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Short communication

Chronic oral etoposide in advanced breast cancer

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Abstract. Chronic oral etoposide has shown activity in some metastatic refractory tumors. To test its activity in previously treated metastatic breast cancer patients, we started a study in 18 consecutive patients given etoposide orally at 50 mg/m^2 daily for 21 days. A partial response was observed in 4 of 18 patients (22%); of the responding patients, 3 had visceral metastases and 1 had multiple bone metastases. Leukopenia of grade 3 or 4 was the main hematological toxic effect (23% of patients) and alopecia was the most important nonhematological toxicity. Chronic oral etoposide shows some activity in pretreated patients with metastatic breast cancer, with tolerance being good and toxicity, acceptable. Further studies of this drug given as first-line chemotherapy or in combination with other drugs can establish all its potential activity in this cancer.

Introduction

The overall prognosis for chemotherapy-pretreated patients with advanced breast cancer remains unfortunately poor [3]. First-line chemotherapy with various combination schedules produces an objective remission of disease in 40%–70% of cases, but the median duration of response usually ranges between 6 and 15 months and the toxicity is considerable [4, 5]. Nonresponders and relapsing patients are treated with second-line chemotherapy as palliative treatment or are offered investigational drugs.

Chronic oral etoposide is a new schedule form that has shown promising results in some tumors [9–11, 13]. Although etoposide given on a classic 5-day schedule produces a response rate of less than 10% in advanced breast cancer [1], a potential increase in the response rate could be expected with chronic oral administration because of prolonged inhibition of topoisomerase II in malignant cells [6, 12, 18]. To evaluate the antitumoral activity of this new schedule in pretreated patients with advanced breast cancer, a phase II trial was performed.

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Patients and methods

Between April 1991 and April 1992, 18 consecutive pretreated metastasic patients with histologically or cytologically proven breast carcinoma were included in a phase II clinical trial of oral etoposide [22]. In all, 5 of 18 patients (28%) had previously been treated with hormonal therapy, 2 of them with tamoxifen alone and 3 with tamoxifen plus chemotherapy (patient 1, fluorouracil, Adriamycin, and cyclophosphamide; patient 2, mitoxantrone; and patient 3, etoposide, Adriamycin, and cyclophosphamide), and 13 of 18 (72%) had received chemotherapy alone for advanced disease (Table 1). Other inclusion criteria were a white blood cell count of $>4 \times 10^9$/l, a platelet count of $>100 \times 10^9$/l, a serum creatinine level of <1.4 mg/dl, and a serum bilirubin value of <1.5 mg/dl. Other requirements were an Eastern Cooperative Oncology Group (ECOG) performance status below 3, no prior chemotherapy or hormonal therapy within 1 month of the start of oral etoposide treatment, and a life expectancy of 3 months or more.

Pretreatment evaluation included a history and complete blood cell (CBC) counts, laboratory values for kidney and liver function, a chest X-ray examination, mammography, and bone scintigraphy. Other appropriate examinations were performed on the basis of symptoms and physical examination. CBC counts were repeated on day 14 of the first course and subsequently before each treatment. Liver and kidney chemistries were performed every 4 weeks.

Since oral etoposide is supplied in 50-mg capsules, a daily dose of 50 mg/m^2 is reached over 2–3 days of dose adjustment, depending on the patient's body surface area; hence, the daily dose should be one or two capsules. For instance, 80 mg being the daily dose for a patient with a body surface area of 1.62 m^2, the drug was given at doses of 100, 100, and 50 mg on 3 consecutive days, and this schedule was repeated for 21 days (median daily dose, 83 mg). Each patient was provided with a calendar in which the daily number of capsules for intake were stipulated [7]. Patients were given etoposide at 50 mg/m^2 daily for 21 consecutive days. Before the next course, patients were given no therapy for 1 week so as to recruit bone marrow reserve.

Response and toxicity were assessed according to the World Health Organization (WHO) criteria [20, 21]. Two courses were mandatory before evaluation. Responders and patients with stable disease were given etoposide courses until the development of tumor progression or

Table 1. Previous treatment

Chemotherapy +/– hormonal therapy	Patients
CAF	4
CMF + CAF	2
Mitoxantrone	2
CAF + tamoxifen	1
CAF + UFT/L	1
CAF + UFT/L + megestrol	1
CAF + megestrol	1
CMF + CARBO-E	1
CMF + mitoxantrone	1
E-C + CAF	1
E-A-C	1
Tamoxifen alone	1

F, 5-Fluorouracil; C, cyclophosphamide; CARBO, carboplatin; UFT, tegafur-uracil; A, Adriamycin; L, leucovorin; E, etoposide

Table 2. Patients' characteristics

Age (years):		
	Median	53
	Range	26–69
Hormonal status:		
	Premenopausal	2
	Postmenopausal	16
Estrogen receptor status:		
	Positive	9
	Negative	6
	Unknown	3
Performance status:		
	0	8
	1	10
Number of metastatic sites:		
	1	9
	2 or more	9
Dominant site of disease:		
	Soft tissue	5
	Bone	6
	Visceral	7

excessive toxicity, for a maximum of six cycles per patient. The duration of response was not considered in this phase II trial, as most patients (both responders and nonresponders) were later given other oncological treatment modalities, if indicated.

Results

A total of 18 consecutive patients were entered in this study. Their median age was 58 years (range, 26–69 years). Patients had been pretreated for their extensive disease with a median of 2 systemic treatments per person (range, 1–3). In all, 16 of 18 patients had received previous chemotherapy (1 line in 8 patients and 2 lines in the remaining 8 patients), 12 of whom had received an Adriamycin-containing regimen. The pretreatment characteristics of the patients are shown in Table 2.

The total number of courses given to all patients were 49. Overall, 2 patients received 1 course, 6 patients were given 2 courses, and 10 patients received 3 or more courses. In 4 of 49 courses (8%), the next course was delayed because of myelotoxicity.

Table 3. Toxicity

Toxic effect	WHO	Patients	%
Leukopenia	1–2	10	56
	3–4	4	22
Neutropenia	1–2	9	50
	3–4	2	11
Anemia	1	5	28
	2	2	11
Thrombocytopenia	1–4	0	
Alopecia[a]	2–3	8	89
Nausea and vomiting	1	5	28
	2	4	22
Diarrhea	1	3	16
Mucositis	1–2	3	16
Liver	1	1	5

[a] Nine patients were unevaluable because of prior alopecia

All patients included were fully evaluable. Partial responses were obtained in 4 of 18 patients (22%). In all, 3 of the 4 responding patients had previously been treated with chemotherapy (patient 1, mitoxantrone; patient 2, cyclophosphamide + etoposide/cyclophosphamide + doxorubicin + 5-fluorouracil; and patient 3, cyclophosphamide + methotrexate + 5-fluorouracil/cyclophosphamide + Adriamycin + 5-fluorouracil). Another responder had previously been treated by hormonal therapy (tamoxifen). A minor response occurred in 1 patient (5%); disease stabilization, in 5 other patients (28%); and progressive disease, in the remaining 8 patients. According to the predominant site of metastases, 3 partial responses were seen in viscera (2 in the lung and 1 in the liver) and 1 was observed in multiple bone metastases (partial decrease in the density of blastic lesions). A minor response was observed in a patient with skin lesions.

The incidence of toxic effects during etoposide chemotherapy is listed in Table 3. Hematological toxicity mainly consisted of grade 3 or 4 leukopenia in 4 patients (22%) and grade 3 or 4 neutropenia in 2 patients (11%). Grade 3 or 4 leukopenia was observed just before the next course of chemotherapy. No episode of neutropenia-related fever or other infection was observed. No patient developed thrombocytopenia. The most important nonhematological toxic effect was alopecia of grade 2 or 3, noted in 8 of 9 (89%) evaluable patients. The remaining patients were unevaluable because of alopecia caused by prior chemotherapy. There was no treatment-related death.

Discussion

Etoposide as a single agent has been investigated in metastatic breast cancer [15, 16, 19]. The low response rate obtained suggests that etoposide plays a minor role in pa-

tients with breast cancer. The analysis of dose intensity has shown no relationship between dose intensity and response [8]. Nevertheless, in preclinical and clinical studies, the administration of etoposide at a low daily dose for several days seems to enhance its activity [2, 17, 18]. Etoposide induces single- and double-strand DNA breaks, even at low concentrations. Recently it has been reported that etoposide damages DNA by interacting with topoisomerase II, which catalyzes DNA topoform interconversions, introducing a transient enzyme-bridged, double-strand break in one of the two crossing DNA segments [14]. This interaction is reversible after the withdrawal of etoposide; therefore, prolonged exposure of cells to etoposide is necessary for the achievement of its optimal cytotoxic activity. The daily administration of oral etoposide has yielded encouraging response rates in some tumors [10, 11].

The 22% response rate obtained in our group of previously treated patients with metastatic breast cancer suggests that etoposide has moderate activity in this disease. Two of four partial responses were seen in a patient with liver metastases and a patient with bone metastases, sites of disease that are associated with a low percentage of success. In addition, as the vast majority of our patients had received prior chemotherapy and made progress during treatment, their low rate of response was probably due to their belonging to a subgroup of patients with a poor response to chemotherapy.

The toxicity was low, mainly comprising tolerable myelosuppression. Alopecia was the main non-hematological toxic effect occurring in nearly all evaluable patients. Since our patients did not have their serum etoposide levels measured, the high incidence (89%) of alopecia of different grades reassured us about the patients' home drug compliance. As judged on the basis of our present results, chronic oral etoposide might be considered on its own or in combination with other drugs in previously untreated patients with metastatic breast cancer.

References

1. Ahmann DL, Bisel HF, Eagan RT, et al (1976) Phase II evaluation of VP16-213 (NSC-141540) and Cytembena (NSC-104801) in patients with advanced breast cancer. Cancer Treat Rep 60: 633–635
2. Cavalli F, Sonntag RW, Jungi F, et al (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
3. Glark GM, Sledge GW Jr, Osborne CK, McGuire WL (1987) Survival from first recurrence: relative importance of prognostic factors in 1,015 breast cancer patients. J Clin Oncol 5: 55
4. Haskell CM, et al (1985) Breast cancer. In: Haskell CM (ed) Cancer treatment. W. B. Saunders, Philadelphia, pp 137–180
5. Henderson IC, Harris JR, Kinne DW, Hellman S (1989) Cancer of the breast. In: De Vita VT Jr, Hellman S, Rosenberg SA (eds) Cancer, principles and practice of oncology. J. B. Lippincott, Philadelphia, p 1197
6. Dombernbwsky P, Nissen NI (1973) Schedule dependency of the antileukemic activity of the podophyllotoxin derivative VP16-213 (NSC-141540) in 11210 leukemia. Acta Pathol Microbiol Scand [A] 81: 715
7. Estapé J, Palombo H, Sanchez-Lloret J, et al (1992) Chronic oral etoposide in non-small cell lung carcinoma. Eur J Cancer 28A: 835
8. Fraschini G, Esparza L, Holmes F, et al (1989) High-dose etoposide (HD-E) in metastatic breast cancer (abstract). Breast Cancer Res Treat 14: 142
9. Greco FA, Johnson DH, Hainsworth JD, et al (1989) Chronic oral etoposide. Cancer 67 [Suppl]: 303
10. Hainsworth JD, Greco A, Johnson D, et al (1990) Chronic daily administration of oral etoposide: a phase I trial. J Clin Oncol 3: 395
11. Johnson DH, Greco FA, Strupp J, et al (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
12. Liu LF, Rowe TG, Yang L, et al (1984) Cleavage of DNA by mammalian DNA topoisomerase II. J Biol Chem 259: 13560
13. Miller JC, Loehrer FJ, Williams SD, et al (1989) Phase II study of daily oral VP-16 in refractory germ cell tumours (abstract). Proc Am Soc Clin Oncol 8: 145
14. Ross W, Rowe T, Glisson B, Yalowich J, Liu L (1984) Role of topoisomerase II in mediating epipodophyllotoxin induced DNA cleavage. Cancer Res 44: 5857
15. Schell FC, Yap HY, Hortobagyi GN, et al (1982) Phase II study of VP-16-213 (etoposide) in refractory metastatic breast carcinoma. Cancer Chemother Pharmacol 7: 223
16. Sledge GW Jr (1991) Etoposide in the management of metastatic breast cancer. Cancer 67 [Suppl]: 266
17. Slevin ML, Clark PI, Osborne RJ, et al (1986) A randomized trial to evaluate the effect of schedule on the activity of etoposide in small cell lung cancer. Proc Am Soc Clin Oncol 5: 175
18. Sullivan DM, Glisson BS, Hodges PK, et al (1986) Proliferation dependence of topoisomerase II mediated drug action. Biochemistry 25: 2248
19. Vaughn CB, Panettiere F, Thigpen T, et al. (1981) Phase II evaluation of VP-16-213 in patients with advanced breast cancer: a Southwest Oncology Group study. Cancer Treat Rep 65: 443
20. World Health Organization (1979) Handbook for reporting results of cancer treatment. World Health Organization, Geneva
21. Miller AB, Hoogstraten B, Staquet M, et al (1981) Reporting results of cancer treatment. Cancer 47: 207–214
22. Gehan EA (1961) The determination of the number of patients required in a preliminary and a follow-up trial of a new chemotherapeutic agent. J Chronic Dis 13: 4