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Original article

Oral etoposide in heavily pre-treated metastatic breast cancer: A retrospective series

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ABSTRACT

Background: Patients with metastatic breast cancer (MBC) can derive clinical benefit from several subsequent lines of chemotherapy. However, in heavily pre-treated patients, agents with clinical activity, a favourable side effects profile and a convenient administration modality are preferred.
Patients and Methods: We retrospectively analyzed 110 patients with previously treated MBC, who received oral etoposide at the dose of 50 mg/day for 20 days in 28 days cycles, between 2003 and 2017. Because this was not a prospectively planned study, to describe the clinical performance of oral etoposide we adopted the approach suggested by Dzimitrowicz and colleagues (*J Clin Oncol*. 2016; 34:3511–17); Tumour Response (TR) was defined as the proportion of physician-reported clinical or imaging response; Prolonged Duration on Therapy (PDT) as the proportion of non-progressing patients whose treatment lasted more than 6 months. Furthermore, we evaluated median duration on therapy (TD) and median Overall Survival (OS) by the Kaplan Meier method.
Results: The median number of previous chemotherapy lines was 5 (range 2–8). TR, PDT, median TD and median OS were 6.4%, 18.2% 4 (range 3.5–4.5) and 10.6 (range 8.4–12.8) months respectively. Interestingly, etoposide activity was unrelated to the number of previous lines and type of metastatic involvement. Oral etoposide was well tolerated with only two patients discontinuing therapy due to toxicity.
Conclusions: In this large, single Institution, real practice analysis oral etoposide is a valuable and safe option for pre-treated metastatic breast cancer patients and might be considered in patients failing other approaches, but still suitable for chemotherapy.

1. Introduction

Mortality due to breast cancer is constantly decreasing, as a result of advances in early diagnosis and improvement in treatments [1]. However, metastatic breast cancer is still an incurable disease, with a median overall survival (OS) of 2–3 years [2]. Although a wide range of therapeutic first and second line treatment options [3] are now available (i.e. chemotherapy [2,3], endocrine therapy and CDK4/6 inhibitors [4–6] and antiHER2 agents, [7–9]), only eribulin demonstrated an improved OS in patients failing multiple lines of prior treatments [2].

Etoposide is a semi-synthetic derivative of podophyllotoxin [10]. It damages DNA, inducing single and double-strand breaks [11,12] and interfering with topoisomerase II action [13]. This leads to cells arrest in G2 phase of the cell cycle [14]. Etoposide is widely used for the treatment of several types of neoplasms [15]. Although not being frequently mentioned in breast cancer guidelines as a preferred agent, etoposide, especially in the oral formulation, has also shown activity in trials recruiting breast cancer patients [16–33]. In these trials, however, patients were treated with different doses and schedules of the compound, alone or in combination with other drugs.

In 2015, we retrospectively analyzed 66 patients who had received oral etoposide at the dose of 50 mg/day for 20 consecutive

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days, repeated every 28 days. We found that this regimen was safe and active in a population of heavily pre-treated patients [34]. In the current manuscript, we expand our retrospective analysis considering a cohort of 110 heavily pre-treated metastatic breast cancer patients treated with oral etoposide at our Institution.

1.1. Patients and methods

We retrospectively evaluated 110 women with histologically confirmed metastatic breast cancer treated between 2003 and 2017 at the Candiolo Cancer Institute. Data were obtained from medical records and include age, Performance Status (PS), histotype, grade, stage, previous treatments, site of metastatic disease. All patients had failed at least two previous lines of chemotherapy and, similarly to patients recruited in prospective trials investigating drugs in advanced lines of treatment [35], could be defined as "heavily pre-treated". The majority of our patients were previously exposed to anthracyclines or a taxane. As part of routine clinical practice, all patients with endocrine positive breast cancer had received at least one endocrine treatment and all patients with HER2 positive breast cancer according to ASCO-CAP guidelines [36] received at least one, but usually, several, anti-HER2 treatments. All our patients were still eligible for chemotherapy according to performance status, expected survival and organ function (evaluated by the treating physician on the basis of blood count, chemistry and physical examination at the beginning of each cycle). All patients signed written informed consent before the first etoposide administration as per Institutional guidelines.

Patients received oral etoposide at the dose of 50 mg/day for 20 consecutive days. Cycles were repeated every 28 days, following the schedule that we adopted in our previous retrospective work. All patients were treated with oral etoposide until progression, unacceptable toxicity or consent withdrawal. Treatment eligibility, tumour response and toxicities were evaluated by the treating physician in the context of the routine clinical practice. Patients were evaluated for symptoms or signs of clinical progression on day 1 of each cycle. Imaging (type and frequency) was performed according to local practice and patient characteristics and tumour regression, disease stability or progression were recorded in the medical records. Because of the retrospective nature of this analysis, to describe the clinical performance of oral etoposide we adopted the approach recently described by Dzimitrowitz and colleagues [37]. In particular we defined:

- Tumour response (TR): physician reported clinical or imaging response;
- Prolonged duration on therapy (PDT): duration on therapy for at least 6 months;
- Progressive Disease (PD): symptomatic deterioration or progression on routine radiological assessment.

Additionally, we evaluated median duration on therapy (TD), defined as the time between the first and the last dose of etoposide, and OS, measured from the beginning of therapy to death for any cause. We reviewed medical records and recorded hematologic toxicities, graded according to CTCAE (National Cancer Institute Common Toxicity Criteria) version 4.02.

1.2. Statistics

The median TD and OS (with 95% Confidence Intervals [CIs]) were calculated with the Kaplan– Meier method. We performed subgroup analysis using a Cox Regression model according to Hormone Receptor and HER2 status, number of previous lines (with a cut off of 3 lines) and metastatic involvement (visceral, soft tissues and CNS). All statistical analyses have been done using the SPSS 20 software.

2. Results

2.1. Activity of oral etoposide

Main characteristics of patients are summarized in Table 1. Median age at diagnosis was 51. The median number of previous chemotherapy lines for the metastatic disease was 5 (range 2–8). 71.8% of patients received previous anthracyclines, 82% received taxanes and 89% received capecitabine. Most patients (66.7%) had visceral involvement (mainly lung and/or liver), 33.3% had bone or soft tissue only disease; 10 patients (9.1%) had CNS (Central Nervous System). Patients with CNS metastasis were often symptomatic (7 out of 10 patients, 70%) and were mostly pre-treated with radiotherapy (6 out of 10 patients, 60%) or surgery (2 out of 10 patients, 20%).

110 patients received at least one dose of etoposide. 107 patients were evaluable for TR and TD; all patients were evaluable for OS. A total of 7 (6.4%) and 20 (18.2%) patients achieved a TR and a PDT, respectively (Table 2). Median TD was 4 months (C.I. 3.48–4.53) (Fig. 1), and median OS was 10.6 months (C.I. 0.44–12.84) (Fig. 2). There were no statistical differences in TD according to ER expression, HER2 overexpression and "triple-negative" status [Hazard ratio (HR) 0.74 (0.42–1.3), $p = 0.301$, HR 1.23 (0.74–2.02), $p = 0.41$, and 1.068 (0.53–2.12), $p = 0.851$, respectively]. There was no statistical difference in TD in patients who had received more than 3 previous regimens [HR 1.3 (0.74–2.6), $p = 0.307$] or who had been exposed to anthracyclines or taxanes, compared to patients who had not received these compounds. Both patients with visceral metastasis or soft tissue involvement benefited from the treatment

Table 1
Baseline Characteristics of patients.

	Number	Percentage
Median age at the first diagnosis (years)	51 (range 25–80)	
Stage at first diagnosis		
I	39	35.5
II	44	40.0
III	14	12.7
IV	10	9.1
Unknown	3	2.7
Histotype		
IDC	98	89.1
ILC	5	4.5
Others	2	1.8
Unknown	5	4.5
Grading (G)		
G1/G2	50	45.5
G3	36	32.7
Unknown	24	21.8
Hormone –receptor status		
ER+	91	82.7
PgR+	68	61.8
ER- and PgR-	9	8.2
HER2 over-expression		
HER2 positive	25	22.7
HER2 negative	85	77.3
Previous lines (*median*)	5 (range 2–8)	
Previous anthracyclines	79	71.8
Previous taxanes	90	81.8
Previous capecitabine	98	89.1
Metastatic site		
Bone – soft tissue only disease	36	33.3
Visceral (liver, lung)	72	66.7
Central nervous system	10	9.1

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