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Phase II Evaluation of Vindesine in the Treatment of Colorectal and Esophageal Tumors

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Summary. *A phase II study of vindesine was carried out in 33 patients with colorectal cancer and nine patients with esophageal cancer. With the exception of six previously untreated patients with esophageal cancer, all others were refractory to 5-FU-containing regimens, which included vincristine in ten patients. The initial dose of vindesine was 4 mg/m² administered intravenously over 30 min every 2 weeks. Tumor regression >50% was seen in three patients (two colorectal and one esophageal) and an additional eight patients (six colorectal and two esophageal) achieved minor responses. Prior treatment with vincristine did not seem to influence response to vindesine. In general, the treatment with vindesine was well tolerated. The hematologic toxicity was acceptable and manifested mainly as moderate and transient neutropenia. The major nonhematologic toxicity was peripheral neuropathy, which became limiting. It occurred in 33% of patients who received two or more courses of vindesine. Because of the apparent antitumor activity and dose-limiting neurotoxicity of vindesine in this study, further investigations of this compound should be conducted in combination chemotherapy programs for patients with metastatic gastrointestinal cancers.*

Introduction

The status of present chemotherapy for metastatic gastrointestinal malignant neoplasms is poor. The fluorinated pyrimidine, 5-fluorouracil (5-FU), is the most common agent employed for the treatment of such patients [11]. The nitrosourea compounds and mitomycin C have also shown some degree of activity against gastrointestinal neoplasms and in combination with 5-FU represent the backbone of most therapy programs [2]. Unfortunately, their efficacy against colorectal and esophageal cancer is very limited and despite reported tumor responses ranging from 9% to 43%, improvement in patient survival has not occurred [4, 9, 11]. Accordingly, there exists the pressing need for the active investigation of newer antitumor agents.

Vindesine[1] (desacetyl vinblastine amide sulfate, NSC 245467) is a newer member of the vinca alkaloid family introduced to clinical trials because of its experimental antitumor activity, which is more potent than that of the parent compound, vinblastine, similar to that of vincristine, and apparently devoid of neurotoxicity [3, 5]. In Phase I-II clinical studies, vindesine demonstrated some degree of activity in a variety of tumors including acute leukemia [10, 13, 16], lymphoma [10, 16], malignant melanoma [14], and breast carcinoma [13, 14]. We therefore conducted a phase II evaluation of this compound in patients with gastrointestinal malignancies.

Patients and Methods

Forty-two consecutive adult patients with histologically proven metastatic gastrointestinal cancer were entered into this study (Table 1). Thirty-three patients had adenocarcinoma of the colorectal area and nine patients had squamous cell carcinoma of the esophagus. All patients with colorectal cancer and three with esophageal cancer had received extensive prior chemotherapy including 5-FU in all instances and vincristine in ten. A signed consent form was obtained from all patients prior to entry into the study, according to institutional policies.

Based on our phase I studies [1], vindesine was administered as a single intravenous injection of 4 mg/m² repeated at two-week intervals. Patients with significant liver dysfunction (direct bilirubin >2 mg %) received a reduced dose of 3 mg/m². Each dose of vindesine was administered dissolved in 100 ml 5% glucose solution and over a 30-min period. Doses were modified during the study to maintain a tolerable degree of hematologic (absolute neutrophil counts of 750 to 1000/mm³ and platelet counts of 75,000 to 100,000/mm³) and nonhematologic toxicities.

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Table 1. Patient characteristics

No. of evaluable patients	42
Sex: Male	24
Female	18
Age (years): Median	53
Range	34 – 70
Diagnosis: Colorectal cancer	33
Esophageal cancer	9
Prior therapy with vincristine	10

Table 2. Responses to vindesine in patients with colorectal and esophageal cancer

Response	Colorectal	Esophageal
Complete	1	–
Partial ≧50%	1	1
Minor (25% – 50%)	6	2
Stabilization	7	1
Progression	18	5
Total	33	9

Table 3. Hematologic toxicities by courses

No. of evaluable courses	96
Granulocytes × 10^3 lowest count:	
Median	1.8
Day	10
% Courses ≦1,000	16
% Courses ≦500	11
Platelets × 10^3 lowest count:	
Median	184
Day	7
% Courses ≦100,000	11
% Courses ≦50,000	2

Table 4. Nonhematologic toxicities

No. of evaluable courses	124
% Courses with toxicity	29
% Fever due to vindesine	10
% Phlebitis	7
% Nausea and vomiting	6
% Constipation	6
% Diarrhea	4
% Alopecia	2
% Stomatitis	1
% Peripheral neuropathy[a]	33

[a] Percent patients who received ≧2 courses of vindesine

While no other chemotherapeutic agents were administered concomitantly with vindesine, 18 patients with colorectal cancer participated in a phase I evaluation of intravenous methanol extract residue of BCG (MER). MER was given at doses ranging between 0.01 and 1 mg/m^2 on day 2 of vindesine and weekly thereafter. Both groups of patients with colorectal cancer were comparable, however.

Patients were evaluable for response if they received more than one course of vindesine chemotherapy. Complete response was defined as disappearance of all evidence of disease. Partial response was defined as 50% or greater reduction of the sum of the products of all measurable lesions and without the appearance of new lesions. Minor response was defined as 25% or greater reduction of the sum of the products of all measurable lesions, although insufficient to qualify for partial response, and without the appearance of new lesions. Stable disease was defined as less than 25% increase or decrease in measurable disease for at least 8 weeks without the appearance of new lesions. Progressive disease was defined as greater than 25% increase in measurable disease or the appearance of new lesions.

All patients had complete evaluations including history and physical examinations, complete blood counts, urinalysis, and determinations of serum creatinine, alkaline phosphatase, bilirubins, and serum glutamic oxaloacetic transaminase levels prior to the start of chemotherapy. Ongoing analyses included twice weekly complete blood counts, renal and liver function tests prior to each treatment, and monthly determinations of plasma levels of carcinoembryonic antigen (CEA). Tumor measurements were done prior to each course of chemotherapy and appropriate radiologic and isotopic examinations at 4- to 6-week intervals. Nerve conduction studies were performed on patients suspected to have developed peripheral neuropathy as a result of vindesine administration. All side effects associated with the administration of the treatment were recorded and analyzed.

The survival calculations were made from the day of initiation of chemotherapy by the method of Kaplan and Meier for censored and uncensored data [7]. The statistical analyses of the difference between the survival curves were made by the two-tailed generalized Wilcoxon test, according to Gehan [6].

Results

The administration of vindesine resulted in three responses greater than 50%, and eight minor responses for an overall objective tumor response rate of 26% (Table 2). All three major responses occurred in ambulatory patients. A complete response occurred in a patient with metastatic colon cancer to the liver and prior 5-FU – vincristine therapy. Response consisted of disappearance of hepatomegaly and normalization of liver scan, abdominal ultrasound, plasma CEA and liver enzyme examinations. The response continues at 9+ months. Another patient with colon cancer achieved >50% regression of multiple pulmonary metastases associated with reduction of plasma levels of CEA. His response lasted for 3 months. A third patient with unresectable esophageal cancer achieved >50% regression of the primary tumor that lasted for 3 months. This patient had received no prior chemotherapy. Disease stabilization occurred in eight patients, two of whom had prior vincristine therapy. Tumor regressions were seen in metastases of the liver (4/10), lung (2/15), bone (1/7), intra-abdominal masses (2/6), and lymph nodes (1/4). With the exception of the complete responder who received MER in addition to vindesine, there were no apparent differences in the response obtained among patients who received vindesine alone and those who received vindesine plus MER.

The median survival duration for all patients with colorectal cancer was 4 months. However, the two patients who had >50% tumor regression survived longer than the 13 patients who achieved minor responses and disease stabilization (12+, 13+ months versus median, 5 months; $P=0.05$), who in turn survived significantly longer than patients who had disease progression (median, 4 months; $P=0.05$). The treatment needed to be discontinued in eight patients with objective tumor regression or disease stabilization because of significant neuropathy in seven and paralytic ileus in one. There was no significant difference in survival duration between patients who received chemotherapy alone and those who received chemoimmunotherapy (median, 5.1 versus 3.5 months; $P=0.1$).

The toxicities associated with the administration of vindesine are summarized in Tables 3 and 4. The degree of leukopenia and thrombocytopenia was moderate (Table 3). Toxicities other than myelosuppression occurred in 51% of patients during 29% of evaluable courses of vindesine treatment (Table 4). Except for moderate to severe constipation, which was present exclusively in patients treated with vindesine alone, there were no significant differences in the toxicities between patients who received chemotherapy alone and those who received chemoimmunotherapy. Severe paralytic ileus simulating acute surgical abdomen occurred in two patients. Peripheral neuropathy manifesting as paresthesias and loss of deep tendon reflexes when mild, and as marked weakness of the extremities when severe, occurred in 13 patients, 12 with colorectal cancer. Three patients with neuropathy had received prior therapy with vincristine. Six of 13 patients who developed clinical signs of peripheral neuropathy underwent electromyographic examinations. All were found to have different degrees of delayed peripheral nerve conduction. Of patients who received two or more courses of vindesine, 33% developed neuropathy. Neuropathy occurred most frequently following three courses of vindesine (range, 2–5 courses) and increased in severity with repeated courses of vindesine. There was no correlation between prior vincristine treatment and the rate of appearance or the severity of vindesine neuropathy.

Discussion

Vindesine showed definite, though limited, activity against colorectal and esophageal cancer despite the extensive prior chemotherapy of the patients studied. Tumor regressions and disease stabilization in three of eight patients with prior vincristine therapy suggests the possibility of lack of cross-resistance with vincristine, an observation shared with others[1, 5, 10].

The administration of vindesine was tolerated moderately well. Contrary to the preclinical data, however [5, 15], and in accordance with our phase I study with this compound [1], clinical manifestations of peripheral neuropathy developed and became dose limiting. In fact, eight responding patients entered into this phase II study required discontinuation of vindesine because of unacceptable neurotoxicity, preventing us, therefore, from appreciating fully the efficacy of vindesine in the therapy of gastrointestinal cancers. By contrast with the neurotoxicity of vincristine, the peripheral neuropathy associated with vindesine therapy is more rapidly reversible.

The limited efficacy of vindesine in this study and the problems of neurotoxicity we encountered should not prevent us from further evaluating this compound in this group of disorders. In fact, the development of a complete remission and partial remissions in patients with metastatic colorectal cancer and extensive prior chemotherapy suggest the need to investigate the efficacy of vindesine in patients with no prior chemotherapy. Because of the potential of developing neurotoxicity, it does appear that vindesine might be more helpful if used in combination with other agents. An additional point of attractiveness to conduct such studies is the apparent lack of immunosuppression associated with the administration of vindesine to man [8] and animals [12]. Therefore, the combination of vindesine with 5-FU and methyl nitrosourea is currently under investigation at our institution as a first-line treatment for patients with metastatic gastrointestinal cancers.

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