Cancer Chemother Pharmacol (1987) 19: 250–252

Cancer Chemotherapy and Pharmacology

Phase I study of high-dose cytosine arabinoside and etoposide in patients with advanced malignancies*

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Summary. Cytosine arabinsodie (ara-C) and etoposide (VP-16) display synergy in the laboratory. Twenty-six patients participated in a phase I study of high-dose ara-C in combination with VP-16. The dose of VP-16 was held constant at 50 mg/m^2 as an intermittent infusion over 33 h; escalating doses of ara-C were given as infusions during hours 9–12 and 21–24. Myelosuppression was the dose-limiting toxicity and occurred with doses considerably less than those expected from studies of the two drugs as single agents. The suggested initial doses for phase II trials with this schedule are 750 mg/m^2 × 2 doses of ara-C and 50 mg/m^2 of VP-16. Nonhematologic toxicity was minimal; therefore, further dose escalation is feasible in patients in whom myelosuppression is acceptable.

Introduction

The combination of ara-C and VP-16 (ara-C/VP-16) has enhanced activity in murine [1, 2] and human [3] leukemia. Ara-C produces a dose-dependent improvement in survival of mice bearing L1210 ascites tumor cells; the addition of VP-16 potentiates this improvement, but potentiation is not dependent upon the VP-16 dose [1]. In vitro studies with ara-C/VP-16 have shown additive effects on DNA single-strand breaks and cytotoxicity in L5178Y cells [2]. Ara-C, given in standard doses and schedules, has demonstrated limited activity in solid tumors, but the efficacy of higher doses has not been adequately evaluated. Given the improved activity of high-dose ara-C (HiDAC) as opposed to standard-dose therapy in patients with relapsed and refractory acute leukemia [4], and laboratory evidence of synergistic activity of HiDAC plus VP-16 [1], a phase I trial of HiDAC and VP-16 was undertaken in patients with solid tumors.

The initial dose of ara-C was based upon results of our phase I study of HiDAC alone where the maximal tolerated dose (MTD) for three doses of ara-C by 3-h infusion at 12-h intervals was 750 mg/m^2 [5]. In the present trial we began ara-C at 500 mg/m^2 × 3 doses and VP-16 at 50 mg/m^2 (total dose) with plans to escalate doses. The schedule was chosen to maximize the time of simultaneous ara-C/VP-16 exposure so as to duplicate the conditions of our in vitro studies. The VP-16 infusion was interrupted for HiDAC infusions to avoid the need for an additional intravenous access; since the elimination half-life of VP-16 is in excess of 4 h [6], this interruption would not be expected to result in a substantial decrease in plasma concentration of this agent.

* Supported in part by grants from the National Cancer Institute (CA-12197 and CA-09422) and the American Cancer Society CF-85-182

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Materials and methods

Eligibility required advanced malignancy for which effective or higher priority therapies were not available. Patients were required to be ≧ age 18, have a Zubrod performance status (PS) ≦3, serum bilirubin <1.5 mg%, serum creatinine ≦2.0 mg%, serum alkaline phosphatase less than 3 times the upper limits of normal, and white blood cell and platelet counts >3000/μl and >100000/μl, respectively. All patients gave written informed consent consistent with federal, state, and institutional guidelines. Measurable or evaluable sites of disease were followed when present but were not required for study entry.

All patients received 50 mg/m^2 VP-16, diluted to a concentration ≦0.4 mg/ml in 0.9% NaCl (NS) or 5% dextrose in water (D_5W), as an intravenous infusion over 33 h. This infusion was interrupted during hours 9–12 and 21–24 for 3-h infusions of ara-C at escalating doses (500, 750, 1000 mg/m^2 per dose). Each dose of ara-C was resuspended in sterile water or solution without preservative (not the package diluent), diluted in 500 ml D_5W or NS, and administered as a 3-h intravenous infusion. Patients were hospitalized for treatment. The first three patients received a third dose of ara-C at 500 mg/m^2 during hours 33–36; however, due to prohibitve toxicity all subsequent patients received only two doses of ara-C as described above. Therapy was repeated at 3-week intervals. Complete blood and platelet counts were monitored weekly; patient examinations and serum electrolytes and chemistries were repeated every 3 weeks. Therapy was continued until progressive disease or dose-limiting toxicity (DLT) was noted. Patients in whom there was no DLT after three courses had ara-C dose escalation, while those who experienced DLT received the next lower dose for subsequent courses. Toxicities were graded according to WHO criteria [7].

Results

Twenty-six patients received 65 courses of therapy. The median age was 55 (range 19–76) years. Seventeen patients

Table 1. Maximum toxicity/patient

	Ara-C dose (mg/m²)			
	500 × 3	500 × 2	750 × 2	1000 × 2
Number of patients[a]	3	5	11	13
Number of courses	4	12	24	25
Toxicity				
WBC (× 10³/μl)				
Grade 2 (2.0–2.9)	0	0	0	1
Grade 3 (1.0–1.9)	0	0	2	3
Grade 4 (<1.0)	2	0	0	1
Platelets (× 10³/μl)				
Grade 2 (50–74)	1	0	1	1
Grade 3 (25–49)	1	1	1	3
Grade 4 (<25)	1	0	1	1
Serious infection	1[b]	0	0	1[c]
Therapy-related death	1[b,d]	0	0	1[c]

[a] Six patients were treated at more than 1 dose level (see methods)
[b] Sepsis
[c] Pneumonia
[d] A second patient died on day 7 of unknown causes

tients (65%) had a PS of 1, eight (31%) and one (4%) had PS of 2 and 3 respectively. The median number of prior chemotherapy regimens was two (range zero to six). Seventeen patients (65%) had received prior radiotherapy, in three cases extensive prior radiotherapy to bone marrow sites – the pelvis in two and a mantle field with subsequent treatment of the pelvis and femur in one. One of the three developed dose-limiting myelosuppression (grade 3 leukopenia at 750 mg/m² × 2). The sites of primary cancer included head and neck and non-Hodgkin's lymphoma in six patients each, kidney and colon in three each, breast in two, and ovary, cervix, pancreas, melanoma, lung, and stomach in one each.

The only dose-limiting toxicity observed was grade 3 or 4 myelosuppression (Table 1). Initial treatment with three doses of 500 mg/m² of ara-C resulted in grade 4 leukopenia (<1000/μl) accompanied by grade 3 (25000–49000/μl) or grade 4 (<25000/μl) thrombocytopenia in two of three patients. One of these three patients suffered a septicemia-related death, while a second who had a WBC count of 3500/μl and a platelet count of 53000/μl 5 days after therapy died suddenly of unknown causes 2 days later. After five patients received two doses of 500 mg/m² ara-C with minimal myelosuppression, the dose was escalated to 750 mg/m², where three of 11 patients developed dose-limiting myelosuppression, including one episode of grade 4 thrombocytopenia. Escalation of the ara-C dose to 1000 mg/m² resulted in dose-limiting myelosuppression in five of 13 patients; one patient who developed grade 4 leukopenia and thrombocytopenia then developed pneumonia and died despite aggressive supportive care and recovery of peripheral WBC and platelet counts to 6300/μl and 108000/μl respectively. Leukopenia and thrombocytopenia usually appeared 7–14 days after therapy, with recovery generally occurring within 7 days; subsequent courses were delayed because of myelosuppression in two patients. Granulocytopenia generally paralleled leukopenia, except in one instance where grade 3 granulocytopenia without dose-limiting leukopenia was noted in a patient treated with 1000 mg/m². There was no evidence of cummulative toxicity but the number of patients who received multiple courses was small; nine of ten episodes of grade 3 or 4 toxicity occurred with the first course. In the group of patients who developed DLT, the median number of prior chemotherapy regimens (1.5, range 1–6) and the percentage who had received prior radiotherapy did not differ from the group as a whole.

Nonhematologic toxicity was not dose-limiting and was limited to nausea with or without vomiting in 24 of 65 courses (despite prophylactic antiemetics), fever temporally related to therapy in three of 65 courses, and mild to moderate alopecia in six patients. These toxicities were not dose-related.

Three patients, two with head and neck cancers and one with lymphoma, had transient improvements in their disease.

Discussion

Myelosuppression was the dose-limiting toxicity for this schedule of HiDAC and VP-16 and occurred in five of 13 patients treated with two doses of 1000 mg/m² ara-C plus 50 mg/m² VP-16. The recommended initial doses for phase II trials are 750 mg/m² × 2 ara-C and 50 mg/m² VP-16; however, it is likely that a better risk group of patients who have received less prior therapy may tolerate higher doses of these agents. The occurrence of dose-limiting bone marrow suppression at the above doses was unexpected in view of the myelosuppression reported when these drugs are given as single agents. Our prior phase I experience with 3-h infusions of HiDAC at 12-h intervals for two doses in a similar group of heavily treated patients indicated an MTD >5500 mg/m² [5]. The reported MTD for single-dose VP-16 as a bolus is ≧290 mg/m² [8]. Moreover, a recent phase I study of VP-16 as a continuous infusion over 3 days resulted in an MTD (125–150 mg/m²/day) [9] similar to that established with bolus VP-16 on days 1, 3, and 5 (125–140 mg/m²/day) [10, 11]. Myelosuppression was the DLT in both trials.

Synergistic myelosuppression for ara-C/VP-16 as administered in this trial is suggested, since dose-limiting myelosuppression occurred with doses considerably less than those expected from the MTDs of the drugs used singly. The occurrence of myelosuppression in the absence of other DLT suggests that further dose escalation will be possible in clinical situations where myelosuppression is not considered to be a DLT (e. g., acute leukemia). Phase II trials are needed to define the therapeutic index of this potentially synergistic combination in the clinical setting; it is anticipated that the current regimen may be more applicable to patients with hematologic malignancies.

Although data from the L1210 murine leukemia model showed ara-C to be the major contributor to the efficacy of this combination [1], it is possible that VP-16 may be relatively more active in humans, especially in patients with solid tumors. Therefore, a phase I study of escalating doses of VP-16 in combination with a fixed dose of ara-C is needed.

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Received September 26, 1986/Accepted November 26, 1986