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Etoposide in patients with previously untreated non-small-cell lung cancer: a phase I study

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Summary. In a phase I study, a range of doses of etoposide (200–370 mg/m^2 given i.v. daily on 3 consecutive days) were evaluated for tolerance and response as first-line treatment in 26 patients with non-small-cell lung cancer. The dose-limiting toxicity was myelosuppression, especially leukopenia. At dose levels of 350 and 370 mg/m^2 etoposide per day, leukopenia of WHO grade 4 occurred in two and one of seven patients, respectively. No thrombocytopenia of this degree was observed. Myelosuppression was quickly reversible and noncumulative. Apart from alopecia, nonhematologic organ toxicities above WHO grade 2 were not seen. Toxicity analysis suggests that the recommended dose of single-agent etoposide for phase II studies in untreated patients is 330–370 mg/m^2 given i.v. daily for 3 days. At the dose levels tested, 6 (23%) major responses could be induced. All responses were seen at a starting dose of >300 mg/m^2 per day. The median duration of response was 4 months. The median survival for all patients was 8 months and that for responding patients was 15 months.

Introduction

Etoposide has been shown to be active in patients with a variety of malignancies including non-small-cell lung cancer (NSCLC). In three disease-oriented phase II studies [3, 13, 17] and in two prospective randomized trials [2, 26], a total of 261 patients with NSCLC who had not been pretreated with cytostatic drugs received i.v. etoposide at 300–450 mg/m^2 fractionated over 3–5 days. Overall response rates were in the range of 10%–15% and corresponded well to results obtained after single-agent therapy with ifosfamide [4, 16, 20, 21], cisplatin [4, 10, 20, 25], mitomycin C [4], and vindesine [4, 20, 28]. However, no data are available on the maximum tolerable dose (MTD) of etoposide in previously untreated patients, although recently published clinical and animal studies suggest that this drug has dose- and schedule-dependent antineoplastic activity in different tumor types [7, 11, 12, 14, 15, 27, 29].

We initiated a phase I study in previously untreated patients with NSCLC. On the basis of two other studies of heavily pretreated patients with solid tumors [1, 8], we chose 600 mg/m^2 i.v. etoposide per course, fractionated over 3 days, as the starting schedule. Our objectives were to investigate the MTD of etoposide in previously untreated patients with NSCLC, to evaluate its non-dose-limiting toxicities, and to ascertain the activity of higher doses of etoposide in NSCLC.

Patients and methods

Patient selection. Eligible patients had histologically confirmed, inoperable NSCLC and at least one measurable lesion that had clearly been progressive over 6–8 weeks prior to study entry, a WHO performance status of 2, a life expectancy of >10 weeks, an age of <70 years, and no brain metastases. Other requirements included pretreatment WBC counts of ≥4,000/μl, platelet counts of ≥100,000/μl, serum bilirubin levels of <2 mg%, creatinine clearance of ≥60 ml/min, and serum electrolyte values within the normal range. All patients gave informed consent.

Staging and follow-up procedures. Pretreatment evaluations consisted of a complete history, physical examination, and laboratory work-up, including a complete hemogram (differential and platelet counts), and determinations of serum creatinine, SGOT, SGPT, alkaline phosphatase (AP), bilirubin, electrolytes, and creatinine clearance. The staging procedurs included bronchoscopy; chest X-ray; computer-assisted tomography (CT) of the chest, brain, and abdomen; ultrasound examination of the abdomen; bone marrow biopsy (Jamshidi); and bone scan. Bone lesions were evaluated by X-ray.

Limited disease (LD) was defined as tumor that was confined to one hemithorax, including involvement of the contralateral mediastinal and ipsilateral supraclavicular lymph nodes. Extensive disease (ED) denoted any involvement beyond these confines [19, 23]. Extensive disease stage I (ED I) included locally advanced disease showing cytologically positive pleural effusion and chest-wall invasion or bilateral supraclavicular lymph-node involvement but no distant metastases. The definition of extensive disease stage II (ED II) was locally advanced disease with distant metastases [19].

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Table 1. Patients' characteristics

Number of patients:	
Entered	29
Evaluable	26
Sex ratio (M/F)	26/0
Age	45–70 (median, 57; mean, 58) years
WHO performance status	0–2 (median, 1; mean, 1)
Stage of disease (number of patients):	
Limited	2
Extensive 1	2
Extensive 2	22
Histology (number of patients):	
Squamous-cell carcinoma	13
Adenocarcinoma	6
Large-cell carcinoma	7

The size of neoplastic lesions was determined before each cycle and at 4 weeks after the last cycle. A complete laboratory work-up (cellular and serologic) was done before each cycle and at 4 weeks after the last cycle. During chemotherapy, complete blood counts were monitored weekly. After completion of the treatment, follow-up examinations were done every 3 months.

Treatment. The starting etoposide dose was 200 mg/m^2 given i.v. in 1,500 ml normal saline for 2 h on 3 consecutive days. For dose escalations, the following five levels were planned: 270, 330, 400, and 440 mg/m^2 given i.v. per day.

Three patients were entered at the starting dose level. Subsequently, three other patients received the next higher doses until hematologic toxicity of WHO grade 4 had occurred in one of three subjects. At this dose level, between five and ten patients were treated so as to determine safely the MTD. Cycles were to be repeated either every 3–4 weeks or when leukocytes and platelets had recovered to values of >4,000 and >100,000/μl, respectively.

Patients showing progressive disease after the first course or at any time thereafter and subjects with intolerable nonhematologic toxicity were withdrawn from the study. In cases in which objective responses were achieved or no change was observed, treatment was continued until either disease progression or the development of unacceptable toxicity.

Response and toxicity. Patients were considered to be evaluable for response and toxicity if they had received at least one treatment cycle. Tumor response and response duration were classified according to the WHO criteria [22]; toxicity was evaluated according to the worst event for each organ system using WHO criteria [22].

Statistical analyses. The MTD was defined as the dose that induced leukopenia of grade 4 in ≤20% of patients, thrombocytopenia of grade 3 in ≤60% of patients, and no nonhematologic toxicity above grade 2 except alopecia. The median duration of response and median survival were based on actual data. Survival was calculated from the 1st day of treatment.

Results

Patient characteristics

A total of 29 consecutive subjects entered the trial. As 3 patients were not eligible due to poor performance status (>2, WHO scale), 26 patients received at least one cycle of etoposide and were assessed for toxicity and response. Their clinical characteristics are summarized in Table 1. All patients were men and their median performance status was 1 (range, 0–2). In all, 2 subjects were classified as having LD; 2, as having ED I; and 22, as having ED II. These 26 patients received a total of 86 cycles of etoposide at dose levels ranging from 600 to 1,110 mg/m^2 per course, fractionated over days 1–3. The median number of cycles completed per patient was 3 (range, 1–14) at a treatment interval of 3–4 weeks.

Side effects

After the first cycle of etoposide at doses of 600–810 mg/m^2 per course, hematologic toxicity of grade 4 did not occur. Leukopenia of grade 3 was observed in one case (Table 2); nonhematologic toxicities, except alopecia, above grade 2 were not seen (Table 3).

At a total dose of 990 mg/m^2 per course, etoposide induced leukopenia of grade 4 in three of five patients and thrombocytopenia of grade 3 in two of five subjects. After 2 days, leukocytes and platelets recovered to values of >1,000 and >50,000/ μl, respectively. However, because of the very rapid hematologic recovery we felt that further escalations were feasible as long as they did not exceed 5% of the previous dose.

Seven patients received etoposide at a dose of 1,050 mg/m^2, and seven received 1,100 mg/m^2 per course. After the first course at both doses, leukopenia of grade 4 was observed in 2 cases (28%) and in 1 (14%) subject, respectively. No grade 4 thrombocytopenia occurred. However, grade 3 leukopenia was seen in 3 (42%) and 2 (28%) patients respectively, and grade 3 thrombocytopenia was observed in 1 (14%) and 2 (28%) subjects, respectively. No anemia above grade 2 occurred (Table 2).

Table 2. Hematologic toxicities after the first cycle according to WHO criteria

Dose per cycle (mg/m^2 i.v.)	Patients (*n*)	Toxicity (number of patients)														
		Leukocytes: Grade					Thrombocytes: Grade					Hemoglobin: Grade				
		0	1	2	3	4	0	1	2	3	4	0	1	2	3	4
600	4	0	3	1	0	0	4	0	0	0	0	4	0	0	0	0
810	3	0	1	1	1	0	1	2	0	0	0	2	1	0	0	0
990	5	0	0	1	1	3	2	1	0	2	0	2	2	1	0	0
1,050	7	0	0	2	3	2	5	1	0	1	0	3	3	1	0	0
1,110	7	0	2	2	2	1	3	1	1	2	0	5	1	1	0	0

Table 3. Worst nonhematologic toxicities during all cycles according to WHO criteria

Dose per cycle (mg/m² i. v.)	Patients (*n*)	Cycles (*n*)	Toxicity (number of patients)					
			Hair loss: Grade	Mouth: Grade	Skin: Grade	CNS: Grade	Fever: Grade	Infections: Grade
			0 1 2 3 4	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4
600	4	12	1 0 2 1 0	4 0 0 0 0	4 0 0 0 0	4 0 0 0 0	3 1 0 0 0	4 0 0 0 0
810	3	3	3 0 0 0 0	3 0 0 0 0	3 0 0 0 0	2 1 0 0 0	2 1 0 0 0	3 0 0 0 0
990	5	19	0 0 2 3 0	4 0 1 0 0	4 0 1 0 0	5 0 0 0 0	3 0 1 1 0	3 1 1 0 0
1,050	7	19	0 2 1 4 0	5 1 1 0 0	6 0 1 0 0	7 0 0 0 0	5 0 2 0 0	3 1 2 1 0
1,110	7	33	0 1 0 6 0	5 1 1 0 0	4 3 0 0 0	6 1 0 0 0	5 1 1 0 0	4 0 2 1 0

Myelosuppression was quickly reversible and noncumulative. The leukocyte nadir was reached between days 12 and 15 and the platelet nadir occurred at days 10–14. An increase in leukocytes to >4,000/μl was observed between days 16 and 19 and platelets increased to >100,000/μl at days 13–16. No thrombocytopenia of WHO grade 4 or anemia of grade 3 was observed after any cycle of etoposide at the dose levels tested. Two cases of grade 3 infection occurred, one at a dose of 1,050 mg/m² and one at 1,110 mg/m². No nonhematologic organ toxicity of worse than WHO grade 2 was seen except for grade 3 alopecia, which occurred in 54% of patients (Table 3).

Tumor response

Altogether, 6 (23%; 95% confidence limits, 6%–40%) objective responses, including 1 complete remission (CR), were achieved; 10 (39%) cases were classified as showing no change (NC) and another 10 (39%), as having progressive disease. The CR was achieved in one of the two patients with LD. Although no objective response was seen in the two subjects classified as having ED I, 5 (23%; 95% confidence limits, 5%–41%) of the 22 patients with distant metastases (ED II) achieved a partial remission (PR). According to histologic subtypes, among 13 patients with squamous-cell carcinoma, we registered 1 CR, 3 PRs, and 5 NCs; among 6 subjects with adenocarcinoma, we observed 1 PR; and among 7 patients with large-cell carcinomas, we noted 1 PR.

Dose-response analyses showed no remission in seven patients who had received etoposide at doses of 600 or 810 mg/m². However, at doses of 990–1,110 mg/m² per course, 6 (32%; 95% confidence limits, 11%–53%) objective responses were induced in 19 patients. At dose levels of 990, 1,050, and 1,110 mg/m², etoposide induced 2 remissions each in 5, 7, and 7 subjects, respectively.

Remission duration/survival

The median duration of remission was 5 months and the median survival for all patients was 8 months. Although patients showing a major response survived for a median of 15 months, the median survival of patients showing NC was 7 months and that of subjects with PD was 5 months. Patients who had received etoposide at doses of 990, 1,050, and 1,110 mg/m² survived significantly longer than did those who had been treated with lower doses (419 vs 199 days; $P < 0.007$).

Discussion

The MTD of etoposide in heavily pretreated patients has previously been investigated in two phase I studies in which the drug was given as a continuous infusion over 3 and 5 days, respectively [1, 8]. Based on the results, one study recommended a dose of 450 mg/m² for phase II studies in heavily pretreated patients and the other recommended 625 mg/m² i.v. per course. In two other phase I trials of high-dose therapy, the MTD of etoposide was determined, hematologic toxicity being excluded [24, 30]. One study used bone marrow transplantation as supportive treatment [30]. Apart from myelosuppression, mucositis was the nonhematologic dose-limiting toxicity, which occurred after patients had received 2.7–3.5 g/m² etoposide per course [24, 30].

On the basis of these data, we initiated a phase I trial to determine the MTD of etoposide that can routinely be given to previously untreated patients with NSCLC. Our results indicate that myelosuppression is the dose-limiting toxicity, with leukocytopenia being more pronounced than thrombocytopenia. According to our data, the recommended dose for phase II studies in previously untreated patients with NSCLC is 990–1,110 mg/m² i. v. per course, fractionated over 3 days. This suggested dose is 40%–80% higher than the recommended dose in heavily pretreated patients [1, 8]. Because of the very rapid hematologic recovery, further dose escalations might be feasible. We did not further increase the dose, since our goal was the development of a suitable outpatient schedule. Moreover, in a phase II study in previously untreated patients, etoposide doses of 1,200 mg/m² per course induced leukocytopenia and thrombocytopenia of WHO grade 4 in most patients [18].

At the dose range of 990–1,110 mg/m² in previously untreated patients with NSCLC, 6 (32%) remissions were induced in 19 patients, including 5 (28%) remissions in 18 subjects with extensive disease, whereas no response was seen at lower doses in 7 cases. These data are in accordance with previously reported results [6] investigat-

ing a dose of 900 mg/m^2 etoposide per course; in this trial, 6 (23%) remissions were achieved in 23 previously untreated patients with NSCLC [5, 6].

The present data suggest that etoposide has significant activity at doses of 990–1,110 mg/m^2 i.v. per course in previously untreated patients with NSCLC. The response rates and median survival were at least comparable with those observed in extensive disease treated with combination chemotherapy programs [9]. Since the nonhematologic toxicities were low and myelosuppression was pronounced but of very short duration, further prospective randomized studies are indicated for the comparison of optimal doses of etoposide with standard combination chemotherapy in the treatment of NSCLC.

References

1. Aisner J, Van Echo DA, Whitacre M, Wiernik PH (1982) A phase I trial of continuous infusion VP16–213 (etoposide). Cancer Chemother Pharmacol 7: 157–160
2. Anderson G, Payne H (1985) Response rate and toxicity of etoposide (VP-16) in squamous carcinoma of the lung: report from the Lung Cancer Treatment Study group. Semin Oncol 12 [Suppl 2]: 21–22
3. Andersen G, Peel ET, Cheong CMB, Broderick NJ (1982) Etoposide – an effective single drug for treating bronchogenic carcinoma. Clin Oncol 8: 215–218
4. Bakowski MT, Crouch JC (1983) Chemotherapy of non-small cell lung cancer: a reappraisal and a look to the future. Cancer Treat Rev 10: 159–172
5. Bauer G, Bremer K (1986) Sequentielle Therapie nicht-kleinzelliger Bronchialcarzinome mit Etoposid und Cisplatin. Krebsmedizin 7: 10–12
6. Bauer G, Bleifuss J, Bremer K (1986) Sequential therapy of non-small cell bronchiogenic carcinoma (NSCLC) with etoposide (VP-16) and cisplatinum. J Cancer Res Clin Oncol [Suppl] 111: 65
7. Bender RA, Anderson T, Fisher RI, Young RC (1978) Activity of the epipodophyllotoxin VP-16 in the treatment of combination chemotherapy-resistant non-Hodgkin's lymphoma. Am J Hematol 5: 203–209
8. Bennett CL, Sinkule JA, Schilsky RL, Senekjian E, Chou KE (1987) Phase I clinical and pharmacological study of 72-hour continuous infusion of etoposide in patients with advanced cancer. Cancer Res 47: 1952–1956
9. Bonomi PD, Finkelstein DM, Ruckdeschel JC, Blum RH, Green MD, Mason B, Hahn R, Tormey DC, Harris J, Comis R, Glick J (1989) Combination chemotherapy versus single agents followed by combination chemotherapy in stage IV non-small-cell lung cancer: a study of the eastern Cooperative Oncology Group. J Clin Oncol 7: 1602–1613
10. Bunn PA Jr (1989) The expanding role of cisplatin in the treatment of non-small cell lung cancer. Semin Oncol 16: [Suppl 6]: 10–21
11. Cavalli F, Sonntag RW, Jungi F, Senn HJ, Brunner KW (1978) VP-16-213 monotherapy for remission induction of small cell lung cancer: a randomized trial using three dosage schedules. Cancer Treat Rep 62: 473–475
12. Cecil JW, Quagliana JM, Coltman CA, Al-Sarraf M, Thigpen T, Groppe CW Jr (1978) Evaluation of VP-16-213 in malignant lymphoma and melanoma. Cancer Treat Rep 62: 801–803
13. Chapman R, Itri L, Gralla R, Kelsen D, Casper E, Golbey R (1982) Phase II trial of VP-16-213 in non-small-cell lung cancer (NSCLC). Cancer Chemother Pharmacol 7: 205–207
14. Colombo T, Broggini M, Torti L, Erba E, D'Incalci M (1982) Pharmacokinetics of VP16-213 in Lewis lung carcinoma-bearing mice. Cancer Chemother Pharmacol 7: 127–131
15. Dombernowsky P, Nissen NI (1973) Schedule dependency of the antileukemic activity of the podophyllotoxin derivative VP-16-213 (NSC-141540) in L1210 leukemia. Acta Pathol Microbiol Scand 5: 715–724
16. Drings P (1989) European experience with ifosfamide in non-small cell lung cancer. Semin Oncol 16 [Suppl 3]: 22–30
17. Eagan RT, Ingle JN, Creagan ET, Frytak S, Kvols LK, Rubin J, McMahon RT (1978) VP-16-213 chemotherapy for advanced squamous cell carcinoma and adenocarcinoma of the lung. Cancer Treat Rep 62: 843–844
18. Greco FA, Johnson DH, Hande KR, Porter LL, Hainsworth JD, Wolff SN (1985) High-dose etoposide (VP-16) in small-cell lung cancer. Semin Oncol 12 [Suppl 2]: 42–44
19. Havemann K, Wolf M, Holle R, Gropp C, Drings P, Manke H-G, Hans K, Schroeder M, Heim M, Victor N, Georgii A, Thomas C, Pflueger K-H, Bepler G (1987) Alternating versus sequential chemotherapy in small cell lung cancer. Cancer 59: 1072–1082
20. Joss RA, Cavalli F, Goldhirsch A, Mermillod B, Brunner KW (1984) New agents in non-small cell lung cancer. Cancer Treat Rev 11: 205–236
21. Livingston RB (1988) Treatment of advanced non-small cell lung cancer: the southwest Oncology Group Experience Semin Oncol 15 [Suppl 7]: 37–41
22. Miller AB, Hoogstraaten B, Staquet M, Winkler A (1981) Reporting results of cancer treatment. Cancer 47: 207–214
23. Niederle N, Krischke W, Schulz U, Schmidt CG, Seeber S (1982) Untersuchungen zur kurzzeitigen Induktions- und zyklischen Erhaltungstherapie beim inoperablen kleinzelligen Bronchialkarzinom. Klin Wochenschr 60: 829–838
24. Postmus PE, Mulder NH, Sleijfer DR, Meinesz AF, Vriesendorp R, Vries EGE de (1984) High-dose etoposide for refractory malignancies: a phase I study. Cancer Treat Rep 68: 1471–1474
25. Preusser P, Achterrath W, Niederle N, Seeber S (1985) Cisplatin. Arzneimitteltherapie 2: 50–65
26. Rosso R, Ardizzoni A, Salvati F, Gallo-Curcio C, Rubagotti A, Fusco V, Brunetti I, DePalma M, Cruscsiani AR, Portalone L, Aquilini M, Tonachella R, Rinaldi M, Soresi E, Saccani F, Cioffi R, Monaco M, Scoditti S, Folco U, Rimoldi R, Logroscino C, Pedicini T, Botta M, Ferrara G, Belli M, for the Italian Task Force for Lung Cancer (FONICAP) (1988) Etoposide vs etoposide plus cisplatin in the treatment of advanced non-small cell lung cancer: a FONICAP randomized trial. Semin Oncol 15 [Suppl 7]: 49–51
27. Slevin ML, Clark PI, Joel SP, Malik S, Osborne RJ, Gregory WM, Lowe DG, Reznek RH, Wrigley PFM (1989) A randomized trial to evaluate the effect of schedule on the activity of etoposide in small-cell lung cancer. J Clin Oncol 7: 1333–1340
28. Sørensen JB, Østerlind K, Hansen HH (1987) Vinca alkaloids in the treatment of non-small cell lung cancer. Cancer Treat Rev 14: 29–51
29. Taylor RE, McElwain TJ, Barrett A, Peckham MJ (1982) Etoposide as a single agent in relapsed advanced lymphomas. A phase II study. Cancer Chemother Pharmacol 7: 175–177
30. Wolff SN, Fer MF, McKay CM, Hande KE, Hainsworth JD, Greco FA (1983) High-dose VP-16-213 and autologous bone marrow transplantation for refractory malignancies: a phase I study. J Clin Oncol 1: 701–705