Phase I study of vincristine and escalating doses of etoposide

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Summary

A phase I trial of vincristine and etoposide was designed following the identification of a potentially synergistic antitumor effect in a murine model. The dose of vincristine was fixed (0.5 mg daily for 3 days). Etoposide was given at 1 of 3 total dose levels (250, 500, or 750 mg/m²) per treatment. Each dose was given in 3 equal fractions and each fraction was given daily for 3 days, i.e., 83.3 mg/m²/d × 3d, 166.7 mg/m²/d × 3d, or 250 mg/m²/d × 3d. A total of 31 patients were entered into study including 10, 18, and 3 patients treated at the 250, 500, and 750 mg/m² dose levels, respectively. Dose-limiting toxicity occurred at the 750 mg/m² level, in which Grade 4 myelosuppression developed in all of the patients. Life-threatening gram negative sepsis occurred in two of these patients and both required platelet transfusions. Grade 3-4 WBC toxicity was observed in 9 of 16 (56%) evaluable patients treated at the 500 mg/m² level, but reversal of toxicity was generally rapid with repeat courses given at 3 week intervals in most patients. Non-hematologic toxicity was negligible. Objective responses were observed in 2 of 4 patients with Hodgkin’s disease. The starting dose of etoposide recommended for phase II trials of this agent in combination with vincristine is 500 mg/m²; dose escalation may be possible in some patients.

Introduction

In a murine model, the combination of vincristine and etoposide produced synergistic antitumor results in P388 and P1534 murine leukemia [1]. Doses of both drugs used were < LD₁₀. The sequencing of the two drugs was not critical for the synergistic effect [2] and time intervals 0–72 hours between them did not significantly influence the results [1,2]. Subsequently, a phase I trial was designed to further explore this two-drug combination. Vincristine was given at a fixed dose and the dosage of etoposide was escalated because of reports suggesting enhanced efficacy of etoposide when given in high doses [3–5].

Materials and methods

Between 9/85 and 6/86, 31 patients with a variety of advanced malignancies were entered into trial after giving informed consent. Entry requirements included the following: no known effective or higher priority therapies available, age > 18 years, Zubrod performance status ≤ 3, recovery from prior cancer therapy, laboratory data with WBC > 3,000/mm³, platelets > 100,000/mm³, serum total bilirubin < 1.5 mg%, alkaline phosphatase less than twice normal unless due to metastatic disease, and serum creatinine < 1.5 mg%. Patients with primary neurological disease or secondary neurological deficits were excluded from study. Measurable or evaluable sites of disease were followed for response but were not required for protocol entry.
Patients were questioned regarding symptoms suggestive of toxicity and reflexes were checked before each treatment.

Treatment consisted of bolus vincristine 0.5 mg IV daily for 3 days with each dose followed immediately by a 2-hour IV bolus infusion of etoposide given at a variable dosage. A somewhat low dose of vincristine was chosen to avoid neurotoxicity and a low dose was all that was required for synergy with etoposide in the animal model [1,2]. The starting etoposide dose was 250 mg/m² divided over 3 days (83.3 mg/m²/d × 3). The total dose per course was escalated in 250 mg/m² graduations, i.e., 500 mg/m² (166.7 mg/m²/d × 3), etc., after tolerance was demonstrated in a minimum of 3 patients. Courses at the same etoposide dose level were repeated in individual patients and were given every 3 weeks in the absence of progressive disease or prohibitive toxicity. In the event of toxicity, dosage reduction following recovery was allowable at the discretion of the attending physician. The daily dose of etoposide was diluted in normal saline or 5% dextrose in water to a maximum concentration of 1 mg/ml. Etoposide at this concentration has been shown to be stable for 2 hours at 25°C (personal communication Marvin Arbus, Bristol Meyers Co.). Patients were generally heavily pretreated. All but 3 patients (2 renal cancers, 1 adenocarcinoma of the lung) had received prior chemotherapy and the number of drugs per patient ranged from 1–10 (median, 5). Radiotherapy had been given to all but 10 patients and 14 patients had been treated extensively (more than one portal and/or large field). In descending order, the types of cancers represented in this trial included the following: breast, 6; lung cancer, 5 (1 with small cell); colon, 5; Hodgkin’s disease, 4; non-Hodgkin’s lymphoma, 4; renal, 3; and 1 each with myeloma, leiomyosarcoma, cholangiocarcinoma, and squamous cell of the larynx.

Follow-up of patients included weekly blood counts. Evaluation of toxicity using WHO criteria [6] and disease status were done every 3 weeks prior to the next planned course of treatment. Patients were removed from study at the discretion of the attending physician or request of the patient and/or if progressive disease occurred.

Results

Three dose levels (of etoposide) were examined before discontinuation of the study: 250, 500, and 750 mg/m² in which 10, 18, and 3 patients, respectively, were evaluated. The number of courses given at each of these dose levels were 34, 48, and 6, respectively. Additional courses at reduced doses were given (Table 1).

Toxicity was primarily hematologic (Table 1). At the first dose level (250 mg/m²), grade 4 WBC toxicity occurred in only 1 of 10 patients and no patients experienced grade 4 thrombocytopenia. Pneumonia not associated with neutropenia (Grade 2 WBC) developed after the third course at this dose level in a patient with Hodgkin’s disease. Following recovery, a partial response was observed and the patient received 7 further courses at 50% dosage until progressive disease occurred. In the second dose level (500 mg/m²), grade 4 WBC toxicity was noted in 3 of 18 (17%) patients and 2 (11%) of the group developed grade 4 thrombocytopenia. Staphylococcal sepsis occurred in one patient with necrotic tumor involving the skin (leiomyosarcoma) after developing grade 3 WBC toxicity following 3 courses. A patient with carcinoma of the larynx also treated at the 500 mg/m² level developed streptococcal sepsis associated with a WBC count of 100/mm³, and died after the first course of treatment; a preexisting cellulitis around the tracheostomy stoma, albeit low grade, may have contributed to this patient’s demise.

Dose-limiting myelosuppression occurred more frequently at the third dose level (750 mg/m²) and was associated with life-threatening infection in 2 of 3 patients, leading to discontinuation of the trial. All 3 patients treated at this level had Grade 4 thrombocytopenia after the first course and 2 of them were given platelet transfusions. Also, two of the patients incurred grade 4 WBC toxicity and both developed gram negative sepsis. Recovery from myelosuppression occurred on day 16 in one of these patients and day 19 in the other. In the third patient treated at this dose level, recovery was observed on day 27 and 2 further courses were given at the same dose with minimal myelosuppression, suggesting a compounding effect on the myelosup-