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A Retrospective Analysis of the Activity and Safety of Oral Etoposide in Heavily Pretreated Metastatic Breast Cancer Patients

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■ **Abstract:** Metastatic breast cancer (MBC) patients derive benefit from chemotherapy, but options become limited after several prior chemotherapeutic regimens. Oral etoposide (VP-16) has previously been found to be clinically active in MBC patients in phase II trials. However, with increasing availability of other drugs, etoposide use has declined in spite of its unfavorable toxicity profile probably being overestimated. We therefore evaluated the clinical benefit and safety of oral etoposide in a population of MBC patients who had failed multiple regimens of currently used therapies. Sixty-six patients with MBC previously treated with a median of eight (range 2–13) regimens of therapy were eligible for the study. Patients received 50 mg/day oral etoposide in 20-day cycles with 1-week of rest. All patients were evaluated for clinical benefit (clinical benefit rate [CBR], complete response, partial response, and disease stabilization >24 weeks), progression-free survival (PFS), overall survival (OS), and toxicities. Median PFS was 4 months, CBR was 18% (overall response rate 4%), and median OS from the start of treatment was 11 months. Little clinically significant or high-grade toxicity were observed. No patients withdrew from treatment due to etoposide-induced toxicity. The favorable clinical response, low toxicity, and low cost of the drug suggest that etoposide is a viable option for patients with heavily pretreated MBC. ■

Key Words: etoposide, heavily pretreated, metastatic breast cancer

Although metastatic breast cancer (MBC) is considered a virtually incurable disease (1), moderate sensitivity to systemic treatments and an abundance of established and emerging therapeutic options (e.g., endocrine therapy (2), anti-HER2 treatments (3–5), and chemotherapy and bevacizumab in triple negative disease (6)) have resulted in prolonged disease control and survival in a significant proportion of patients. Chemosensitivity and effective disease control usually decrease with successive rounds of treatment, and as a consequence of sub-optimal, but often permissive, performance status (PS), and lack of "in-label" therapeutic options, the clinical management of late metastatic progression is challenging. It is therefore important to identify effective treatments with favorable toxicity profiles that can still positively influence clinical outcome.

Etoposide (VP-16) is a semi-synthetic derivative of podophyllotoxin that causes cell cycle arrest during late S phase and early G2 phase (7). Clinical trials have shown that several solid tumors, including small cell lung cancer and nonsmall-cell lung cancer, are sensitive to prolonged exposure to VP-16 (8). The established recommended dose of oral VP-16 from phase I trials is 50 mg/m^2/day for 21 consecutive days of treatment, followed by 7 days off. A few phase II clinical trials in breast cancer have explored different doses and schedules of oral VP-16 from second to fifth line therapy. These trials have reported relevant but heterogeneous clinical activity but, not infrequently, poor tolerance (9). Since these trials were conducted when most of the currently available breast cancer drugs were unavailable, we sought to evaluate oral VP-16 in heavily pretreated (more than eight lines of chemotherapy) patients in the modern context.

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We therefore offered oral etoposide to 66 consecutive patients with MBC who remained eligible for chemotherapy and who had previously been exposed to at least anthracycline and taxane-based regimens, with the great majority also exposed to vinorelbine, capecitabine, and gemcitabine. Oral etoposide was administered at a dose of 50 mg/day in cycles of 20 days with 7 days of rest, and the clinical activity and safety was assessed.

MATERIALS AND METHODS

Patients

Sixty-six women with histologically confirmed MBC treated with single-agent oral etoposide between 2003 and 2012 were included in the analysis. Patient demographics, disease characteristics, prior chemotherapy, etoposide treatment, toxicity, median time to progression (TTP), and overall survival (OS) after the start of treatment were assessed. Written informed consent for VP-16 administration was obtained from all patients. The IRCC internal review board approved the off-label treatment for all patients.

All patients had received previous chemotherapy for metastatic disease; in addition, endocrine-receptor positive patients had received one or more lines of endocrine therapy and HER2-positive patients had received two or more lines of anti-HER2 treatment.

All patients had the following characteristics: relatively normal liver function (serum bilirubin 1.5× upper limit of normal (ULN), alkaline phosphatase, aspartate aminotransferase, and alanine aminotransferase 2.5× ULN or 5.0× ULN if liver metastases were present) and renal function (serum creatinine <1.5 times the ULN or a creatinine clearance of >60 mL/minute). For patient demographics, see Table 1.

Treatment

Patients received oral etoposide (50 mg/day, given as a single dose) on days 1 to 20 at home. The treatment cycle was repeated every 4 weeks until confirmed disease progression or intolerable toxicity.

Efficacy and Safety Assessment

All patients received baseline assessment that included a full medical history, full blood count and clinical chemistry, chest x-ray, and upper and lower abdominal echography, CT scan, or total-body PET. Full blood counts and clinical chemistry were repeated for each cycle. Tumor response assessment was carried out every 3–4 months unless there was clinical evidence of tumor progression.

The following outcomes were considered: objective response rate, progression free survival (PFS), clinical benefit rate (CBR), OS, and side effects. All tumor response evaluations were performed according to RECIST criteria (version 1.1). PFS was defined as the period from the start of the treatment until disease progression. OS was calculated from the start of treatment to death by any cause, or to the last date the patient was known to be alive. Objective response was defined as complete response (CR) plus partial response (PR) (10). CBR was defined as CR+PR+SD at 24 weeks.

Safety was assessed on the basis of reported adverse events and laboratory abnormalities. All toxicities were graded according to the National Cancer Institute Common Toxicity Criteria (version 3.0).

Statistics

The median PFS and OS (with 95% confidence intervals [CIs]) (11) were estimated using the Kaplan–Meier method. Response rate (RR) was calculated as the proportion of patients with CR or PR out of the total number of patients. CBR was calculated as the proportion of patients with a CR, PR, or SD lasting 24 weeks. All statistical analyses were done using the SPSS 18 software.

RESULTS

Efficacy and Activity or Oral Etoposide

The patient demographics are summarized in Table 1. All 66 patients treated with etoposide were evaluable for tumor response. There were no complete remissions and three partial remissions giving an overall RR of 4% (95% CIs 0–7%, Table 2). A total of 12 patients achieved a partial remission or disease stabilization lasting 6 months or longer, resulting in a CBR of 18% (95% CIs 4–20%, Table 2). At the time of analysis, all patients had progressed on treatment with etoposide, and 51 had died from tumor progression. Median TTP was 4 months (95% CIs 3–5 months, Fig. 1). Median OS was 11 months (95%

Table 1. Patients' Demographics

Characteristic	Number	% or range
Median age (years) at the first diagnosis of metastatic disease	51	28–79
Median age (years) at the time of treatment with VP 16	60	33–83
Stage at first diagnosis of breast cancer		
I/II	49	74
III	15	23
IV	2	3
Not evaluable	0	0
Histotype		
IDC	64	97
ILC	2	3
Others	0	0
Tumor grade		
I/II	39	59
III	22	33
Unknown	5	8
Hormone receptor status		
ER and/or PgR positive	53	80
ER and PgR negative	13	20
HER2 status		
Positive	21	32
Negative	45	68
Median disease-free interval in months	48	3–346
Metastatic site(s)		
Liver	22	33
Lung	12	18
Bone	59	89
Soft-tissue/nodes	56	84
Effusions	3	5
Central nervous system	5	8
Number of prior lines of chemotherapy for metastatic disease (median)	8	2–13

IDC, infiltrating ductal carcinoma; ILC, infiltrating lobular carcinoma; ER, estrogen receptor; PgR, progesterone receptor.

Table 2. Tumor Response to VP-16

Response	Number	Proportion (%)	95% C.I. (%)
ORR	3	4	0–7
CR	0	0	–
PR	3	4	0–7
SD	22	33	12–32
PD	41	62	29–53
NE	0	0	0
CBR	12	18	4–20

C.I., confidence interval; ORR, overall response rate (proportion of complete-CR + partial responses-PR); SD, stable disease; PD, Progressive disease; NE, not evaluable; CBR, clinical benefit rate (CR+PR+ SD lasting ≥6 months).

CIs 8–14 months, Fig. 2). The small number of patients precludes subset analysis; however, no significant differences in etoposide activity were observed according to HER2 status. It is worthwhile to notice that among the 66 patients, 5 were triple negative. The median number of previous treatments in these patients was 6 (8 in HR+ patients). None of them had

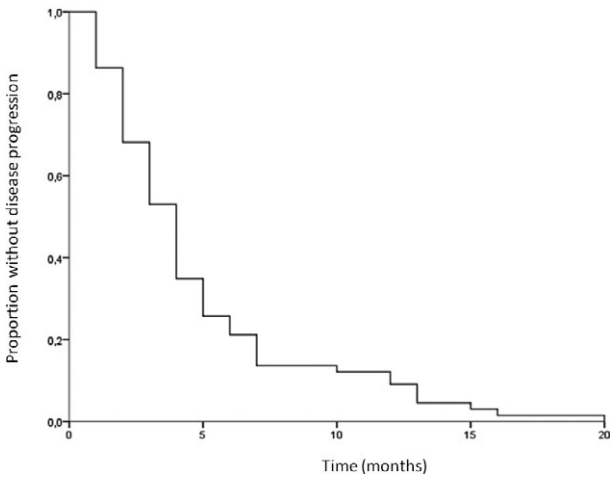

Figure 1. Kaplan–Meier curve of progression-free survival from the date of VP-16 initiation. *X*-axis: Time: months; *Y*-axis: proportion without disease progression.

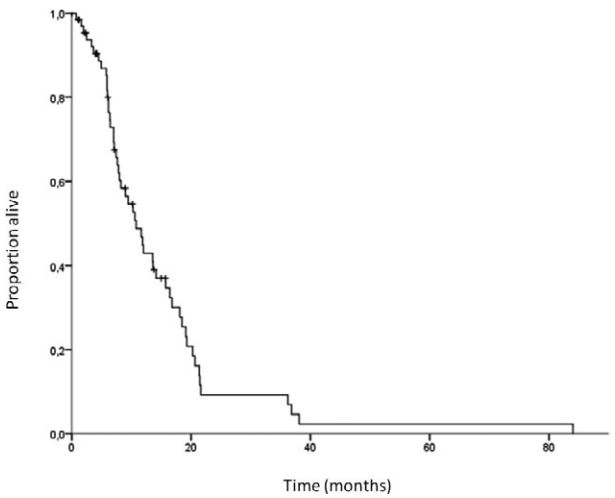

Figure 2. Kaplan–Meier curve of overall survival from the date of VP-16 initiation. *X*-axis time: months; *Y*-axis proportion alive.

clinical benefit from treatment (data not shown). The median OS in these patients was 6 months (data not shown).

Safety of Oral Etoposide

No patient discontinued treatment due to side effects or intolerance, with disease progression being the only cause of treatment interruption. Hematologic and nonhematologic toxicities are summarized in Table 3. There were no treatment-related deaths. The most common hematologic adverse events were neutropenia (21%) and anemia (25%). Most treatment-related hematologic adverse events were grade 1 or grade 2 in

Table 3. Hematologic and NonHematological Toxicities (NCI-CTC Criteria)

Toxicity	Number of patients (%)	G1-2 (%)	G3-4 (%)
Neutropenia	14 (21)	9 (14)	5 (7)
Anemia	17 (25)	10 (15)	7 (10)
Trombocytopenia	7 (10)	7 (10)	0 (0)
Diarrhea	3 (4)	3 (4)	0 (0)
Emesis	23 (34)	17 (26)	6 (8)
Liver function	2 (3)	2 (3)	0 (0)
Stomatitis	16 (24)	16 (24)	0 (0)

severity; grade 3 and grade 4 neutropenia and anemia were observed in 7% and 10% of patients, respectively. Nausea/vomiting was the most frequent nonhematologic adverse event, with an incidence of 34%. Grade 3 nausea/vomiting occurred in 8% of patients. No grade 4 nonhematologic adverse events were observed. Other treatment-related nonhematologic adverse events are summarized in Table 3.

DISCUSSION

Here we evaluate the activity of oral etoposide in women with heavily pretreated MBC. Our study population was relatively homogeneous with respect to tumor burden, number of previous chemotherapy cycles, and disease characteristics. We show that, contrary to previous reports, etoposide may play a role in the treatment of late-stage, heavily pretreated MBC without significant adverse effects.

Previous studies on the use of oral etoposide in MBC have generally investigated less heavily pretreated patients exposed to only anthracyclines and taxanes using a "classical" 50 mg/m^2/day 1-20/28 etoposide schedule. One trial (9) contained a subset of patients who were chemo-naïve and, in the trial by Erkisi et al. (12), patients were previously exposed only to CMF. Only one trial has considered a patient population with over four prior chemotherapy regimens (13). Overall, clinical response rates for etoposide range from 6% to 70%, depending on how heavy the pretreatment is (10,11,14–19). Etoposide treatment has been observed to induce hematologic toxicity, mucositis, nausea, and vomiting, although the observed toxicity was rarely G3 and G4 and the incidence varied according to the schedule used and the round of treatment.

Although comparison of the current data with these trials is difficult due to heterogeneity, comparison with the control arm of the EMBRACE trial deserves special note (20). In EMBRACE, heavily pretreated MBC patients (median number of previous chemotherapies 4, range 2–7) were randomized to receive either eribulin or a treatment of the physicians' choice (TPC). Eribulin was superior to TPC: RR was 12% versus 5%, CBR 23% versus 17%, and OS 13.1 months versus 10.6 months. Since our results are similar to the TPC arm (RR 4%, CBR 18%, OS 11 months) etoposide appears to be of only marginal interest. However, our patient population was even more heavily pretreated than those in EMBRACE and our selection criteria were less stringent. Therefore, a direct comparison between eribulin and VP-16 may be of clinical interest.

Most of the published trials have utilized etoposide at 50 mg/m^2/day or 100 mg/day. In the palliative setting, quality of life is an important issue. Although quality of life was not formally and prospectively assessed using evaluation forms, our 50 mg/day schedule resulted in good tolerance, since no patient discontinued treatment specifically due to side effects or intolerance to the agent, but due to the symptoms of progressive disease.

In conclusion, our findings indicate that frail, heavily pretreated MBC patients can be efficaciously treated with a low cost drug that has well known and easily manageable side effects, with the 50 mg/day dose an attractive option in this setting.

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