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Clinical report

Selection of candidates for oral etoposide salvage chemotherapy in heavily pretreated breast cancer patients

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Metastatic breast cancer (MBC) is still in most cases an uncurable disease and the main goal of treatment is a good quality of life for these patients. Therefore it is very important to select patients who are appropriate candidates for the particular salvage chemotherapy (CT) schedule. The aim of our study was to assess treatment response to oral etoposide, and to analyze its relationship with patients' and disease characteristics. Seventy-five patients with bidimensionally measurable MBC were included into our study. For most of the patients treatment with etoposide was third-line CT regimen and most of them (90%) had been exposed to previous anthracycline-based CT. Etoposide was administered orally at a dose of 100 mg/day for 10 days every 3 weeks. The overall response rate was 37% (95% CI: 27–50%) with a median time to progression (TTP) and survival of 4.5 and 12 months, respectively. Patients with a long disease-free interval, predominant soft tissue and bone metastases, and less than three metastatic sites responded better to oral etoposide; however, a significantly better response was achieved only in those who had responded to previous CT (46 versus 19%, $p = 0.04$), especially to anthracyclines (50 versus 17%, $p = 0.016$). Response to previous anthracycline-based regimen was the only characteristic that significantly influenced TTP (median TTP: 7 versus 2.5 months, $p = 0.0066$) and survival (median survival: 13.8 versus 5 months, $p = 0.0072$). Toxic side effects were generally mild. Salvage CT with oral etoposide is an appropriate treatment for patients who respond to previous CT, particularly to anthracyclines. It combines a favorable toxicity profile with the major advantage of an oral drug administered at home.

Key words: Metastatic breast cancer, oral etoposide, salvage chemotherapy.

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Introduction

Metastatic breast cancer (MBC) is still in most cases an uncurable disease. When treatment with standard combination chemotherapy (CT), such as CMF (cyclophosphamide, methotrexate, 5-fluorouracil) and anthracycline-based CT schedules, has failed, other cytotoxic drugs are used as salvage CT. Salvage CT regimens that are used most commonly are combinations of mitomycin and vinblastine, cisplatin and etoposide or ifosfamide and monotherapy with taxanes. With these salvage CT schedules response rates range between 10 and 57%;[1–10] however, clinically useful activity in anthracycline-resistant patients has been so far achieved with taxanes only.[10]

There are some clinical reports of efficacy and mild toxicity of oral etoposide in patients with different malignancies after failing standard CT.[11,12] Because the treatment can be applied on an outpatient basis and has moderate side effects, prolonged oral etoposide seems to be a convenient salvage therapy also for MBC. According to the results published so far, the administration of oral etoposide can induce a response in about one-third of patients with MBC.[13–21] Our preliminary results with oral etoposide in heavily pretreated MBC patients were promising—an objective response was observed in 11 out of 21 patients and the treatment-related toxicity was moderate.[21]

Since the main goal of salvage therapy is palliation of symptoms and a good quality of life, it is very important to select patients with a high probability of response to such a treatment. It is known that some characteristics, such as performance status, disease-free interval, dominant metastatic site, tumor burden and dose intensity, can predict a better response to standard as well as to salvage CT in MBC patients.[4,9,15–17,22–25]

The influence of different factors on the effectiveness of oral etoposide in MBC patients has not been studied profoundly, yet. There are only few data about the influence of dominant metastatic site, drug dose, and the number and type of previous CT regimens on the efectiveness of etoposide treatment. A better response to oral etoposide was achieved in soft tissues compared to visceral sites.[16,17] In the study performed by Calvert *et al.*[15] much better response was achieved in patients treated with higher daily and cumulative dose of etoposide and in patients not treated with CT before.[15] On the contrary, in the study performed by Martin *et al.*[16] no significant difference in response between patients previously treated with one or two CT regimens was found.[16] However, the patients without previous exposure to anthracyclines responded better. It is expected that due to similar mechanisms of chemoresistance, such as multidrug resistance (MDR), tumors that do not respond to anthracyclines, i.e. anthracycline-resistant tumors, are also resistant to etoposide. The aim of our study was to evaluate the response rate to oral etoposide in heavily pretreated MBC patients according to some patients' and disease characteristics.

Patients and methods

Seventy-five patients with histologically proven MBC pretreated by standard CT were enrolled in our study. All patients had at least one measurable lesion; patients with metastases in the central nervous system were excluded.

The median age of the patients was 53 years. Two-thirds of patients had a short disease-free interval from the primary treatment, less than 24 months and predominant visceral disease. More than half of patients had up to two metastatic sites, defined as the number of involved organ systems irrespective of the number of metastatic lesions in each particular organ system. All patients had previously been treated with CT, most by anthracycline-based regimens, 71% received two CT regimens prior to etoposide treatment. More than half of the patients had responded to previous CT and the response to previous anthracycline-containing schedules was high, i.e. over 60%. Patient characteristics are presented in Table 1. Etoposide was administered orally at a dose of 100 mg/day for 10 consecutive days every 3 weeks.

Patients were classified as resistant or not resistant to any CT according to the response of the metastatic disease to the agent. We considered them resistant when the best response to CT was stagnation or progressive disease and not resistant when the best response to CT was complete or partial remission. Response to treatment with oral etoposide and toxicity were categorized according to WHO criteria. The disease-free interval was defined as the time interval from the primary treatment to the time of the first recurrence and was considered short if it was shorter than 24 months. The time to disease progression (TTP) was defined as the time from the beginning of treatment with oral etoposide to the progression of the disease and survival time was defined as the time from the beginning of treatment with oral etoposide to the date of death. The same time intervals were used when presenting TTP and survival according to response to previous anthracyclines. Correlation between response to CT and different patient and disease characteristics was tested by the χ^2 test, based

Table 1. Patient characteristics

Characteristics	No. of patients	%
Total no.	75	100
Age (years)		
median	53	
range	33–73	
Disease-free interval[a]		
$\leqslant$24 months	50	67
$>$24 months	24	32
unknown	1	1
Dominant metastatic site		
soft tissues and bones	27	36
visceral organs	48	64
No. of metastatic sites		
$\leqslant$2	43	57
$>$2	32	43
Prior CT		
yes, adjuvant	9	12
yes, metastatic disease	44	59
adjuvant and metastatic	22	29
Prior exposure to anthracyclines		
no	7	9.5
yes, adjuvant	7	9.5
yes, metastatic disease	61	81
No. of previous CT schedules		
1	14	19
2	53	71
3	8	10
Response to any previous CT		
yes	41	55
no	21	28
unknown	13	17
Response to previous anthracycline-based CT		
yes	40	66
no	18	29
unknown	3	5

[a]Measured from the date of primary treatment to first recurrence.

on contingency tables. Survival curves were calculated according to the method of Kaplan–Meier[26] and the differences were tested by the log-rank test.[27]

Results

The overall response was 37% (28/75, 95% CI: 27–50%) (Table 2). The median duration of response was 9 months (range 3–22 months). There was only one complete response observed in a patient, with soft tissue metastases in the right supraclavicular fossa. The duration of complete response in this patient was 9 months. Ten patients (13.5%) had stable disease with a median duration of 5.5 months, whereas in 37 (49%) patients the disease progressed while on etoposide therapy.

Response to CT was analyzed according to the pretreatment characteristics. As presented in Table 3 the treatment was found to be more effective in patients with a longer disease-free interval, in patients with a dominant metastatic site in soft tissues and bones, and in patients with fewer metastatic sites, but the differences were not significant. However, a significantly better response was achieved in responders to any previous CT and the difference was even more pronounced in the responders to anthracycline-based CT.

The median TTP for all evaluable patients was 4.5 months (95% CI: 3.3–7.6 months) and the median survival time of all patients after the introduction of oral etoposide treatment was 12 months (95% CI: 9.6–15.6 months). The only pretreatment characteristic that significantly influenced TTP and survival was the response to previous anthracycline-based CT. The median TTP in responders to previous anthracycline-based CT was 7 months (95% CI: 4.1–8.3 months), whereas it was found to be only 2.5 months (95% CI: 1.6–3.6 months, $p = 0.0066$) in non-responders (Figure 1). The median survival time was 13.8 months (95% CI: 10.2–23 months) in responders to previous anthracycline-based CT and only 5 months (95% CI: 3.4–11.2 months, $p = 0.0072$) in non-responders (Figure 2).

The toxicity of oral etoposide was moderate. The most frequent adverse effects observed in almost all patients were alopecia and myelosuppression. Neutropenia of any grade was observed in 74% of patients overall during the treatment; however, in most of the patients (64%), it was grade 1 or 2. Only two patients developed neutropenic fever during treatment. Anemia was recorded in 55% of patients (WHO grade 1 or 2 in 50.5% and WHO grade 3 in 4.5%) and 7% of patients developed trombocytopenia (WHO grade 1 in 4% and WHO grade 3 in 3%). Oral etoposide treatment did not require discontinuation of therapy in any of our patients and none of them died due to treatment-related complications.

Table 2. Response to treatment

Response	No. of patients	%	Median duration of response (months)
Complete response	1	1	9
Partial response	27	36	9 (range 3–22)
No change	10	14	5.5 (range 2–11)
Progressive disease	37	49	

Table 3. Response to oral etoposide according to patient characteristics

Characteristics (no. of patients)	Response (%)		*p*
Disease-free interval (74)			
⩽24 months	18/50	(36)	0.66
>24 months	10/24	(42)	
Dominant metastatic site (75)			
soft tissues and bones	12/27	(44)	0.33
visceral organs	16/48	(33)	
No. of metastatic sites (75)			
⩽2	17/43	(39.5)	0.65
>2	11/32	(34.5)	
No. of previous CT schedules (75)			
1	4/14	(29)	0.26
2	19/53	(36)	
3	5/8	(62.5)	
Response to any previous CT (62)			
yes	19/41	(46)	0.04
no	4/21	(19)	
Response to anthracycline based CT (58)			
yes	20/40	(50)	0.016
no	3/18	(17)	

Discussion

According to our observations, treatment with oral etoposide seems to be an effective salvage CT in heavily pretreated breast cancer patients. As expected, the efficacy of oral etoposide depends on the predominant tumor site and tumor burden. However, the most important factor influencing the response is the response to previous anthracycline-based therapy. Our main finding is that the sensitivity to anthracyclines predicts the response to oral etoposide treatment.

The objective response rate of 37%, with a median TTP of 4.5 months, achieved in our patients is comparable with objective responses achieved by other investigators.[13–21] The objective response to oral etoposide reported by these investigators ranged from

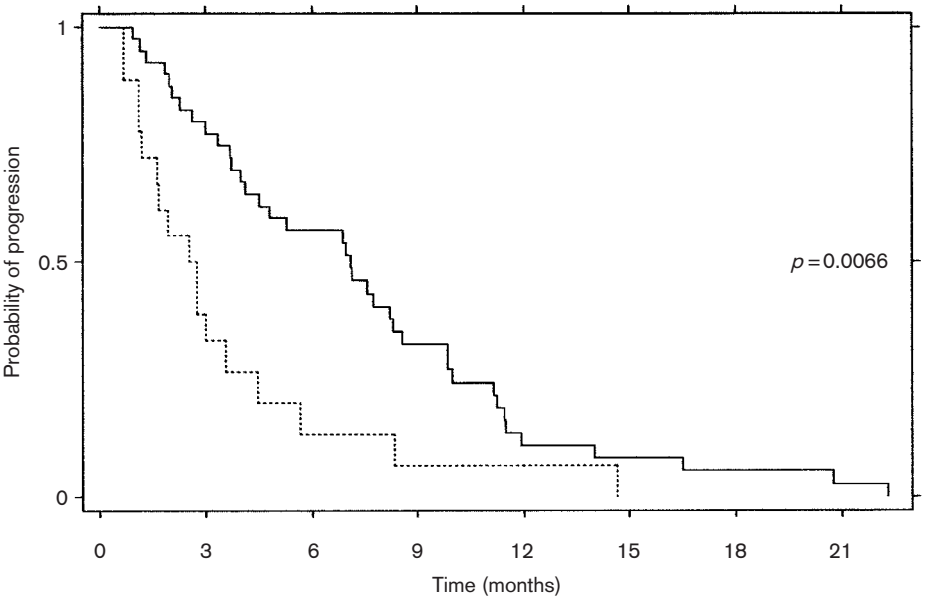

Figure 1. TTP after oral etoposide introduction by response to previous anthracyclines. Solid line, response to anthracyclines ($n=40$). Dashed line, no response to anthracyclines ($n=18$).

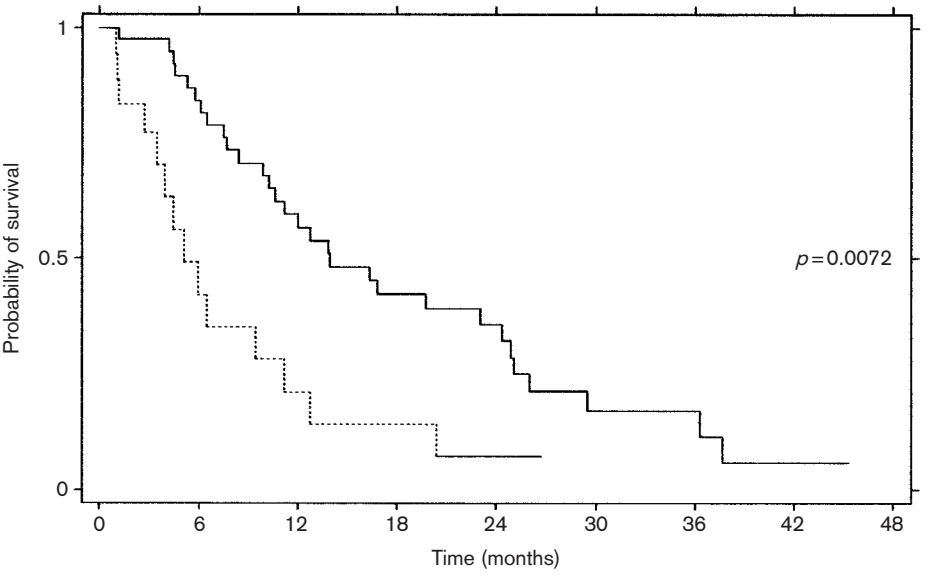

Figure 2. Survival after oral etoposide introduction by response to previous anthracyclines. Solid line, response to anthracyclines ($n=40$). Dashed line, no response to anthracyclines ($n=18$).

10 to 70%.[13–21] The response rate of 70% reported by Erkisi is surprisingly high; the reason for such a high activity could be in patient selection, all patients had been pretreated by only one CT regimen and in a dose-dense schedule of oral etoposide.[14] The response rate of only 10% reported by Calvert could be explained with a low daily and cumulative dose of oral etoposide.[15] The response rates achieved in all other trials were around 30%. The response rate achieved with oral etoposide in our patients is also comparable to the effectiveness of other commonly used salvage CT schedules, such as mitomycin and vinblastine, cisplatin and etoposide, cisplatin and ifosfamide, and to monotherapy with taxanes.[1–10] We are aware that these comparisons are only based on the reported response rates in the literature; however, a real

comparison could be based only on a prospective randomized trial.

It is already known that the effectiveness of any CT regimen in MBC depends to some extent on the number and type of previous CT regimens.[22] As a rule, the probability of response to any salvage CT is found to be lower in patients who received more previous CT regimens, especially in patients who did not respond to previous anthracycline-containing schedules. In patients previously treated with anthracyclines, particularly in anthracycline-resistant patients, the response rate to most salvage CT regimens available is lower than in anthracycline-sensitive patients.[28] Also, in the study of Martin *et al.*,[16] a higher response rate to oral etoposide was achieved in the subset of patients without previous exposure to anthracycline combinations, although some responses have been observed among the patients progressing while on doxorubicin treatment. Generally, patients who did not respond to previous CT containing most active agents are unlikely to respond to other subsequent CT agents, whatever they are. However, this is not always true. Taxanes[10] and capecitabine[29,30] are cytotoxic drugs with proven effectiveness in MBC patients who did not respond to previous anthracycline-containing CT (i.e. anthracycline-resistant patients). In addition, Nabholtz found equal response rates to docetaxel in anthracycline-resistant and non-resistant patients, whereas only a minor response to salvage CT with mytomicin and vinblastine was found in anthracycline-resistant patients in his study.[1] Therefore, we consider it is reasonable to analyze the effectiveness of other cytotoxic drugs, such as etoposide, according to response to previous CT. Findings of such studies would help us to select the best CT for the particular patients and allow them to take advantage of every possibly effective cytotoxic agent.

Our study has shown that a significantly better response (46 versus 19%) to oral etoposide with significantly longer TTP (7 versus 2.5 months) can be achieved in responders to previous performed CT and especially in patients who respond to anthracycline-containing regimens (i.e. anthracycline-sensitive patients). There are no other data on the response to oral etoposide with respect to the response to a previous anthracycline-based CT in the literature available. A better response to salvage CT with mytomicin and vinblastine in anthracycline-sensitive patients was only reported by Nabholtz.[1] Our results can be expected, since resistance to anthracyclines which is mainly due to the MDR mechanism, based on the so-called P-glycoprotein, involved in the efflux of lipophilic cytotoxic drugs out of the cell, usually means simultaneus resistance to the majority of other available cytotoxic drugs. Most of the cytotoxic drugs with a confirmed activity against breast cancer, such as doxorubicine, epidoxorubicine, mitoxantrone, vincristine, vinblastine, paclitaxel, mitomycin and also etoposide, belong to the group of lipophilic drugs.[31] Therefore, as confirmed by our and Nabholtz's results, treatment with the drugs that are a substrate for P-glycoprotein, such as etoposide, mitomycin and vinblastine, does not seem to be the best choice in anthracycline-resistant patients. However, biochemical and clinical resistance mechanisms are not necessarily equivalent. In the case of taxanes, which are also P-glycoprotein substrates, other mechanisms of resistance besides MDR seem to play a clinically important role. According to the results available, a high rate of response, approaching 50%, can be obtained by taxanes in anthracycline-resistant patients.[10] Capecitabine, an oral tumor-activated fluopyrimidine, seems to be another exciting new option for the treatment of anthracycline-resistant patients—a high rate of response was obtained in anthracycline pretreated patients in two studies.[29,30]

Our study added new information about patients who are the most appropriate candidates for salvage CT with oral etoposide. The previously published studies[13–21] only concluded that oral etoposide is an effective drug for salvage CT in MBC patients. According to our findings, salvage CT with oral etoposide is an appropriate treatment for patients who respond to previous CT, particularly to anthracyclines. In these subset of patients a fairly high rate of objective response can be achieved, while in anthracycline-resistant patients the use of taxanes and perhaps capecitabine would be preferred. The major advantage of oral etoposide over other types of salvage CT with similar effectivenes is low toxicity, apart from alopecia, and oral aplication that can be performed at home.

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