Cancer Chemother Pharmacol (1994) 34: 79–80

Cancer Chemotherapy and Pharmacology

Clinical trial report

Phase IV trial of daily oral etoposide in the treatment of advanced soft-tissue sarcoma

Jonathan D. Licht[1,*], Rosemary Mazanet[1], Patrick J. Loehrer[3], René Gonin[2,3], Karen H. Antman[1]

[1] Division of Clinical Oncology, Dana-Farber Cancer Institute, 44 Binney Street, Boston, MA 02115, USA
[2] Division of Biostatistics, Dana-Farber Cancer Institute, 44 Binney Street, Boston, MA 02115, USA
[3] Hoosier Oncology Group, 3202 North Meridian Street, Indianapolis, IN 46208, USA

Received: 12 November 1993/Accepted: 7 January 1994

Abstract. Intravenous-bolus etoposide has modest activity in sarcomas when given daily for 3–5 days. Low frequent doses theoretically inhibit topoisomerase II activity over a longer duration and have been reported to have increased activity in small-cell lung cancer. A phase I trial of oral etoposide resulted in partial responses in two patients with soft-tissue sarcomas. To estimate more accurately the response rate for daily oral etoposide in sarcomas, we treated 25 patients with 50 mg/m^2 per day by mouth for 21 days every 4 weeks. Treatment-related toxicity included ≥ grade 2 neutropenia in 6 of the 25 patients and thrombocytopenia in 3. One brief partial response was observed (4%; 95% confidence interval for true response rate, 0–11%). Disease stabilized in five patients for periods ranging from 3 to 18 months. At this dose and on this schedule, daily oral etoposide appears to have little activity against soft-tissue sarcomas.

Introduction

Etoposide has become a standard agent in the treatment of many malignancies, including lymphoma, leukemia, and small-cell lung cancer [1–4]. Laboratory studies have indicated a substantial schedule dependence of etoposide. In the L1210 leukemia model, five consecutive daily doses of the drug were superior to dosing at 6- to 8-day intervals [5]. Clinically, the most convincing schedule dependency has been observed in small-cell lung cancer, where for a given equivalent intravenous dose intensity over a 3-week period, a five-daily-dose schedule every 3 weeks was superior to a weekly or every-3-week schedule [6]. Daily oral dosing was also found to be active in patients who had failed a standard intravenous five-daily-dose schedule [3, 4].

Conventional doses of etoposide in the treatment of soft-tissue sarcoma have yielded response rates of 3% in a total of 92 patients treated [7–10]. In addition, the combination of intravenous etoposide with ifosfamide does not appear to offer increased response rates as compared with ifosfamide alone in adult sarcomas [11]. However, given the theoretical advantage of prolonged topoisomerase inhibition, the schedule dependence documented in other tumors, and the two responses of sarcomas observed in phase I trials of the oral formulation [2], evaluation of daily oral etoposide seemed appropriate [4, 6].

Patients and methods

The eligibility criteria included histologically documented metastatic or inoperable sarcoma (including mesothelioma); pathology review at Brigham and Women's Hospital (Boston) or Indiana University; a Cancer and Leukemia Group B (CALGB) performance status of 0–2; an age of ≥18 years; measurable disease on physical examination or radiographs; 0–1 prior chemotherapy regimens; no chemotherapy or radiotherapy in the 4 weeks before the start of the treatment; a WBC of >3,000/μl; a platelet count of >100,000/μl; and blood urea nitrogen (BUN), creatinine, bilirubin, and SGOT levels of <1.5 times the normal values. Informed consent was obtained from each patient and the protocol was approved by the Institutional Review Board of the Dana-Farber Cancer Institute and of Indiana University.

Etoposide was given orally at a dose of 50 mg/m^2 per day for 21 days, with a 1-week therapy-free hiatus being introduced between cycles. As etoposide is available only in 50-mg tablets, the number of tablets was varied over a 3-day period to achieve the desired dose as described previously [2, 3]. For example, an intended dose of 85 mg per day was given as 100 mg for 2 days and 50 mg for 1 day, and the 3-day sequence was repeated during the 21 days of treatment. Complete blood counts were obtained weekly during therapy. Cycles were repeated at 28-day intervals if there was no evidence of disease progression and if the WBC was >3,000/μl and platelet count was >100,000/μl. If neutrophil nadirs were <1,000/μl the dose for the subsequent cycle was reduced to 75% of the original dose.

Results and discussion

A total of 25 patients were entered and treated with daily oral etoposide. All were evaluable for toxicity and response

* *Present address:* Molecular Medicine Division, Department of Medicine, Box 1126, Mount Sinai School of Medicine, One Gustave L. Levy Place, New York, NY 10029, USA

Correspondence to: Jonathan D. Licht

Table 1. Patients' characteristics

Number entered	25
Number evaluable for toxicity	25
Number evaluable for response	25
Men/women	17/8
Median age (range)	43 (20–68) years
Performance status (CALGB):	
0	6
1	15
2	4
Prior chemotherapy	18
Prior radiotherapy	6
Histologic subtype:	
Leiomyosarcoma	9
Mesothelioma	7
Peripheral nerve sheath	2
Synovial cell	3
Rhabdomyosarcoma	1
Endometrial stromal sarcoma	1
Soft-parts melanoma	1
Unclassified	1
Sites of disease:	
Lung/pleura	12
Chest wall	3
Bone marrow	1
Abdominal/retroperitoneal	8
Extremity	3
Pelvis	
Mean number of cycles (range)	3 (1–7)
Toxicity (CALGB grade):	
Granulocytopenia (cells/μl):	
3,000–3,900	3
2,000–2,900	6
1,000–1,900	5
<1,000	1
Thrombocytopenia (cells/μl):	
75,000–150,000	
50,000– 74,900	3
25,000– 24,900	
<25,000	1
Fever and neutropenia	2
Bleeding	1
Nausea (grade)	
1	6
2	1
3	2
Pruritis/rash	1
Mucositis/diarrhea	1

(Table 1). Antiemetics were used as needed but were generally not required. Toxicity was primarily hematological, with grade 3 or 4 neutropenia being noted in 6 of 25 patients. Two patients developed fever requiring hospitalization and intravenous antibiotic therapy. Both patients were previously treated with MAID (mesna, ifosfamide, Adriamycin, dacarbazine) chemotherapy. Thrombocytopenia was less prominent, with 1 of 25 patients exhibiting grade 3 or 4 toxicity. One febrile pancytopenic patient also developed spontaneous gum bleeding requiring a platelet transfusion. One brief (5-week) partial response was noted (4% response rate) in a patient with a small-bowel leiomyosarcoma. Six patients had stable disease while on therapy for 3–18+ months. The patient with 18+ months of stable disease had indolent epithelial mesothelioma that had recently accelerated in growth rate prior to the start of etoposide therapy. The 95% confidence interval (exact binomial method [12]) for the true response rate of soft-tissue sarcomas to low-dose, daily oral etoposide was 0–11%.

The current study indicates that in a pretreated population of patients with a variety of soft-tissue sarcomas, daily oral etoposide, like intermittent bolus etoposide, has little antitumor effect. In a similar study, Kampe et al. [13] gave oral etoposide daily at a higher dose of 150 mg/m^2 for 15 days to a group of 15 patients with advanced soft-tissue sarcoma. No response was observed. The 3% response rate for bolus etoposide in the treatment of soft-tissue sarcomas is not improved by the daily oral dosing schedule. This might reflect de novo insensitivity of the tumors to etoposide therapy or resistance induced by prior anthracycline treatment.

References

1. Cavalli F, Sonntag RW, Jungi F, Senn HJ, Brunner KW (1978) VP16-213 monotherapy for remission induction of small-cell lung cancer: a randomized trial using three dosage schedules. Cancer Treat Rep 62: 473–475
2. Hainsworth JD, Johnson DH, Frazier SR, Greco FA (1989) Chronic daily administration of oral etoposide – a phase I trial. J Clin Oncol 7: 396–401
3. Johnson DH, Greco FA, Strupp J, Hande KR, Hainsworth JD (1990) Prolonged administration of oral etoposide in patients with relapsed or refractory small-cell lung cancer: a phase II trial. J Clin Oncol 8: 1613–1617
4. Greco FA, Johnson DH, Hainsworth JD (1991) Chronic oral etoposide. Cancer 67: 303–309
5. Dombernowski P, Nissen NI (1973) Schedule dependency of the antileukemic activity of the podophyllotoxin derivative VP-16-213 (NSC-141540) in L210 leukemia. Acta Pathol Microbiol Scand [A] 81: 715–724
6. Slevin ML (1990) Low-dose oral etoposide: a new role for an old drug. J Clin Oncol 8: 1607–1609
7. Bleyer W, Chard R, Krivit W, Hammond D (1978) Epipodophyllotoxin therapy of childhood neoplasias. A comparative phase II analysis of VM26 and VP16-213. Proc Am Assoc Cancer Res 19: 373
8. Radice P, Bunn PJ, Ihde D (1979) Therapeutic trials with V16 and VM26. Cancer Treat Rep 63: 1231
9. Welt S, Magill GB, Sordillo PP (1983) Phase II trial of VP16-213 in adults with advanced soft tissue sarcoma. Proc Am Soc Clin Oncol 3: 234
10. Dombernowski P, Buesa J, Pinedo HM, Santoro A, Mouridsen H, Somers R, Bramwell V, Onsrud M, Rouesse J, Thomas D et al (1987) VP16 in advanced soft-tissue sarcoma: a phase II trial of the EORTC Soft Tissue and Bone Sarcoma group. Eur J Cancer Clin Oncol 23: 579–580
11. Edmonson JH, Buckner JC, Long HJ, Loprinzi CL, Schaid DJ (1989) Phase II study of ifosfamide-etoposide-mesna in adults with nonosseous sarcomas. J Natl Cancer Inst 81: 863–866
12. Zar JN (1984) Biostatistical analysis, 2nd edn. Prentice-Hall, Englewood Cliffs, New Jersey
13. Kampe CE, Lowenbaum S, Foster J, Rosen G (1992) Oral etoposide in the treatment of advanced refractory sarcomas. J Natl Cancer Inst 84: 1836–1837