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Clinical report

Daily oral etoposide in metastatic breast cancer

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Etoposide, administered i.v. or orally, as a single agent, in 1- to 5-day courses, was found to be minimally effective in pretreated advanced breast cancer patients. Clinical data suggested an effectiveness of a chronic low-dose oral etoposide schedule, in refractory and those malignancies otherwise unresponsive to the drug. Therefore, the aim of our open-labeled, non-randomized, phase II clinical study was to investigate the efficacy and toxicity of chronic daily etoposide (50 mg/m^2 daily, for 21 consecutive days, every 28 days) as a first-line chemotherapy for metastatic breast cancer. Twenty-one advanced breast cancer patients, with or without previous adjuvant CMF chemotherapy, were included. One complete (CR) and five partial remissions (PR) were obtained in 18 patients evaluable for response. Disease stabilization was obtained in 10 patients (55%), while two patients (11%) failed to respond. Grade 3–4 hematological toxicity developed in seven out of 21 patients evaluable for toxicity or in 15 out of 96 cycles. Non-hematological toxicity was moderate. Our results showed the efficacy and relative low toxicity of a chronic oral etoposide regimen in advanced breast cancer patients. Adjuvant CMF chemotherapy did not influence the therapeutic response. Previous irradiation of the breast tended to increase the etoposide hematological toxicity.

Key words: Advanced breast cancer, oral etoposide.

Introduction

Etoposide has been used in clinics for more than 20 years. The mechanism of etoposide action has been well known for several years,[1] but, nevertheless, the optimum dose and schedule of administration are still not fully established. The research on the model of small cell lung cancer has suggested marked schedule dependency.[2] It was then postulated that chronic administration might be superior to a 3- to 5-day course. In a phase I trial, Hainsworth *et al.*[3] established that the dose of 50 mg/m^2 oral etoposide daily, given for 21 consecutive days, was the maximum tolerated dose. Chronic oral etoposide has been shown to be effective in refractory and previously untreated small cell lung cancer, lymphoma and germ cell tumors.[4–7] On the other hand, etoposide was found to be minimally effective in advanced breast cancer patients, given as a single agent, in short-term courses.[8] Therefore, we started a non-randomized, phase II clinical study in April 1993, to test the efficacy and toxicity of chronic daily oral etoposide as a first-line chemotherapy for metastatic breast cancer. Two studies, with a similar design, have been published in the meantime[9,10]

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Patients and methods

The main inclusion criteria were: histologically confirmed breast cancer in metastatic stage and measurable and/or evaluable lesions located outside of previously irradiated fields, in patients younger than 70. Previous adjuvant CMF chemotherapy, adjuvant endocrine or endocrine therapies for metastatic disease were allowed, as well as radiotherapy to no more than 25% of red bone marrow; adequate peripheral platelet and white blood cell count (WBC) were necessary, as well as normal liver, renal and cardiac function.

Patients with pleural or ascitic effusion, osteoblastic bone metastases, carcinomatous lymphangitis or brain metastases, as the only manifestation of disease, were not eligible. The other exclusion criteria were: adjuvant chemotherapy other than CMF, active infectious process and history of other malignancy (except localized, adequately cured basal or squamous skin carcinoma and uterine cervical cancer).

The study was approved by the institutional Ethic Committee. Informed verbal consent was obtained from all patients, according to national regulations.

Complete history, physical examinations, tumor measurements, performance status, surface area, hematological and biochemical parameters, mammography, and computer tomography scan (if necessary), chest X-ray, bone X-ray, liver ultrasonography, ECG and blood pressure test were done before the first cycle. WBC with differential was evaluated at least weekly or more often if necessary. Clinical and laboratory evaluations were done before each cycle. Chest X-ray and liver ultrasonography, if positive, were repeated after the first and then after every second cycle. Bone X-rays, if negative at baseline, were evaluated after every third cycle and, if positive, after every second cycle.

Etoposide (VP 16) was used in a daily oral dose of 50 mg/m^2, over 21 consecutive days, every 28 days. Treatment schedule was determined on the basis of daily dose, according to body surface, then the weekly dose was established and the number of 50 mg capsules for 1 week was found. The capsules were then given by altering two capsules with one capsule.

Chemotherapy was started only in the case of normal WBC. Dose modification depended on hematological toxicity: in case of grade 2 and 3 (WHO) granulocytopenia and/or thrombocytopenia, the therapy was temporarily discontinued for 1 week. If, after 1 week the platelets and neutrophils recovered, the therapy was continued till the end of the cycle with full dose. There was no prolongation of the cycle for replacement of the days lost due to toxicity. If there was no recovery after 2 weeks, the patient was off study. If neutropenia and thrombocytopenia recovered incompletely (to 1.0–1.5 $\times$ 10^9/l and 75–100 $\times$ 10^9/l, respectively) at the beginning of the next cycle, the cycle was delayed and a 25% dose reduction was done. The same was done if grade 3 hematological toxicity occurred again during the next cycle. If the cycle was delayed, for incomplete recovery, the WBC was then repeated every day till normal values were met. Patients were then treated according to the results of nadir evaluation. Once a dose was reduced, no re-escalation should have been attempted. If Hb was found to be below 8 g/dl, the therapy was discontinued or the beginning of the cycle was delayed. The patient received a red blood cell transfusion and the treatment was continued when Hb became above 8 g/dl. All patients who had received at least one cycle of treatment were considered to be evaluable for toxicity.

Patients were intended to receive six cycles of chemotherapy, with three more cycles in those with CR or PR, and after that to be followed-up until progression, without any other anitcancer treatment. Therapy was discontinued only in the case of tumor progression, unacceptable toxicity or refusal. At the time of disease progression, or treatment discontinuation due to toxicity, the patients received further systemic therapy according to the physicians' judgment.

Efficacy of daily oral etoposide was assessed according to the criteria of Hayward *et al.*,[11] assuming that the patient was evaluable for efficacy, if she received at least two cycles. Assessment of toxicity was based on the Common Toxicity Criteria established by the Division of Cancer Treatment, National Cancer Institute. The analyses of the differences between the patients' sub-groups were done using the Fisher's test.

Results

Patients included

Twenty-one eligible adult female patients, with newly diagnosed or recurrent breast cancer, were included in the study (Table 1). Most patients included were previously treated with the adjuvant CMF or tamoxifen therapy, and/or with endocrine therapies for metastatic disease (nine, three and seven patients, respectively), but none had received any other chemotherapy for metastatic disease. Previous radiotherapy of the breast or thoracic wall was performed in 11 out of 21 patients. The most

Table 1. Patients' characteristics ($n = 21$)

Age (years)	
range	36–69
median	56
Menopausal status (patients)	
premenopausal	2
postmenopausal	19
Previous treatment (patients)	
adjuvant CMF	9
adjuvant tamoxifen	3
endocrine therapy for metastatic disease	7
radiotherapy	
breast or chest wall	11
bones, palliative	1
Metastatic localizations (patients)	
visceral	10
soft tissue	10
bones	4
No. of metastatic localizations (patients)	
1 (soft tissue or visceral)	10
≥ 2 (soft tissue or visceral $\pm$ bones)	11

common metastatic sites were visceral and/or soft tissue, while only four patients had also bone metastases. Ten patients had only one metastatic localization (visceral or soft tissue) and 11 had two or three localizations (including bones).

Therapeutic results

A total of 96 cycles was given (mean 4.5 per patient). Eighteen patients were evaluable for therapeutic response. Three patients were non-evaluable (NE) because they received only one cycle of chemotherapy, due to hematological toxicity (one patient), or early refusal, unrelated to the treatment or toxicity (two patients). Table 2 shows the therapeutic results. The objective response (CR + PR) was obtained in six out of 18 (33%) evaluable patients (95% CI 16.3–56.3%), lasting from 3 to 8 months (median 7). Only one CR was observed in a premenopausal, previously untreated woman, aged 36, with lung metastases at diagnosis. Ten patients (55%) experienced disease stabilization (SD) and two patients (11%) failed to respond. The response of visceral and soft tissue metastatic sites was nine out of 21 (81%) and 12 out of 20 (60%), respectively; the difference not reaching statistical significancy. Objective remissions were seen in all particular metastatic sites, except bones. The best response of bone lesions, judged as 'stabilization', was still present at the time of disease progression in three of four patients. There was no statistical difference in objective response between patients with only one metastatic localization (visceral or soft tissue) and those with two or three localizations (RR = 4/11 versus 2/7 patients). Three of six responders had previously received adjuvant CMF chemotherapy, which, thus, was not likely to influence the response rate in a whole group.

Toxicity

All patients included were evaluable for toxicity (Table 3). The grade 3 or greater hematological toxicity was noted in seven out of 21 patients evaluable for toxicity (granulocytopenia developed in six, anemia in two and trombocytopenia in two of these seven patients) or in 15 out of 96 cycles of chemotherapy. Six of seven patients with grade 3 hematological toxicity had previous irradiation of the breast or the chest wall. In the sub-group experiencing only grade 2 or less hematological toxicity, five out of 14 had been previously irradiated. It appeared that previous irradiation increased etoposide hematological toxicity with

Table 2. Therapeutic response ($n = 18$)

	No. of patients	%	Duration of response (months)
CR + PR	6(1 + 5)	33	3–8 (median 7)
NC	10	55	> 2–8 (median 4)
PD	2	11	—
NE	3	—	—
Response of particular localizations and metastatic sites			
	no. of sites	CR + PR	NC
Visceral	21	9	8
liver	7	2	4
lung	10	4	3
pleura	2	1	1
spleen	1	1	0
adrenal gland	1	1	0
Soft tissue	20	12	2
Skin	6	4	1
peripheral lymph-nodes	9	6	1
retroperitoneal lymph-nodes	1	0	0
inflammatory cancer	1	1	0
local recurrency	3	1	0
Bones	4	0	3

Table 3. Toxicity, grade 3–4 ($n = 21$)

Hematologic toxicity	No. of patients	No. of cycles
neutrophils	6	12
Hb	2	4
platelets	2	2
total no.	7/21	15/96
Non-hematologic toxicity	**Grade**	**No. of patients**
nausea and vomiting	2–3	6
alopecia	2	14
diarrhea	2	1
stomatitis	2	3
loss of appetite	2–3	6
weakness	2–3	6

the borderline significancy (Fisher's test, $p = 0.063$). One patient was excluded due to prolonged granulocytopenia. The 25% dose reduction was performed in three out of 21 patients.

Non-hematological toxicity was mild and acceptable (Table 3). Alopecia grade 2, vomiting, loss of appetite and weakness grade 2–3, were the most serious side effects. Nausea grade 1–2 in most of the patients was almost continuous during the treatment in about 25% of patients.

Discussion

It has been shown in several malignancies that etoposide, given orally in a low daily dose, was less toxic and at least equally effective as standard etoposide administration.[4–6,12] In advanced breast cancer, comparison of the standard i.v. and chronic daily administration was never done. Two studies, recently published, using oral etoposide (50–100 mg/day over 14 days and 50 mg/m^2 over 21 days, respectively), in pretreated advanced breast cancer patients, showed response rates of 22–27%[9] and 30.4%.[10] It was concluded that oral etoposide is active and well tolerated. Their results, compared with previously reported i.v. or short-term oral use, indirectly confirmed that dose and schedule dependency of etoposide certainly exists in breast cancer.

The dose and schedule used in the study of Martin *et al.*[10] were nearly identical to those in our study, whilst the design differed by the inclusion of patients treated by chemotherapy for metastatic disease. The results were also very similar (30.4 versus 33% response rate in our study). We found, although with a small number of patients, that adjuvant CMF chemotherapy did not influence the therapeutic response significantly. In the other study,[9] the authors found a better response in previously untreated patients, compared with those treated by more than one-line chemotherapy (45 and 22% response rate, respectively). In two mentioned studies,[9,10] many patients received doxorubicin, but it was not stated whether the use of doxorubicin, or previous response to this drug, had any particular influence on the etoposide efficacy. In other words, these studies, including ours, confirmed that chronic oral etoposide is effective in pretreated patients, either as secondary to adjuvant chemotherapy or as salvage chemotherapy. It might be interesting to find out whether it is effective in breast cancer patients refractory to primary chemotherapy, as it seems to be in small cell lung cancer.

The other aspects of interest for further research in breast cancer are more frequently discussed: the role of etoposide in combination chemotherapy and in dose-intensive chemotherapy regimens. As the chronic oral mode of administration seems to be more effective, it is reasonable to use this drug regimen in combination chemotherapy. Finally, the two uninvestigated fields in breast cancer that should be of particular interest are the possible synergism of etoposide with radiotherapy and with endocrine therapy.

In conclusion, our study confirmed the efficacy and relative low toxicity of the chronic oral etoposide regimen in advanced breast cancer patients. Adjuvant CMF chemotherapy did not influence the therapeutic response. Previous irradiation of the breast tended to increase the etoposide hematological toxicity.

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References

1. Henwood JM, Brogden RN. Etoposide: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential in combination chemotherapy of cancer. *Drugs* 1990; **39**: 438–90.
2. Slevin ML, Clark PI, Joel SP, *et al.* A randomized trial to evaluate the effect of schedule on the activity of etopo-

side in small-cell lung cancer. *J Clin Oncol* 1989; **7**: 1333–40.
3. Hainsworth JD, Johnson DH, Redlin Frazier S, Greco FA. Chronic daily administration of oral etoposide—a phase I trial. *J Clin Oncol* 1989; **7**: 396–401.
4. Greco FA, Johnson DH, Hainsworth JD. Chronic daily administration of oral etoposide. *Semin Oncol* 1990; **17** (suppl 2): 71–4.
5. Einhorn LH, Pennington K, McClean J. Phase II trial of daily oral VP-16 in refractory small cell lung cancer: a Hoosier Oncology Group study. *Semin Oncol* 1990; **17** (suppl 2): 32–5.
6. Einhorn LH. Daily oral etoposide in the treatment of cancer. *Semin Oncol* 1991; **18** (suppl 2): 43–7.
7. Sessa C, Zucchetti M, Torri V, *et al.* Chronic oral etoposide in small-cell lung cancer: clinical and pharmacokinetic results. *Ann Oncol* 1993; **4**: 553–8.
8. Wander HE, Rauschning W, Meyer D, Achterrath W, Nagel GA. Phase II study with Etoposide in previously untreated advanced breast cancer. *Cancer Chemother Pharmacol* 1989; **24**: 261–3.
9. Calvert AH, Lind MJ, Millward MM, *et al.* Long-term oral etoposide in metastatic breast cancer: Clinical and pharmacokinetic results. *Cancer Treat Rev* 1993; **19** (suppl C): 27–33.
10. Martin M, Casado A, Lluch A, Adrover E, Diaz-Rubio E, Garcia-Conde J. Preliminary results of a phase II trial of chronic oral etoposide in breast cancer. *Cancer Treat Rev* 1993; **19** (suppl C): 47–52.
11. Hayward JL, Carbone PP, Heuson JC, *et al.* Assessment of response to therapy in advanced breast cancer. *Cancer* 1977; **39**: 1289–94.
12. Hainsworth JD, Greco FA. Etoposide: twenty years later. *Ann Oncol* 1995; **6**: 325–41.

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