienced constipation, alopecia, or fever. Phlebitis and cellulitis were less frequent when the drug was administered via an established free-flowing IV line, with small quantities of fluid given before and after chemotherapy. There were no drug-related deaths.

Hematologic toxicity was markedly increased on the daily schedule in patients with germ-cell tumors (in 14 evaluable patients who received 21 courses). One-fourth of the patients treated daily had leukocyte nadirs below 1,000 cells/mm^3; fewer than 5% reached this level on the weekly schedule. Although thrombocytopenia occurred with daily administration, there was a relative platelet-sparing effect with less than one-fourth of the nadirs below 125,000 platelets/mm^3 (versus 10% on the weekly schedule). Neurotoxicity and other symptoms (as outlined in Table 1) were similar to those observed on the weekly schedule.

Results

Therapeutic

Table 2 outlines the responses of patients treated with vindesine. Unless otherwise noted, all patients received the drug weekly. Major therapeutic activity (PR) occurred in 22% of the 44 adequately treated patients with non-small-cell lung cancer. Responses were noted in all histologic categories (adenocarcinoma, 6 of 28 patients; epidermoid carcinoma, 3 of 13 patients, large-cell anaplastic carcinoma, 1 of 3). The median duration of PR was 5 months (range 2–9 months), and the median survival for these patients has not been reached but will exceed 8 months (versus 4 months' median survival for nonresponding patients). These statistics

Table 3. Phase-II trial of vindesine in hematologic malignancies

Condition	Entered	Adequate	CR	PR	MR	Number (adequate) on weekly schedule
Hodgkin's disease	14	12	0	3	5	8
Non-Hodgkin's lymphoma[a]						
Histiocytic	8	6	0	1	3	5
Lymphocytic	15	11	0	0	3	7
Acute lymphocytic leukemia[b]	10	10	0	1	4	1
Acute myelocytic leukemia	6	6	0	0	2	3

[a] All PRs in lymphoma ocurred in patients on the weekly schedule
[b] PR was attained by 1 ALL patient, who received the daily schedule

Table 4. Phase-II trial of Vindesine in pediatric malignancies

	Weekly schedule					Daily schedule				
	Entered	Adequate	CR	PR	MR	Entered	Adequate	CR	PR	MR
Acute leukemia										
Lymphocytic[a]	8	6	1	2	0	8	8	2	2	0
Nonlymphocytic	3	2	0	0	0	1	1	0	0	0
Lymphoma										
Hodgkin's	2	2	0	0	1	2	2	0	0	1
Lymphocytic	3	2	0	0	0	4	2	0	0	0
Wilm's tumor	1	1	0	1	0	1	1	0	0	1
Primary brain tumor	2	2	0	0	1	2	2	0	0	0
Ewing's sarcoma						1	1	0	0	0

[a] Except for the 2 CRs on the daily schedule, all responses in acute leukemia patients were of brief duration

compare favorably with more toxic studies using combinations of conventional agents [2, 6] as initial chemotherapy.

The phase-II trial of vindesine in small-cell carcinoma of lung is incomplete at present; however, the results are encouraging. All patients entered have received extensive prior therapy, including vincristine. Despite this, one PR and two CRs (duration: 2 and 6+ months) have occurred in eight patients receiving weekly vindesine. One patient with CR had resolution of an ocular metastasis as well as clearing of all intrathoracic disease.

Fourteen of the 17 adequately treated patients with renal cell carcinoma [12] received weekly vindesine. Two patients experienced brief minor regression of metastases; however, no major therapeutic activity was noted and it has been concluded that vindesine is not active as a single agent in this malignancy.

Two PRs have occurred in patients with metastatic malignant melanoma. Of the three previously untreated patients entered, one has had a PR and one a MR. The current plan is for patients to receive vindesine as initial chemotherapy to allow better definition of its role in melanoma.

To date, only MRs have been observed in 14 patients with breast cancer and ten with ovarian cancer. The PR in a patient with esophageal carcinoma is encouraging in this tumor which is generally unresponsive to conventional chemotherapy. Of interest are the two patients with PRs (3 and 7 month's duration) in a group of eight treated for adenocarcinoma of unknown origin. None of the patients in this group had received any prior chemotherapy, and all tolerated the vindesine without difficulty.

As previously mentioned, patients with germ cell neoplasms (13 men with non-seminoma testicular carcinoma and 2 women with choriocarcinoma) received vindesine on the daily schedule. Of the 14 evaluable patients, PRs were observed in two men with embryonal cell carcinoma; all patients were extensively treated with chemotherapy before this trial, including with vinblastine.

Table 3 outlines the results of trials in adults with hematologic malignancies and indicates the number of patients treated weekly (the remainder received the above-mentioned daily schedule). In patients with lymphomas, PRs were observed more frequently in Hodgkin's disease than in lymphocytic or histiocytic lymphoma. No CRs have occurred; all responses have been of short duration in these patients who received prior vinca alkaloids and other conventional agents. The four patients with PRs were all treated on the

weekly schedule. Beneficial therapeutic activity has been unusual in patients with acute leukemias, with bone marrow improvement occurring in only one patient. However, trials in these conditions have not been extensive and have been performed in patients with advanced and resistant disease.

Pediatric patients with hematologic and solid tumors have been enlisted in phase-II trials. Table 4 shows the preliminary results of the weekly and daily administration schedules. To date, in acute leukemias and in lymphomas, meaningful responses have been seen only in lymphocytic leukemia, with three patients having had CRs. Although more responses have been seen with the daily schedule, no clear trend has emerged, and toxicity has been somewhat greater on this schedule. Only eight children with solid tumors have received vindesine in phase-II studies; one PR has been observed in a patient with Wilms' tumor.

Discussion

The early results of phase-II trials of vindesine have shown evidence of antineoplastic activity in several diseases. Overall toxicity has been mild and acceptable when the drug has been administered at 3–4 mg/m^2 IV weekly. Leukopenia appears to be similar to that experienced with vinblastine, and neurotoxicity is similar to that of vincristine; but both toxic manifestations may be somewhat less than those associated with these related agents. The platelet-sparing effect of the vinca alkaloids is present in vindesine and should be considered in any combination chemotherapy trial including this drug. Persistent questions that can be answered only by completion of current trials and by further study of vindesine are: (1) whether this agents cross-resistant with the older vinca alkaloids; and (2) whether vindesine has a different antitumor spectrum, or a greater response rate than vinca alkaloids in current use. Our results in both small- and non-small-cell carcinoma of the lung are encouraging; however, continued studies in these and in other neoplasms are needed.

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