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CLINICAL TRIAL

Oral etoposide in heavily pre-treated metastatic breast cancer: results from the ESME cohort and comparison with other chemotherapy regimens

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Abstract

Introduction HER2-negative metastatic breast cancer (MBC) is a common setting in which chemotherapy could be effective even in later lines of treatment. Oral etoposide has demonstrated clinical activity in this setting in small-scale studies, but its efficacy has not been compared to that of other chemotherapy regimens.

Methods We used the ESME database (Epidemiological Strategy and Medical Economics), a real-life national French multicentre cohort of MBC patients initiating therapy between 1 January 2008 to 31 December 2014. HER2-negative MBC patients who received oral etoposide as > 3rd chemotherapy line and for more than 14 days were included. Primary objective was progression-free survival (PFS); secondary objectives were overall survival (OS), and propensity-score matched Cox models including comparison with other therapies in the same setting.

Results Three hundred forty-five out of 16,702 patients received oral etoposide and 222 were eligible. Median PFS was 3.2 months [95% CI 2.8–4] and median OS 7.3 months [95% CI 5.7–10.3]. Median PFS did not significantly differ according to the therapeutic line. The only prognostic factor for both PFS and OS was the MBC phenotype (hormone receptor-positive versus triple-negative, HR = 0.71 [95% CI 0.52–0.97], $p = 0.028$ for PFS and HR = 0.65 [0.46–0.92], $p = 0.014$ for OS). After matching for the propensity score, no differential effect on PFS or OS was observed between oral etoposide and other chemotherapy regimens administered in the same setting (HR = 0.94 [95% CI 0.77–1.15], $p = 0.55$ for PFS and HR = 1.10 [95% CI 0.88–1.37], $p = 0.40$ for OS).

Conclusion Oral etoposide retains some efficacy in selected heavily pre-treated patients with HER2-negative MBC, with the advantages of oral administration.

Keywords Etoposide · Metastatic breast cancer · Oral drug

Introduction

Breast cancer consists of a heterogeneous group of diseases characterized by different immunohistochemical subtypes, mainly classified according to Estrogen Receptor (ER), Progesteron Receptor (PR), and HER2 status [1]. Metastatic breast cancer (MBC) is the leading cause of cancer death among women worldwide [2]. The median overall survival (OS) of MBC according to immunohistochemical subtypes ranges from 14 to 50 months [1]. In HER2-negative MBC, systemic therapy consists of endocrine-based therapy for hormone-positive (HR+) MBC, and chemotherapy after

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failure of endocrine therapy or in triple-negative (TN) breast cancer [1]. The most active and recommended chemotherapy drugs in HER2-negative MBC are anthracyclines, taxanes, capecitabine, eribulin and vinorelbine [1].

Daily oral etoposide, a topoisomerase II inhibitor, has demonstrated clinical activity in MBC in small single-arm studies after failure of endocrine therapy or previous chemotherapy [3–8]. A pooled analysis study, derived from 12 studies with 483 patients, found a response rate (RR) of 18.5% [95% CI 11.5–25.5%], a clinical benefit rate (CBR) of 45.8% [95% CI 38.6–53.0%], a median progression-free survival (PFS) of 3.6 months [95% CI 2.6–4.6] and a median overall survival (OS) of 11.7 months [95% CI 9.6–13.8] [9]. These results are clinically meaningful in a heavily pretreated population. However, all of these studies included only small numbers of patients, were derived from single-center and/or retrospective analyses, and did not compare the efficacy of etoposide with that of other chemotherapy regimens.

In this study, we analysed the effectiveness of oral etoposide from the ESME database (Epidemiological Strategy and Medical Economics), a real-life cohort of MBC.

Methods

Methods, study design, patients, and treatments

Details regarding the study design of ESME MBC database (NCT03275311) and primary results have been published elsewhere [10–12]. A brief overview of ESME MBC database is provided below. The global aim of the ESME research program is the centralization of real-life data on oncology care for epidemiological research purposes. The first disease addressed by ESME was MBC using a dynamic retrospective data collection called ESME MBC Cohort. The primary objective is to describe clinical features, treatment patterns and outcomes over a period of years through reports available in the electronic medical records, pharmacy records and inpatient stays. This population-based prospective cohort is designed to select all consecutive patients who initiate anticancer therapy for metastatic breast carcinoma in 1 of the 18 French comprehensive cancer centers (FCCC) participating in the ESME Research program, from 1 January 2008 to 31 December 2014. Diagnostic, therapeutic and follow-up data (demographics, primary tumor, metastatic disease, treatment patterns and vital status) were collected throughout the course of the disease. To date, the cohort comprises more than 16,700 patients initially treated for metastatic disease from 2008 to 2014 with possible patient follow-up until November 2016.

The primary objective of the present study was to assess PFS, defined as the time between the date of the new systemic line introduction and the date of first disease progression or death, in HER2-negative MBC patients who initiated oral etoposide as third-line or beyond chemotherapy among women.

Secondary objectives were determination of OS, defined as the time between the date of the new systemic line introduction and the time of death (from any cause), and descriptive and prognostic analyses. The following patients were excluded: HER2-positive and unknown HER2-status MBC patients, patients who received etoposide less than 14 days and/or, patients received etoposide as first- or second-line systemic therapy and men were excluded.

Propensity score matching methods

Covariates selected to calculate propensity scores

Available guidance suggests that covariates used to estimate propensity scores (PS) should focus on those that may impact the outcome alone or both the outcome and the treatment assigned [13]. Patient characteristics considered important for balancing treatment groups were established a priori and were used to calculate propensity scores.

Propensity score calculation and matching

PS were calculated for all selected patients by fitting a multivariate logistic regression model that included the selected covariates (Supplementary Appendix A) as predictive variables and the treatment received ('Oral etoposide' or 'Never oral etoposide') as the dependent variable. Since patient characteristics, initial disease, metastatic disease and overall survival or PFS are highly dependent on the chemotherapy line, all analyses were conducted separately according to treatment lines (3rd line, 4th line, 5th line, 6th line and 7th line and beyond).

After fitting the logistic regression model in each treatment line stratum, the logit transform of PS for all patients was stored for matching. After estimating PS, the degree of overlap of the patients' PS from the two treatment groups was assessed. This was studied by reviewing histograms and distributions of the logit-transformed PS (LTPS) in each treatment group, and by assessing the mean, standard deviation (SD), median, interquartile range, and minimum and maximum values within each group.

Patients from the 'Oral etoposide' group were matched with patients from the 'Never oral etoposide' group according to the treatment line. When matching without replacement, a patient from the 'Never oral etoposide' group who had already been matched to an 'Oral etoposide' patient for a defined treatment line was no longer eligible for matching to another 'Oral etoposide' patient for another treatment line.

Matching was performed by the *nearestneighbor matching* algorithm with a 1:1 ratio [14].

Finally, all treatment lines strata were grouped for the final analysis.

Statistical methods

The primary objective was PFS and the main secondary objective was OS. PFS and OS were both evaluated from the date of the treatment line considered. PFS, OS and hazard ratios (HRs) were estimated by using Cox proportional hazards models comprising matching, in which the hazard of death was regressed on the treatment received. All statistical analyses were performed with R version 9.4.2 [15] and Match It package. Statistical significance was defined by a two-tailed p value < 0.05. Comparisons of survival HRs between treatment groups were reported with point estimates and 95% confidence intervals (CIs).

Results

Patient characteristics

Among the 16,702 patients included in this database at the cut-off, 345 patients received oral etoposide, and 222 patients were finally retained considering exclusion criteria (Flow chart, Fig. 1). Forty-nine percent of patients received oral etoposide as third- or fourth-line of systemic therapy, while 50.9% of patients received oral etoposide after the fourth line of systemic therapy (Table 1). Median follow-up was 30.3 months (range 1–67 months).

Characteristics of patients who received oral etoposide are shown in Table 1. Patients who received oral etoposide comprised a significantly higher proportion of triple-negative (TN) MBC (25.2% vs. 14.8%, $p < 0.0001$), de novo MBC or early onset metastatic relapse after primary treatment-defined by the interval between diagnosis of primary tumor and first metastatic recurrence less than 6 months (13.5% vs. 24.2% $p < 0.0001$) and a lower rate of visceral metastasis at metastatic diagnosis (46.8% vs. 54.8%, $p = 0.021$) compared to patients who received other systemic treatments.

PFS and OS for patients treated with oral etoposide and comparison with other chemotherapy regimens

Median PFS was 3.2 months [95% CI 2.8–4.0] and median OS was 7.3 months [95% CI 5.7–10.3] for all patients treated with etoposide, including all lines of treatment (Fig. 2a, c). The PFS was 4.4 months [95% CI 3.2–6.0] for patients treated in the third line while PFS after subsequent line and OS were shorter (between 2.7 and 3.2 months) and globally similar regardless of the line of treatment (Table 2).

The only prognostic factor for both PFS and OS identified in the cohort of patients treated with oral etoposide was the MBC phenotype (HR + vs. TN, HR = 0.71 [95% CI 0.52–0.97], $p = 0.028$ for PFS and HR = 0.65 [0.46–0.92], p = 0.014 for OS, Fig. 2b, d) and age at diagnosis of MBC for OS ($p = 0.019$) but not for PFS ($p = 0.15$).Tumor grade, number of metastatic sites, presence of visceral metastases, disease-free interval, and line of treatment were not statistically significant prognostic factors for PFS and OS (Table 3).

We constructed a propensity score to account for the differential prescription of oral etoposide versus other chemotherapy/targeted therapy regimens. Other chemotherapy or targeted therapy regimens, administered in more than 2% of 'Never oral etoposide' patients were anthracycline-based chemotherapy (24%), capecitabine (19%), eribulin (16%) vinorelbine (14%) (intra-venous or oral), paclitaxel (11%), oral cyclophosphamide (13%), gemcitabine (8%), everolimus-based endocrine therapy (6%) and carboplatin (2%). After matching for propensity

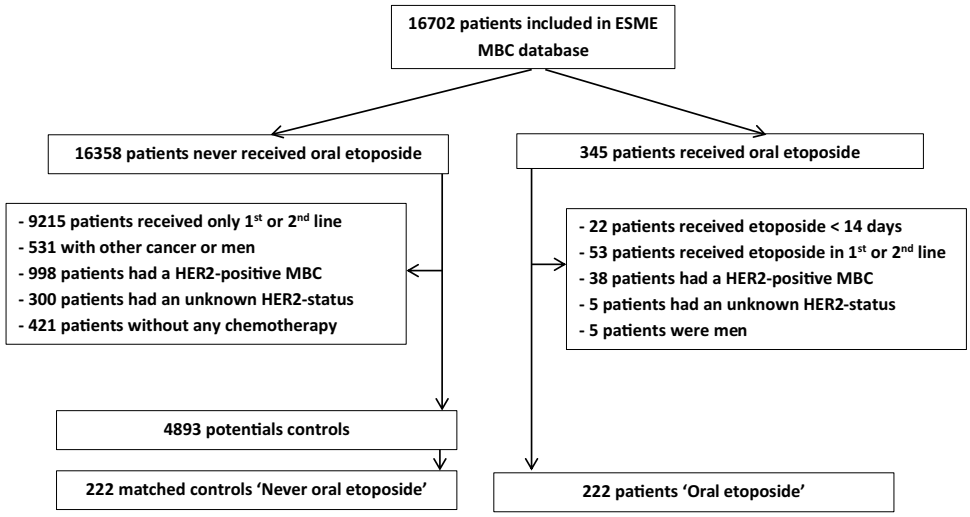

Fig. 1 Flow diagram of patients treated with etoposide in the ESME database

Table 1 Patient characteristics at metastatic relapse

	Oral etoposide $N=222$		Never oral etoposide $N=4893$		p-value
	n	%	n	%	
Phenotype					
Triple-negative	56	25.2	725	14.8	< 0.0001
Hormone receptor-positive	166	74.8	4168	85.2	
SBR grade at diagnosis					
Grade I	13	5.9	348	7.2	0.71
Grade II	95	42.8	2204	45.0	
Grade III	94	42.3	1899	38.8	
NA	20	9.0	442	9.0	
Age at diagnosis of MBC					
< 50 years	67	30.2	1330	27.2	0.33
≥ 50 years	155	69.8	3563	72.8	
Disease-free interval					
< 6 months	30	13.5	1182	24.2	0.001
6–60 months	96	43.2	1732	35.5	
≥ 60 months	96	43.2	1967	40.3	
Number of metastatic sites at diagnosis					
One	136	61.3	2691	55.0	0.066
Two or more	86	38.7	2202	45.0	
Presence of bone metastasis					
No	112	50.5	1916	39.2	0.001
Yes	110	49.5	2976	60.8	
Presence of visceral metastasis					
No	118	53.2	2213	45.2	0.021
Yes	104	46.8	2678	54.8	
Other metastasis					
No	128	57.7	3138	64.2	0.049
Yes	94	42.3	1753	35.8	
Number of lines of systemic therapy					
3	52	23.4	–	–	
4	57	25.7	–	–	
5	36	16.2	–	–	
6	34	15.3	–	–	
7	20	9.0			
≥ 8	23	10.4	–	–	

score, no differential treatment effect on PFS or OS was observed between oral etoposide and other treatments (HR = 0.94, 95% CI [0.77–1.15], $p = 0.55$ for PFS and HR = 1.10 95% CI [0.88–1.37], $p = 0.40$ for OS) (Fig. 3). No significant differential effect on PFS or OS was observed according to hormone receptor status (Fig. 4): HR + subgroup (HR = 1.00 95% CI [0.79–1.26], $p = 0.97$ for PFS, HR = 1.18, 95% CI [0.91–1.52], $p = 0.22$ for OS); TN subgroup (HR = 0.72, 95% CI [0.48–1.08] for PFS, $p = 0.09$), HR = 0.88 95% CI [0.58–1.34], $p = 0.56$ for OS).

Discussion

This study shows that oral etoposide achieves clinically meaningful PFS and OS in heavily pre-treated MBC patients and, for the first time, this study highlights that the effectiveness of oral etoposide in terms of outcome is similar to that obtained with most other forms of active chemotherapy and targeted therapy.

Single-agent chemotherapy is the standard of care in MBC, especially in later lines, to improve quality of life

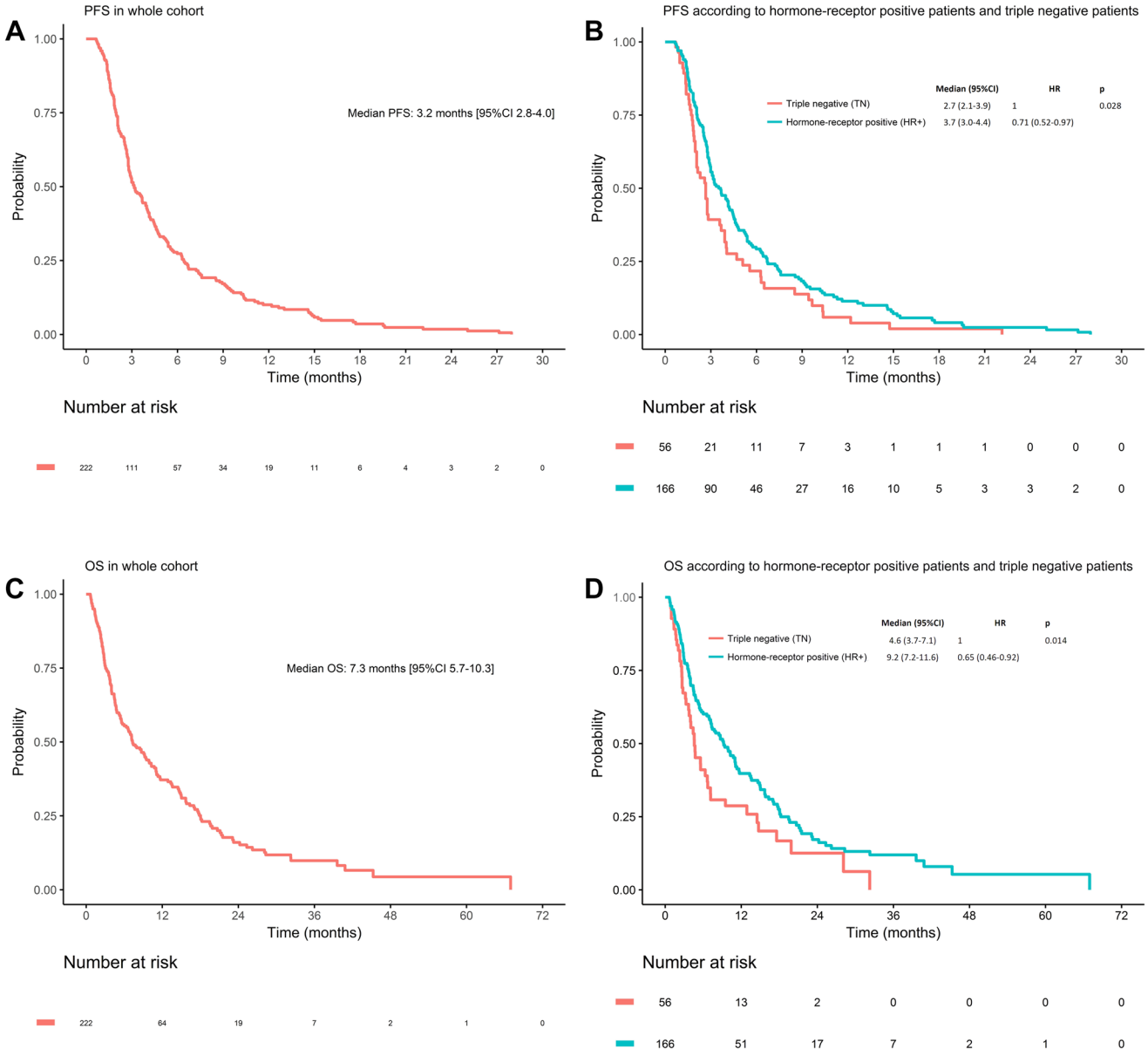

Fig. 2 Progression-free survival (PFS) and overall survival (OS) for patients treated by oral etoposide in the overall population and in hormone receptor-positive or triple-negative patients. **a** PFS in overall cohort. **b** PFS in hormone receptor-positive patients and triple-negative patients. **c** OS in overall cohort. **d** OS in hormone receptor-positive patients and triple-negative patients

Table 2 Progression-free survival and overall survival for patients treated by oral etoposide according to line of treatment

Lines of systemic therapy	*N*	Progression-free survival		Overall survival	
		Events	Median (months) (95% CI)	Events	Median (months) (95% CI)
3	52	48	4.4 (3.2–6.0)	43	7.2 (5.6–15.8)
4	57	56	3.2 (2.7–4.7)	44	10.2 (4.7–16.3)
5	36	34	2.8 (2.1–4.8)	30	5.3 (2.9–12.9)
6	34	31	3.0 (2.8–5.8)	23	7.1 (5.2–15.7)
≥ 7	43	42	2.7 (1.9–4.5)	32	7.7 (3.9–11.0)

Table 3 Prognostic factors for progression-free survival (PFS) and overall survival (OS)

	n	PFS			OS		
		HR	95% CI	*P*	HR	95% CI	*p*
Phenotype							
Triple-negative	56	1		0.029	1		0.015
Hormone receptor-positive	166	0.71	[0.52; 0.97]		0.65	[0.46; 0.92]	
SBR grade at diagnosis							
Grade I	13	1		0.59	1		0.60
Grade II	95	0.67	[0.38; 1.21]		0.85	[0.44; 1.66]	
Grade III	94	0.74	[0.41; 1.33]		1.07	[0.55; 2.06]	
NA	20	0.67	[0.33; 1.36]		1.01	[0.45; 2.25]	
Age at diagnosis of MBC							
< 50 years	67	1		0.15	1		0.019
≥ 50 years	155	0.80	[0.59; 1.08]		0.68	[0.49; 0.94]	
Disease-free interval (months)							
< 6	30	1		0.82	1		0.40
6–60	96	1.07	[0.70; 1.65]		0.88	[0.55; 1.40]	
≥ 60	96	0.98	[0.64; 1.50]		0.75	[0.47; 1.19]	
Number of metastatic sites at diagnosis							
One	136	1		0.73	1		0.46
Two or more	86	1.05	[0.80; 1.39]		1.12	[0.83; 1.53]	
Presence of bone metastasis							
No	112	1		0.43	1		0.39
Yes	110	0.90	[0.68; 1.17]		0.88	[0.65; 1.18]	
Presence of visceral metastasis							
No	118	1		0.71	1		0.55
Yes	104	0.95	[0.72; 1.25]		1.1	[0.81; 1.48]	
Other metastasis							
No	128	1		0.46	1		0.66
Yes	94	1.11	[0.84; 1.46]		1.07	[0.79; 1.45]	
Number of lines of systemic therapy							
3	52	1		0.34	1		0.71
4	57	1.29	[0.88; 1.90]		0.94	[0.61; 1.43]	
≥ 5	113	1.27	[0.90; 1.79]		1.09	[0.75; 1.58]	

[1]. Oral etoposide is a relatively old drug, not currently recommended in MBC by ESO-ESMO ABC 4 [1] or NCCN guidelines. Nonetheless, several studies have demonstrated interesting clinical activity of oral etoposide in heavily pre-treated patients [3–6, 9, 16–19], a commonly observed situation due to the prevalence of MBC, with the advantage of an oral drug regimen (especially avoiding intravenous injection and hospitalization). However, these studies did not compare oral etoposide with other chemotherapy regimens. In the present study, oral etoposide appeared to have a comparable efficacy to that of other drugs, including intravenous or oral drugs considered to be standard treatments in MBC, such as capecitabine, paclitaxel, eribulin or anthracycline.

The relatively low PFS and OS must be interpreted in the context of a heavily pre-treated patient cohort, in which the median PFS is generally reported to be less than 4 months, even in the case of effective treatment, as reported in the phase 3 trial of eribulin, in which patients had received between two and five previous chemotherapy regimens [20] (median PFS 3.7 months [95% CI 3.3–3.9] for eribulin versus 2.2 months [95% CI 2.1–3.4] for other drugs).

Oral daily etoposide is a metronomic chemotherapy, defined as administration of a minimally toxic dose according to a frequent dosing schedule. Metronomic chemotherapy acts via additional mechanisms of action, as it may have antiangiogenic effect and trigger an antitumor immune response [21, 22]. In advanced breast cancer, metronomic chemotherapy has been shown to induce disease control with a lower incidence of adverse events compared to conventional maximum tolerated dose chemotherapy [21, 23]. Although it has not been formally demonstrated, administration of oral etoposide after conventional chemotherapy may

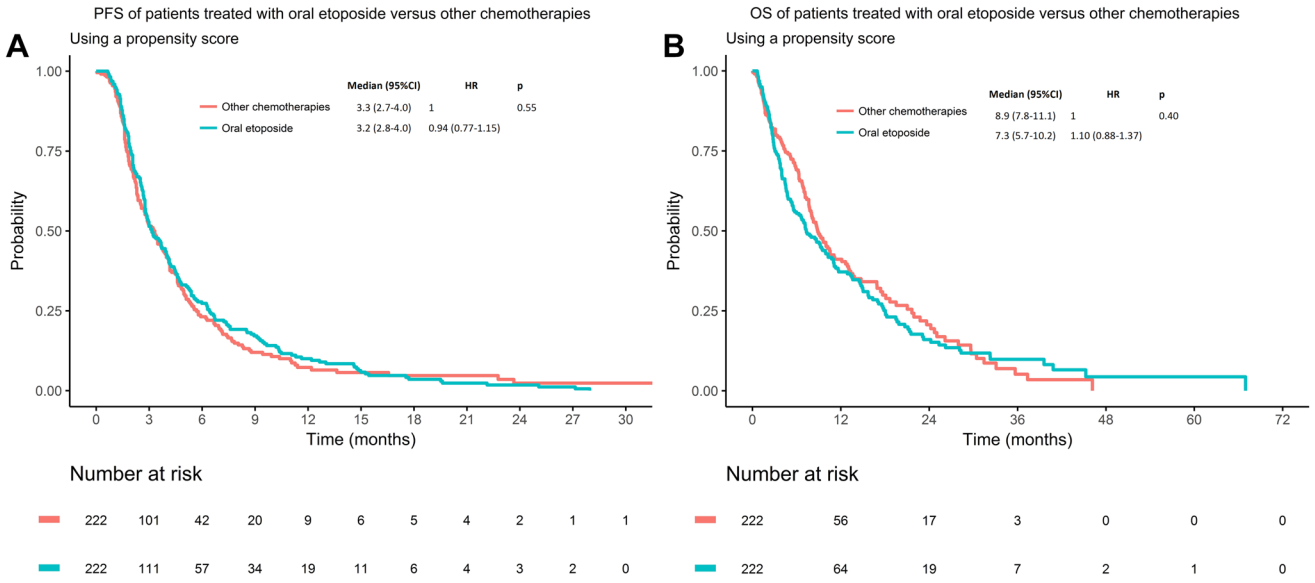

Fig. 3 Progression-free survival (**a**) and overall survival (**b**) in patients treated with oral etoposide versus other chemotherapy regimens, using a propensity score

therefore be effective as a result of the effects of metronomic chemotherapy.

ESME MBC database included 3 data source: patient database, treatment database and hospitalisation database. For the present study, only patient database has been used, therefore, this study does not provide information about cycle duration, daily dose (mg/m^2) and number of days of treatment per cycle. Oral etoposide dose and dosing schedule varied in previously published studies, but the most common regimen was 50 mg/m^2 daily for 21 consecutive days, every 28 days [3–6, 16–18].The most common grade 3–4 toxicities with oral etoposide reported in a pooled-analysis were neutropenia (19.7%), including febrile neutropenia (7.5%), anemia (5.5%), thrombocytopenia (3.7%), nausea/gastrointestinal toxicity (6.2%) and mucositis (2.2%), while the most common grade 1–2 toxicities, other than cytopenia, were mucositis (31.8%) and nausea/gastrointestinal toxicity (59%) [9].

An important question is whether MBC patients really benefit from subsequent lines of chemotherapy. A objective benefit has been suggested in several studies [24–26], reporting a higher OS for patients treated with later-line chemotherapy, with at least 10% of partial responses even after the 5th line [26], but not all patients will benefit from later treatment, especially those with a history of previous chemoresistance [24, 25]. Importantly, a gain of PFS in response to later lines of treatment is correlated with an OS benefit [27–29], although this surrogate marker is only moderately correlated with OS [30, 31]. Jagodic et al. [8] reported that a significantly better response to oral etoposide was achieved in patients who had responded to previous lines of chemotherapy (46 vs. 19%, $p=0.04$), especially anthracyclines (50 vs. 17%, $p=0.016$).

This study has several limitations, mainly related to the method of data collection in the ESME MBC database: the low number of patients treated by etoposide, the precise drug regimen (duration, dosage, etc...) and tumor response are not reported here (the variables populated in the database do not allow to assess retrospectively the tumor response to the treatment according to the standard guidelines RECIST). Oral etoposide was also compared with various treatment regimens, reflecting heterogeneous clinical settings. The propensity score was based on characteristics assessed at the time of metastatic recurrence, and not at the time of administration of etoposide, and does not include certain well-known prognostic factors of MBC, such as performance status, serum albumin or lactate dehydrogenase. However, it is possible that oral etoposide may have been prescribed in patients who were not suitable for intravenous chemotherapy, or in whom MBC was already resistant to most forms of standard chemotherapy, in which case, oral etoposide-treated patients may actually have a more favorable prognosis than that reported here.

In conclusion, oral etoposide is an effective drug in heavily pre-treated patients with HER2-negative MBC, with the advantage of oral administration, low cost and known toxicity.

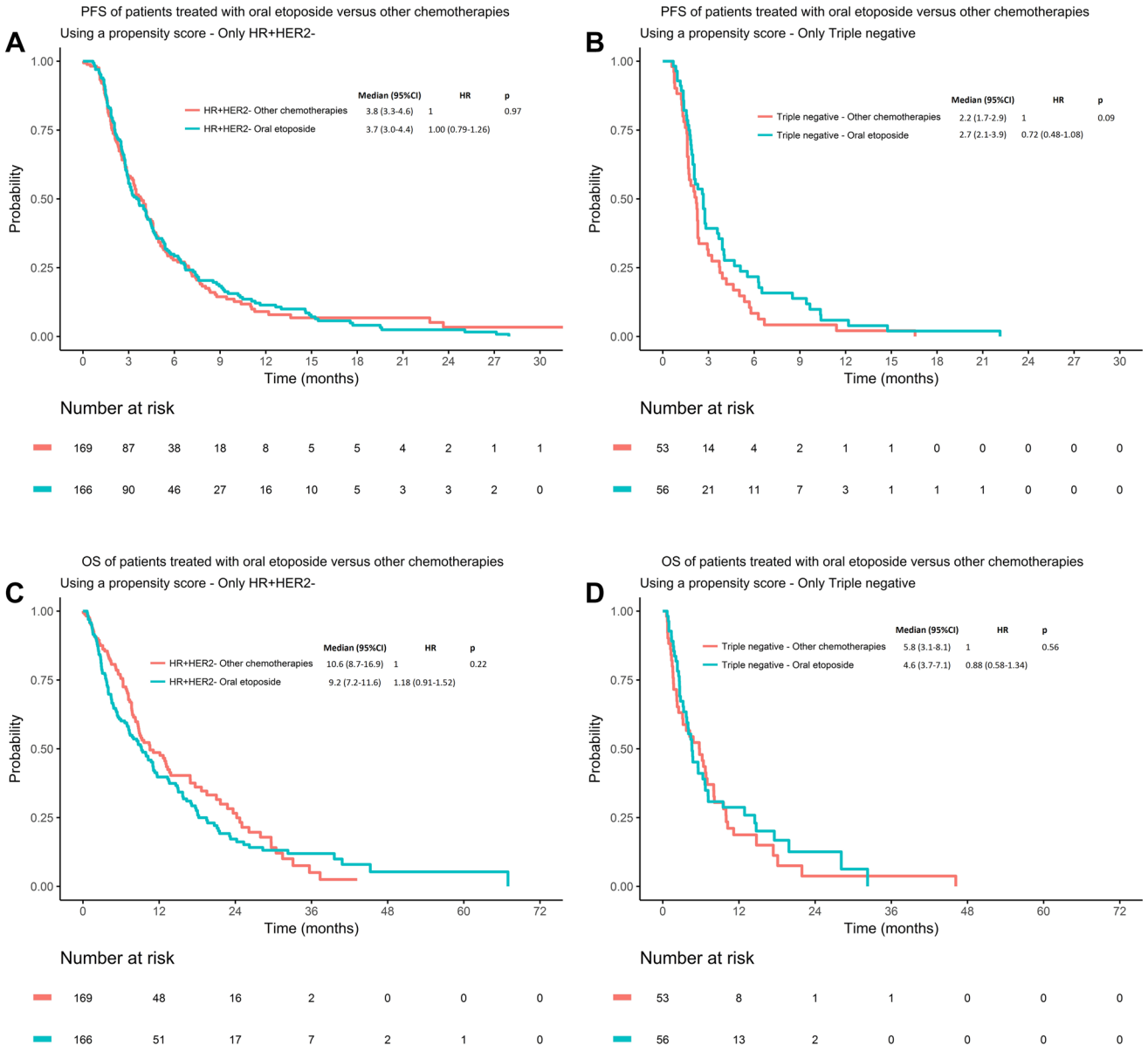

Fig. 4 Progression-free survival (**a, b**) and overall survival (**c, d**) in patients treated with oral etoposide versus other chemotherapy regimens, using a propensity score, according to hormone receptor status. **a** PFS in hormone receptor-positive (HR+) patients. **b** PFS in triple-negative (TN) patients. **c** OS in in hormone receptor-positive (HR+) patients. **d** OS in triple-negative (TN) patients

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval The present analysis was approved by an independent ethics committee (Comité De Protection Des Personnes Sud-Est II- 2015-79). No formal dedicated informed consent was required but all patients had approved the re-use of their electronically recorded data. In compliance with French regulations, the ESME MBC database was authorized by the French data protection authority (Authorization No. 1704113).

References

1. Cardoso F, Senkus E, Costa A et al (2018) 4th ESO-ESMO International Consensus Guidelines for Advanced Breast Cancer (ABC 4)†. Ann Oncol 29:1634–1657. https://doi.org/10.1093/annonc/mdy192
2. Torre LA, Bray F, Siegel RL et al (2015) Global cancer statistics, 2012. CA Cancer J Clin 65:87–108. https://doi.org/10.3322/caac.21262
3. Pusztai L, Walters RS, Valero V et al (1998) Daily oral etoposide in patients with heavily pretreated metastatic breast cancer. Am J Clin Oncol 21:442–446
4. Atienza DM, Vogel CL, Trock B, Swain SM (1995) Phase II study of oral etoposide for patients with advanced breast cancer. Cancer 76:2485–2490
5. Nesković-Konstantinović ZB, Bosnjak SM, Radulović SS, Mitrović LB (1996) Daily oral etoposide in metastatic breast cancer. Anticancer Drugs 7:543–547
6. Martín M, Lluch A, Casado A et al (1994) Clinical activity of chronic oral etoposide in previously treated metastatic breast cancer. J Clin Oncol 12:986–991. https://doi.org/10.1200/JCO.1994.12.5.986
7. Valabrega G, Berrino G, Milani A et al (2015) A retrospective analysis of the activity and safety of oral Etoposide in heavily pretreated metastatic breast cancer patients. Breast J 21:241–245. https://doi.org/10.1111/tbj.12398
8. Jagodic M, Cufer T, Zakotnik B, Cervek J (2001) Selection of candidates for oral etoposide salvage chemotherapy in heavily pretreated breast cancer patients. Anticancer Drugs 12:199–204
9. Voutsadakis IA (2018) A systematic review and pooled analysis of studies of oral etoposide in metastatic breast cancer. Eur J Breast Health 14:10–16. https://doi.org/10.5152/ejbh.2017.3563
10. Delaloge S, Pérol D, Courtinard C et al (2016) Paclitaxel plus bevacizumab or paclitaxel as first-line treatment for HER2-negative metastatic breast cancer in a multicenter national observational study. Ann Oncol 27:1725–1732. https://doi.org/10.1093/annonc/mdw260
11. Gobbini E, Ezzalfani M, Dieras V et al (2018) Time trends of overall survival among metastatic breast cancer patients in the real-life ESME cohort. Eur J Cancer 96:17–24. https://doi.org/10.1016/j.ejca.2018.03.015
12. Jacquet E, Lardy-Cléaud A, Pistilli B et al (2018) Endocrine therapy or chemotherapy as first-line therapy in hormone receptor-positive HER2-negative metastatic breast cancer patients. Eur J Cancer 95:93–101. https://doi.org/10.1016/j.ejca.2018.03.013
13. Austin PC (2008) A critical appraisal of propensity-score matching in the medical literature between 1996 and 2003. Stat Med 27:2037–2049. https://doi.org/10.1002/sim.3150
14. Ming K, Rosenbaum PR (2000) Substantial gains in bias reduction from matching with a variable number of controls. Biometrics 56:118–124
15. R Core Team (2017) R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna
16. Giannone G, Milani A, Ghisoni E et al (2018) Oral etoposide in heavily pre-treated metastatic breast cancer: a retrospective series. Breast 38:160–164. https://doi.org/10.1016/j.breast.2018.01.006
17. Saphner T, Weller EA, Tormey DC et al (2000) 21-day oral etoposide for metastatic breast cancer: a phase II study and review of the literature. Am J Clin Oncol 23:258–262
18. Palombo H, Estapé J, Viñolas N et al (1994) Chronic oral etoposide in advanced breast cancer. Cancer Chemother Pharmacol 33:527–529
19. Yuan P, Di L, Zhang X et al (2015) Efficacy of oral etoposide in pretreated metastatic breast cancer: a multicenter phase 2 study. Medicine (Baltimore) 94:e774. https://doi.org/10.1097/MD.0000000000000774
20. Cortes J, O'Shaughnessy J, Loesch D et al (2011) Eribulin monotherapy versus treatment of physician's choice in patients with metastatic breast cancer (EMBRACE): a phase 3 open-label randomised study. Lancet 377:914–923. https://doi.org/10.1016/S0140-6736(11)60070-6
21. Munzone E, Colleoni M (2015) Clinical overview of metronomic chemotherapy in breast cancer. Nat Rev Clin Oncol 12:631–644. https://doi.org/10.1038/nrclinonc.2015.131
22. Cazzaniga ME, Dionisio MR, Riva F (2017) Metronomic chemotherapy for advanced breast cancer patients. Cancer Lett 400:252–258. https://doi.org/10.1016/j.canlet.2016.12.019
23. Cardoso F, Colleoni M, Di Leo A et al (2016) Oral chemotherapy in advanced breast cancer: expert perspectives on its role in clinical practice. Cancer Treat Commun 6:S1–S10. https://doi.org/10.1016/S2213-0896(16)06001-1
24. Palumbo R, Sottotetti F, Riccardi A et al (2013) Which patients with metastatic breast cancer benefit from subsequent lines of treatment? An update for clinicians. Ther Adv Med Oncol 5:334–350. https://doi.org/10.1177/1758834013508197
25. Planchat E, Abrial C, Thivat E et al (2011) Late lines of treatment benefit survival in metastatic breast cancer in current practice? Breast 20:574–578. https://doi.org/10.1016/j.breast.2011.07.010
26. Tacca O, LeHeurteur M, Durando X et al (2009) Metastatic breast cancer: overall survival related to successive chemotherapies. What do we gain after the third line? Cancer Invest 27:81–85. https://doi.org/10.1080/07357900802290580
27. Beauchemin C, Cooper D, Lapierre M-È et al (2014) Progression-free survival as a potential surrogate for overall survival in metastatic breast cancer. Oncol Targets Ther 7:1101–1110. https://doi.org/10.2147/OTT.S63302
28. Adunlin G, Cyrus JWW, Dranitsaris G (2015) Correlation between progression-free survival and overall survival in metastatic breast cancer patients receiving anthracyclines, taxanes, or targeted therapies: a trial-level meta-analysis. Breast Cancer Res Treat 154:591–608. https://doi.org/10.1007/s10549-015-3643-5
29. Liu L, Chen F, Zhao J, Yu H (2016) Correlation between overall survival and other endpoints in metastatic breast cancer with second- or third-line chemotherapy: Literature-based analysis of 24 randomized trials. Bull Cancer 103:336–344. https://doi.org/10.1016/j.bulcan.2016.01.002
30. Burzykowski T, Buyse M, Piccart-Gebhart MJ et al (2008) Evaluation of tumor response, disease control, progression-free survival, and time to progression as potential surrogate end points in metastatic breast cancer. J Clin Oncol 26:1987–1992. https://doi.org/10.1200/JCO.2007.10.8407
31. Sherrill B, Amonkar M, Wu Y et al (2008) Relationship between effects on time-to-disease progression and overall survival in studies of metastatic breast cancer. Br J Cancer 99:1572–1578. https://doi.org/10.1038/sj.bjc.6604759

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