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# Phase II study with etoposide in previously untreated advanced breast cancer

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**Summary.** A phase II study was carried out to evaluate the efficacy and safety of etoposide used as first-line chemotherapy for patients with advanced breast carcinoma. A total of 20 patients received 230 mg/m$^2$ i.v. etoposide per day for 3 days (total, 690 mg/m$^2$ per course) every 4 weeks. A total of 95 courses were given. Observed responses included 3 partial remissions (PR) and 14 cases of stable disease (NC). The median duration of response was 6 (PR) and 5.6 months (NC). Contrary to the severe hematological toxicity in heavily pretreated patients described in previous studies, no substantial problems were observed in this trial. No dose reduction was necessary, and only once did leukopenia lead to a 1-week delay in therapy. An increase in platelets up to a maximum of 685,000/mm$^3$ was seen in all patients, particularly in those with bone metastases. No relation to the quality of remission or pretreatment was seen. Nausea, vomiting, and fatique were mild and transient, but alopecia occurred in all cases. One patient developed nonfatal anaphylactic shock after etoposide treatment.

## Introduction

Advanced breast cancer is far from being a curable disease; therefore, it is desirable to find non-cross-resistant and less toxic chemotherapeutic drugs for its treatment. Etoposide, a semisynthetic derivative of podophyllotoxine, produces objective remission rates of 0–14% in chemotherapy-refractory breast cancer when given as a single agent [4, 10–12]. In combination with cyclophosphamide [5] or Adriamycin [8, 9], higher objective remission rates (4%–33%) were obtained with this drug.

However, the evaluation of new drugs in refractory carcinomas may result in the underestimation of drugs that are probably highly effective and have few side effects. The efficacy of etoposide cannot be sufficiently judged at present, because experience with this agent in primary monochemotherapy for advanced breast cancer has not yet been reported. Moreover, the optimal dose schedule for etoposide has not been established, varying from i.v. doses of 45 mg/m$^2$ per day for 5 days [11] and 80 mg/m$^2$ per day for 5 days [9], to oral doses of up to 120 mg/m$^2$ per day for 5 days [5].

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The aim of this pilot study was to investigate the efficacy and side effects of etoposide used as first-line monochemotherapy to find alternative drugs for the treatment of advanced breast cancer.

## Patients and methods

A total of 20 patients with histologically proven advanced breast cancer and measurable lesions entered the study; 18 patients had not received prior chemotherapy, and 2 had relapsed after adjuvant chemotherapy (interval, at least 12 months). Exclusion criteria were an estimated survival of $<3$ months or a Karnofsky performance status of $<60\%$. Patient characteristics are shown in Table 1. Eight patients were older than 70 years. In all, 35% of our patients had one and 65% had two or more sites of metastasis.

The following regimen was given on an outpatient basis: 230 mg/m$^2$ i.v. etoposide on days 1–3 (total, 690 mg/m$^2$ per cycle), repeated every 28 days, hematological recovery permitting. The response criteria of Hayward et al. [7] were used, except that tumor response had to last at least 3 months to be classified as a remission. Patients who had received at least one course of etoposide were evaluated for response and toxicity. All patients were evaluable. A total of 95 courses were given ($1\times1$, $4\times2$, $2\times3$, $4\times4$, $6\times5$–7, and $3\times8$–10 courses).

Observed responses included 3 PRs (sites of metastasis: soft tissue + bone + pleura; 2× bone + hepatic) and 14 NCs (70%); 6 of the latter showed a minor response (Table 2). Three patients developed progressive disease. The median duration of response was 6 (PR) and 5.6 months (NC). All 11 patients who had severe bone pain noted dramatic pain relief within the 1st week after the administration of etoposide, but in 5 patients the pain recurred 3–4 weeks later. In three patients treatment was stopped on request after 5, 6, and 7 courses, when a response (PR/minor response) became evident; after 8 weeks all had developed obviously progressive disease.

The side-effects observed are outlined in Table 3. Alopecia occurred in all cases. Nausea, vomiting, inappetence, and fatigue were mild and transient, and in seven patients a weight loss of 8 kg (range, 3–14 kg) was noted. Six patients experienced no side effect other than alopecia. No congestive heart faialure occurred. Treatment was stopped in one patient due to nonfatal anaphylactic shock after course 9.

**Table 1.** Patient characteristics ($n$ = 20)

| | |
|---|---|
| Age (range) | 64 years (42–79 years) |
| Menopausal status: | |
| premenopausal | 3 |
| <2 years postmenopausal | 0 |
| >2 years postmenopausal | 17 |
| DFI ?????: | |
| <2 years | 10 |
| >2 years | 10 |
| Hormone receptors: | |
| positive[a] | 8 |
| negative | 7 |
| unknown | 5 |
| Sites of metastases: | |
| soft tissue | 2 |
| pulmonary/pleura | 4 |
| osseous | 5 |
| osseous + pulmonary | 1 |
| osseous + pleura | 1 |
| osseous + hepatic | 2 |
| 3 sites | 3 |
| >3 sites | 2 |
| Prior treatment: | |
| none | 1 |
| hormonal therapy (HT) | 14 |
| adjuvant HT | 3 |
| adjuvant chemotherapy | 2 |

[a] Positive: ER, >10 fmol and/or PR, 20 fmol

**Table 2.** Results of i.v. injections of etoposide in patients with previously untreated, advanced breast cancer

| | Patients ($n$) | % | Duration of remission in months |
|---|---|---|---|
| CR | 0 | 0 | – |
| PR | 3 | 15 | 6 (range 4–8) |
| NC | 14 | 70 | 5.6 (range 3–10) |
| PD | 3 | 15 | – |
| Totals | 20 | 100 | |

**Table 3.** Side effects of i.v. etoposide in 20 patients with advanced breast cancer

| Toxicity | Patients ($n$) |
|---|---|
| Alopecia (complete) | 20 |
| Nausea [WHO grade 1 (5), 2 (3)] | 8 |
| Vomiting [WHO grade 1 (3), 3 (1)] | 4 |
| Inappetence (transient) | 8 |
| Weight loss (3, 6, 7, 7, 9, 9, 14 kg) | 7 |
| Fatigue | 6 |
| Infections | 3 |
| Headache | 1 |
| Anaphylactoid reaction | 1 |
| Diarrhea | 1 |
| Pain relief | 11 |

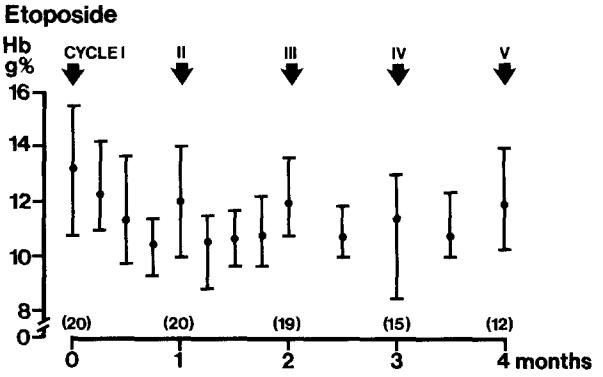


**Fig. 1.** Behavior of hemoglobin (*Hb*) during treatment with etoposide given as a single agent (Hb values are expressed as g/dl)

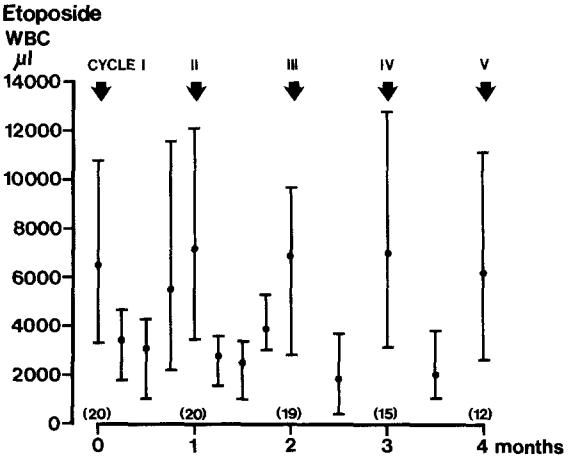


**Fig. 2.** Behavior of white blood cells (*WBC*) during treatment with eposide given as a single agent (WBC values are expressed as $10^9$ cells/l, which is equivalent to cells/ml)

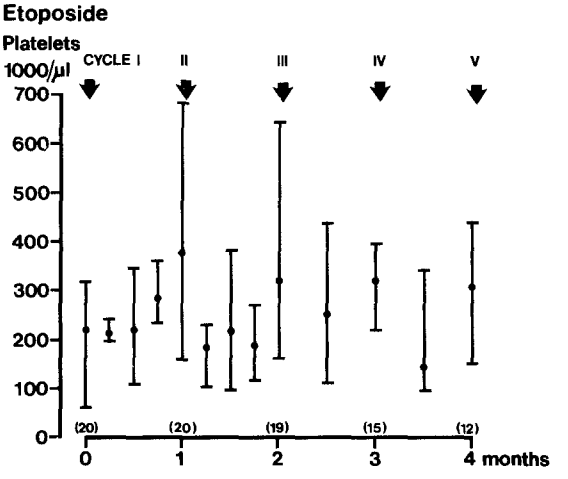


**Fig. 3.** Behavior of platelets during treatment with etoposide given as a single agent (values for platelets expressed as $10^{12}$ cells/l, which is equivalent to 1,000 cells/ml)

Hematological toxicity was tolerable. The behavior of hemoglobin during treatment with etoposide is shown in Fig. 1; on average, a decrease of 1–2 g% was observed. No bleeding occurred, and only one patient received transfusions after course 3. The influence of etoposide on the white blood count was more marked (Fig. 2), although in one case leukopenia led to a treatment delay of 1 week. Usually a leukocyte nadir of 3,000–3,500 cells/mm$^3$ was reached after 14 days; only in one patient did we observe a white blood count of <1,000 cells/mm$^3$.

In contrast, the platelet counts increased by an average of 150,000/mm$^3$ after the first cycle (Fig. 3), even in a patient with extensive bone metastases, who had a platelet count of 61,000/mm$^3$ before treatment. The thrombocyte nadir was reached after 1 week, but recovery occurred late (after day 21). Patients with the highest thrombocyte increase had bone metastases, and marginal increases were seen in those with hepatic (1 patient) and pulmonary/pleural (1) and pulmonary metastases (3). Thrombocyte increases were not related to response or prior adjuvant chemotherapy.

## Discussion

The observed objective remission rate (15%) was disappointing. In our study using etoposide as primary chemotherapy, we noted the same objective remission rate seen in a previous study with the best results in pretreated patients [10]. However, it is noteworthy that 14 of our 20 patients achieved stable disease, and 6 of these had minor responses. Factors contributing to the poor objective remission rate may have been that 65% of the patients had bone metastases, which are known to respond slowly and poorly, and that our response criteria were stricter than those of Hayward et al. [7], as described in *Patients and methods*. Due to hematological toxicity observed (Fig. 1, 2), it is not advisable to repeat the present etoposide regimen more often than every 4 weeks. Therefore, continuous oral administration may be of interest.

In this phase II study a variable increase in platelets was observed, with the highest counts occurring after the first cycle. Patients with the highest platelet increases had bone metastases, whereas marginal increases were seen in patients with visceral involvement. This observation supports the results of Cabanillas et al. [3] but opposes other prior reports that have noted no effect on the thrombocyte count [2], even decreases in thrombocytes (6, 10, 11, 13].

The side effects were comparatively mild [5], although eight patients were older than 70 years. Alopecia always occurred within the first 4 weeks. One patient developed an anaphylactic reaction. In spite of the high dose, the hematological toxicity was mild; this is contrary to the experience gained in pretreated patients [5, 10, 11], where anemia, leukopenia, and thrombocytopenia were dose-limiting. Dose reduction was not at all necessary. Although we noted dramatic pain relief in all 11 patients who had bone pain, in some of them the antitumor effects of etoposide seemed to be of shorter duration than the side effects on the bone marrow. In 5 of these 11 patients, pain recurred before the bone marrow had fully recovered.

On the dose schedule used in this study, monotherapy using etoposide as first-line chemotherapy in patients with advanced breast cancer was tolerated well, but responses were few and of short duration. Furthermore, the dose schedule used was impractical for outpatients.

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