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Real-world Evaluation of Oral Vinorelbine in the Treatment of Metastatic Breast Cancer: An ESME-MBC Study

PIERRE HEUDEL[1], SUZETTE DELALOGE[2], DAMIEN PARENT[3], NICOLAS MADRANGES[4], CHRISTELLE LEVY[5], FLORENCE DALENC[6], ETIENNE BRAIN[7], LIONEL UWER[8], VERONIQUE D'HONDT[9], PAULE AUGEREAU[10], AUDREY MAILLIEZ[11], CHRISTOPHE PERRIN[12], JEAN-SEBASTIEN FRENEL[10], MARIE-PAULE SABLIN[7], MARIE-ANGE MOURET-REYNIER[13], THOMAS VERMEULIN[14], JEAN-CHRISTOPHE EYMARD[3], THIERRY PETIT[15], JEAN-MARC FERRERO[16], SILVIA ILIE[17], ANTHONY GONCALVES[18], GAËLLE CHENUC[19], MATHIEU ROBAIN[20], GAËTANE SIMON[20] and DAVID PEROL[21]

[1]Medical Oncology Department, Centre Léon Bérard, Lyon, France;
[2]Medical Oncology Department, Institut Gustave Roussy, Villejuif, France;
[3]Medical Oncology Department, Institut Jean Godinot, Reims, France;
[4]Medical Oncology Department, Institut Bergonié, Bordeaux, France;
[5]Medical Oncology Department, Centre François Baclesse, Caen, France;
[6]Medical Oncology Department, Institut Claudius Regaud, IUCT-Oncopole, Toulouse, France;
[7]Medical Oncology Department, Institut Curie, Paris, France;
[8]Medical Oncology Department, Institut de Cancérologie de Lorraine, Vandoeurvre-lès-Nancy, France;
[9]Medical Oncology Department, Institut du Cancer de Montpellier, Parc Euromédecine, Montpellier, France;
[10]Medical Oncology Department, Institut de Cancérologie de l'Ouest, Saint-Herblain, France;
[11]Medical Oncology Department, Centre Oscar Lambret, Lille, France;
[12]Medical Oncology Department, Centre Eugène Marquis, Rennes, France;
[13]Medical Oncology Department, Centre Jean Perrin, Clermont-Ferrand, France;
[14]Medical Oncology Department, Centre Henri Becquerel, Rouen, France;
[15]Medical Oncology Department, Centre Paul Strauss, Strasbourg, France;
[16]Medical Oncology Department, Centre Antoine Lacassagne, Nice, France;
[17]Medical Oncology Department, Centre Georges-François Leclerc, Dijon, France;
[18]Medical Oncology Department, Institut Paoli-Calmettes, Marseille, France;
[19]Capionis, Bordeaux, France;
[20]Unicancer, Paris, France;
[21]Biostatistics Department, Centre Léon Bérard, Lyon, France

Abstract. *Background/Aim: Vinorelbine is indicated for use in the treatment of MBC as a single agent or in combination but there is little real world data on this molecule and even less on its oral form. We exploited the Unicancer Epidemiology Strategy Medical-Economics (ESME) metastatic breast cancer (MBC) database to investigate current patterns of use of oral vinorelbine (OV), as well as outcomes of patients receiving this drug. Patients and Methods: Data were collected retrospectively from women and men treated for MBC between 2008 and 2014 at one of 18 French Comprehensive Cancer Centres. The efficacy of OV was evaluated in terms of progression-free (PFS) and overall survival (OS) and treatment duration. The population and patterns of OV usage were also described. Results: A total of 1806 patients (11% of the ESME MBC database) were included in this analysis. OV was prescribed as monotherapy (46%) or in combination (29%), especially with capecitabine. mainly in later treatment lines. Median PFS was 3.3 months: 2.9 months for single agent, 3.6 months for combination therapy. Median OS was 40.9 months. Conclusion: Real-world data offer complementary results to the data from traditional clinical trials, but they concern a much larger population. In this ESME MBC cohort, OV was*

Correspondence to: Pierre Heudel, Medical Oncology Department, Centre Léon Bérard, 28, rue Laennec, 69373 Lyon cedex 08, France. Tel: +33 0478782952, e-mail: PierreEtienne.HEUDEL@lyon.unicancer.fr

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only prescribed to a small subset of MBC patients. OV was mainly given as single agent to patients with heavily pre-treated MBC; less commonly, it was co-administered with capecitabine or anti-HER2, in earlier lines of therapy. PFS was modest but in line with previous reports.

Metastatic breast cancer (MBC) is an incurable disease with a current median overall survival (OS) of around 37 months (1). The goals of treatment in MBC are to extend survival, control symptoms, and maintain quality of life (2). Therapeutic strategies are sought which offer good tumour control balanced with the best possible toxicity profile, as suggested by The European School of Oncology (ESO) and European Society for Medical Oncology (ESMO) first international consensus guidelines for the treatment of advanced breast cancer (ABC). The heterogeneity of breast cancer subtypes and patient specific features need to be taken into account when weighing different treatment options. For some subtypes, in particular HER2-positive MBC, recent therapeutic improvements have prolonged survival up to 56 months (3).

Vinorelbine is a vinca alkaloid that exerts a cytotoxic effect by disrupting mitotic spindle formation and preventing cell division (4). It is available in both intravenous (IV) and oral formulations and it is indicated for use in the treatment of MBC as a single agent or in combination (5). The oral formulation (Navelbine® Oral) is considered as an economically viable treatment by health care systems, with a low toxicity profile and good tumour control (6).

Once marketed, despite registration of many other compounds in the same area, "old" drugs are generally not reassessed. Real-life data help to reappraise drugs that have been available for many years with long-term records. In France, oral vinorelbine (OV) was approved for the treatment of MBC in 2001; however, its use and linked outcomes have not been reappraised since then. The objective of the present study was to exploit real-world data available in the Unicancer Epidemiology Strategy Medical-Economics (ESME) national MBC database to investigate the current patterns of use of OV as well as outcomes of patients receiving this drug for MBC treatment, in France. The primary endpoint was to evaluate the efficacy of OV therapy (monotherapy or in combination) in the treatment of MBC in a real-world setting.

Patients and Methods

Data source and patient selection. We conducted a non-interventional, retrospective study in patients selected from the ESME MBC database (NCT03275311). Selected patients were men or women, aged 18 or over, who started treatment for MBC between January 1st 2008 and December 31st 2014 and received OV at any time between January 1st 2008 and November 30th 2016. A cut-off date of January 15th 2016 was used for survival analyses.

The database was authorised by the French data protection authority (authorisation no. 1704113). It was managed by R&D Unicancer according to Good Pharmacoepidemiology Practices and Good Epidemiology Practices (7, 8) and was approved by an independent Ethics Committee (Comité de Protection des Personnes Sud-Est II 2015-79). Data collection and quality control methods are further described in Pérol *et al*. 2019 (9).

Evaluation criteria. The primary endpoint was PFS defined as the time (months) between the index date (start of OV, or start of treatment line for maintenance therapies) and date of disease progression or death, whichever came first. Disease progression was defined as appearance of new metastatic site, progression of existing metastasis, local or loco-regional recurrence of the primary tumour, discontinuation of chemotherapy and/or targeted therapy due to metastatic progression (according to the reference physician), or death from any cause. The secondary endpoints were descriptive and prognostic analyses, treatment duration rate at 6 months and OS defined as time (months) between the index date and date of death (any cause).

Treatment duration was defined as the length of time between the initiation and the termination dates of OV. Six-month treatment duration rate was defined as the percentage of patients with OV ongoing 6 months after the index date.

First-line treatment was defined as the first therapeutic strategy (chemotherapy, targeted-therapy, or hormonotherapy, alone or in combination) initiated following MBC diagnosis, or any therapeutic strategy initiated prior to (within 12-weeks for chemotherapy or targeted therapy regimens), and ongoing at the time of MBC diagnosis. The start date for first-line treatment was defined as the date of first dose for regimens initiated following MBC diagnosis or the date of MBC diagnosis for regimens ongoing at the time of diagnosis.

Subsequent lines of therapy were defined as any new therapeutic strategy initiated within 12 months following documentation of metastatic disease progression on the previous line. A treatment line could therefore include a single molecule, combination therapies, or a sequence of initial therapies and maintenance.

The index date was defined as the date of first dose of OV. The OV-line was defined as the line of treatment during which OV was initiated. OV treatment was classified as monotherapy (no other chemo- or targeted-therapy was administered concomitantly) or combination therapy (concomitant administration of at least one other chemo- or targeted-therapy) and as initial (first dose received at the start for the treatment line) or maintenance therapy (first dose received after the start date for other molecules in the same treatment line).

Standard ESME platform guidelines were applied for the definition of demographic and disease characteristics (9).

Statistical analysis. Descriptive statistics (including mean, standard deviation) were used to summarise patient characteristics at diagnosis of metastatic disease. Survival curves with associated log-rank tests were estimated using the Kaplan-Meier method. Median follow-up was calculated using the reverse Kaplan-Meier method. Censored data were summarised descriptively.

A minimum set of forced variables (prognostic factors) and unforced variables were selected by univariate analysis. The primary analysis was based on multivariate analysis using a Cox model adjusted and stratified for prognostic factors of survival and potential cofounders. Prognostic factors for which the proportional hazard's assumption was violated (*i.e.* significant interaction of

Table I. *Patient and disease characteristics for the study population (N=1806).*

	Study population (N=1806)
Female, n (%)	1792 (99.2%)
Age at BC diagnosis (years) median (Q1-Q3 range)	51.0 (43-60)
Age at MBC diagnosis (years) median (Q1-Q3 range)	58.0 (48-66)
De novo MBC, n (%)	373 (20.7%)
Adjuvant treatment received for early BC (n=1433), n (%)	
Anthracyclin	1081 (95.5%)
Taxane	727 (64.3%)
Other chemo-/targeted therapy	551 (38.5%)
Anti-HER2	103 (9.1%)
Hormonal therapy	989 (69.0%)
Radiotherapy	1285 (89.8%)
Metastasis-free interval (months) median (Q1-Q3 range)	60.6 (31-113)
Number of metastatic sites, n (%)	
<3	1389 (77.0%)
≥3	416 (23.0%)
Metastatic sites, n (%)	
Non-visceral	734 (40.7%)
Visceral except brain or CNS	988 (54.7%)
Brain or CNS	83 (4.6%)
Histological type, n (%)	
Invasive ductal carcinoma (IDC)	1436 (83.0%)
Invasive lobular carcinoma (ILC)	222 (12.8%)
IDC+ILC	28 (1.6%)
Other	45 (2.6%)
IHC profile, n (%)	
HR+	1369 (75.8%)
HR+/HER2–	1098 (60.8%)
HR–/HER2–	260 (14.4%)
HER2+	277 (15.3%)
HR/HER2 status unknown	171 (9.5%)

BC, Breast cancer; MBC, metastatic breast cancer; CNS, central nervous system, HR, hormone receptor, IHC, immunohistochemistry.

covariate with time) were introduced as stratification factors, and factors for which the proportional hazard's assumption was verified were included as covariates. Adjusted survival curves were generated using the Breslow Estimator for OS and PFS analysis. Hazard ratios (HR) are presented on a descriptive basis with 95% confidence intervals (95% CI). Statistical analyses were performed by Capionis (Paris, France) using SAS® software (version 9.4). For quality purposes, a repeat analysis was performed.

Results

Patient and disease characteristics. Among the 16703 patients selected in the ESME MBC database between January 1st 2008 and December 31st 2014, 1806 patients (11%) were included in the current analysis. Patient characteristics are summarised in Table I.

The study population was 99% female, with median age at MBC diagnosis of 58 years (range=48-66). Three-hundred and seventy-three patients (21%) had *de novo* metastatic disease. For patients with early stage breast cancer (BC) at diagnosis, adjuvant treatment included anthracyclines (96%), taxanes (64%), other chemotherapy or targeted therapy (39%) and radiotherapy (90%). Hormonal therapy and anti-HER2 therapy were prescribed to 87% of patients with hormone receptor-positive BC and 62% of patients with HER2-positive BC, respectively. The median metastasis-free interval (time between non-metastatic BC diagnosis and the first metastatic recurrence) was 61 months (range=31-113). Metastatic disease included visceral metastases (55%), and brain/central nervous system metastases (5%).

Available immunohistochemistry data allowed subtype classification for 1635 patients; 1098 tumours (61%) were hormone receptor-positive/HER2-negative, 277 (15%) were HER2-positive, and 260 (14%) were triple-negative BC.

Metastatic breast cancer treatment. Most patients received OV in later lines of therapy (Table II). Specifically, OV was part of first line metastatic treatment for 284 patients (16%), second line for 486 patients (28%), third line for 431 patients (25%), and fourth line or later for 543 patients (31%). The median time between MBC diagnosis and OV treatment initiation was 20 months (range=9.6-33.3).

As an induction therapy, OV was used more frequently as a single-agent (810 patients, 46%), than in combination with other drugs (509 patients, 29%). In hormone receptor-positive patients, the proportion receiving combination therapy decreased in later treatment lines, with more advanced disease. In this subpopulation, when given in combination, OV was mainly co-administered with capecitabine (79%). In the HER2-positive subpopulation, this tendency was reversed; OV was prescribed in combination more frequently than as monotherapy, with no significant decrease in the use of combination treatment in later lines (Table III). In HER2-positive disease, OV was mainly associated with anti-HER2 (88.2%).

OV was used as maintenance in 231 patients (13%) as a single agent and in 194 patients (11%) in combination (Table II). Among these patients, initial treatment (prior to OV maintenance) included capecitabine (34%), hormonal therapy (31%), taxanes (22%), anti-HER2 therapies (16%) and other chemotherapies (24%). For patients with HER2-positive disease, initial anti-HER2 was prescribed prior to OV maintenance in 74% of cases. Hormonal status had no effect on the timing of OV initiation. The reasons for the switch to OV maintenance included toxicity (31%), predefined treatment strategy (25%), disease progression (PD) (8%), patient's choice (5%) and others (23%).

Treatment duration. At the cut-off date, 1518 patients (86%) had discontinued OV therapy, regardless of treatment

Table II. *Summary of oral vinorelbine use according to immunohistochemistry profile (N=1806).*

OV administration protocol	Line of treatment				
	All	1	2	3	≥4
Study population	(N=1806)	284 (16.3%)	486 (27.9%)	431 (24.7%)	543 (30.1%)
Induction monotherapy	810 (46.4%)	37 (13.0%)	168 (34.6%)	225 (52.2%)	380 (70.0%)
Induction combination therapy	509 (29.2%)	98 (34.5%)	191 (39.3%)	127 (29.5%)	93 (17.1%)
Maintenance monotherapy	231 (13.2%)	58 (20.4%)	72 (14.8%)	51 (11.8%)	50 (9.2%)
Maintenance combination therapy	194 (11.1%)	91 (32.0%)	55 (11.3%)	28 (6.5%)	20 (3.7%)
Unknown	62	0	0	0	0
HR+/HER2– MBC patients	(n=1098)	131 (12.3%)	277 (26.0%)	275 (25.8%)	382 (34.8%)
Induction monotherapy	581 (54.6%)	17 (13.0%)	103 (37.2%)	174 (63.3%)	287 (75.1%)
Induction combination therapy	235 (22.1%)	28 (21.4%)	105 (37.9%)	52 (18.9%)	50 (13.1%)
Maintenance monotherapy	155 (14.6%)	35 (26.7%)	52 (18.8%)	34 (12.4%)	34 (8.9%)
Maintenance combination therapy	94 (8.8%)	51 (38.9%)	17 (6.1%)	15 (5.5%)	11 (2.9%)
Unknown	33	0	0	0	0
HER2+ MBC patients	(n=277)	57 (21.7%)	82 (31.2%)	58 (22.1%)	66 (23.8%)
Induction monotherapy	46 (17.5%)	4 (7.0%)	13 (15.9%)	9 (15.5%)	20 (30.3%)
Induction combination therapy	140 (53.2%)	24 (42.1%)	45 (54.9%)	37 (63.8%)	34 (51.5%)
Maintenance monotherapy	17 (6.5%)	6 (10.5%)	2 (2.4%)	4 (6.9%)	5 (7.6%)
Maintenance combination therapy	60 (22.8%)	23 (40.4%)	22 (26.8%)	8 (13.8%)	7 (10.6%)
Unknown	14	0	0	0	0
TN MBC patients	(n=260)	68 (27.4%)	80 (32.3%)	52 (21.0%)	48 (18.5%)
Induction monotherapy	107 (43.1%)	10 (14.7%)	31 (38.8%)	27 (51.9%)	39 (81.3%)
Induction combination therapy	90 (36.3%)	35 (51.5%)	33 (41.3%)	18 (34.6%)	4 (8.3%)
Maintenance monotherapy	30 (12.1%)	11 (16.2%)	10 (12.5%)	5 (9.6%)	4 (8.3%)
Maintenance combination therapy	21 (8.5%)	12 (17.6%)	6 (7.5%)	2 (3.8%)	1 (2.1%)
Unknown	12	0	0	0	0

OV, Oral vinorelbine; HR, hormone receptor; MBC, metastatic breast cancer; TN, triple negative.

strategy. Reasons for treatment discontinuation (non-exclusive) were PD (71%), toxicity (16%), predefined treatment plan (6%), patient's choice (2%), or other reasons (12%). An additional 8% of patients died without reported treatment discontinuation.

The median OV treatment duration was 3.4 months (95% CI=3.3-3.5). For induction treatments, median duration was 3.0 months (95% CI=2.6-4.9) in case of OV monotherapy, and 3.9 months (95% CI=3.5-4.4) for combination regimen. The 6-month treatment persistence rate was 25% (95% CI=23.2-27.5) overall; 18% (95% CI=15.1-21.0) for OV monotherapy and 36% (95% CI=28.3-36.8) for combination regimens.

Progression-free survival. Among the 1763 patients included in the PFS analysis, 6% were alive without progression at the cut-off date, following initiation of OV; 93% had experienced PD, and 2% were lost to follow-up post OV initiation. Forty-three patients with a reported OV start date later than or equal to the cut-off date were excluded from this analysis.

Median PFS was 3.3 months (95% CI=3.1-3.4) for the overall population. The 6-month PFS rate was 27% (95% CI=24.7-29.0). PFS varied from 4.9 months (95% CI=4.4-5.5) for patients receiving OV as first line treatment, to 3.5 months (95% CI=3.0-3.9) as second line, 3.2 months (95% CI=2.9-3.4) as third line, and 2.7 months (95% CI=2.5-2.9) as treatment in fourth line or later (Table IV).

For patients who received OV as monotherapy, median PFS was 2.9 months (95% CI= 2.7-3.0). For patients who received OV in combination, median PFS was 3.6 months (95% CI=3.3-4.2). Among patients who received OV in combination with capecitabine, the median PFS was 4.2 months (95% CI=3.6-4.9) overall and 5.3 months (95% CI=4.0-6.4) if given in first line.

The use of OV as part of a maintenance strategy resulted in a median PFS of 9.3 months (95% CI=8.5-10.2) from the start of the treatment line. Median PFS was 9.8 (95% CI=8.8-10.3) months for single-agent OV maintenance and 9.0 (95% CI=7.0-10.6) months when OV was included in a polychemotherapy maintenance regimen. Best results [PFS of 14.1 months (95% CI=10.9-18.4)] were observed when OV was given in a single-agent maintenance regimen following first-line induction.

Overall survival. At the cut-off date, 67% of the patients included in the study had died. A further 8% were lost to follow-up and censored in the analysis of OS. Median

Table III. *Overall survival*.

	Study population (N=1805)[1]	
Patient status at last news		
Alive[2]	441 (24.4%)	
Dead	1216 (67.4%)	
Lost to follow-up[3]	148 (8.2%)	
Cause of death		
MBC related	563 (46.4%)	
Toxicity	3 (0.2%)	
Concurrent disease	22 (1.8%)	
Other/not specified	625 (51.5%)	
Unknown	3	
Median follow-up[4], in months (95% CI)	47.1 (46.3-47.9)	
Population	Median OS rate (95%CI)[4]	36-month OS[4] rate (95% CI)
ESME MBS (n=16690)	37.6 (36.6-38.4)	51.5 (50.7-52.4)
Study population (n=1805)1	40.9 (38.9-42.5)	56.1 (53.7-58.5)
Patients who received OV as a 1st line treatment regimen (n=135)	23.4 (18.0-27.2)	29.8 (21.8-38.2)

MBC, Metastatic breast cancer; OS, overall survival; ESME, Epidemiology Strategy Medical-Economics; OV, oral vinorelbine. [1]Patients reported as dead but missing date of death were excluded. [2]Patient with no death reported and with follow-up data available in the 9 months preceding the cut-off date, or patients who died after the cut-off date. [3]Patients with no death reported but with no follow-up data available in the 9 months preceding the cut-off date. [4]Survival calculated from the date of MBC diagnosis.

Table IV. *Progression-free survival*.

Population	Median PFS (95% CI)[2]	6-month PFS (95% CI)
Study population (N=1763)[1]	3.3 (3.1-3.4)	26.8 (24.7-29.0)
According to treatment line[1]		
1 (n=284)	4.9 (4.4-5.5)	41.2 (35.4-46.8)
2 (n=481)	3.5 (3.0-3.9)	27.4 (23.5-31.5)
3 (n=422)	3.2 (2.9-3.4)	26.0 (21.9-30.4)
4 or more (n=519)	2.7 (2.5-2.9)	17.9 (14.6-21.6)
Patients who received OV as a treatment regimen[1]		
All (n=1288)	3.1 (2.9-3.3)	24.6 (22.2-27.0)
Monotherapy (n=785)	2.9 (2.7-3.0)	19.2 (16.5-22.2)
Combination (n=504)	3.6 (3.3-4.2)	32.5 (28.5-36.7)
Combination with capecitabine (n=420)	4.2 (3.6-4.9)	37.8 (33.2-42.5)
Patients who received OV as a maintenance regimen[1]		
All (n=417)	9.3 (8.5-10.2)	67.7 (63.0-72.0)
Monotherapy (n=224)	9.8 (8.8-10.3)	72.0 (65.6-77.4)
Combination (n=193)	9.0 (7.0-10.6)	62.7 (55.5-69.1)

OV, Oral vinorelbine. [1]Patients who initiated oral vinorelbine treatment on or after the cut-off date of 15/01/2016 were excluded. [2]PFS calculated from the date of first dose of oral vinorelbine (treatment regimen) or from the start date for the line of treatment (maintenance regimen).

follow-up was 47.1 months (95% CI=46.3-47.9) (Table IV). The median OS for the study population was 40.9 months (95% CI=38.9-42.5), compared to 37.6 months (95% CI=36.6-38.4) for the global ESME MBC dataset; the 3-year OS rates were 56% (95% CI= 53.7-58.5) and 52 (95% CI=50.7-52.4) respectively. For patients who received OV in first line as a treatment regimen, median OS was 23 months (95% CI=18.0-27.2).

Prognostic factors for progression-free survival and treatment duration. A multivariate Cox analysis of patients who received a first line regimen including OV (monotherapy or combination, 284 patients) found the following characteristics to be prognostic factors of PFS: histological grade 3 [HR=0.67 (95% CI=0.51-0.90); p=0.007], hormone receptor status [HR=1.396 (95% CI=0.97-2.00); p=0.003], presence of visceral metastases [HR=1.474 (95% CI=1.11-1.95);

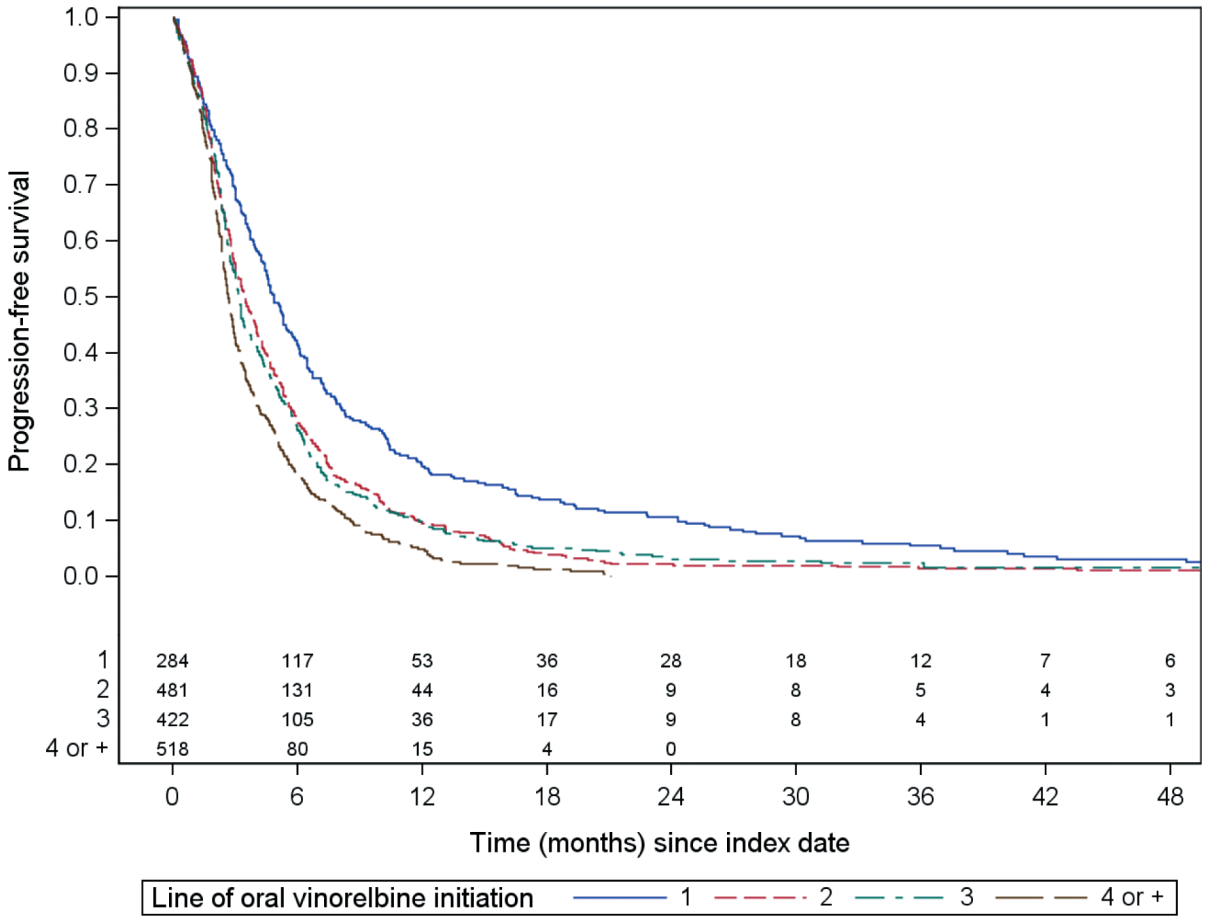

Figure 1. *Progression-free survival according to line in which oral vinorelbine treatment was initiated.*

p=0.007] and OV administration protocol (monotherapy *vs.* combination regimens) [HR=0.627 (95% CI=0.41-0.96); *p*=0.033].

Discussion

The ESME MBC database successfully allowed a reappraisal of the use of OV for metastatic breast cancer. The study population of 1806 patients who received treatment with OV between January 1st 2008 and December 31st 2014 represented 11% of the overall ESME MBC population. This suggests OV is not commonly prescribed by physicians in the French Comprehensive Cancer Centres.

Almost all patients diagnosed with early BC who received OV in a metastatic setting, had received prior anthracyclines (96%) and taxanes (64%). Prescription setting appeared heterogeneous; OV was mostly prescribed as treatment for progressive disease, either as monotherapy (46% of patients) or in combination with other therapies (29%). The inclusion of OV in maintenance regimens was less common. The problem of maintenance treatment has been little studied in the context of metastatic breast cancer. Several studies have shown that prolonged chemotherapy provides better PFS than short-course chemotherapy, but have never demonstrated that it improves OS (10, 11). A previous study that included patients with MBC in complete response, showed that the median PFS was 18.7 months after 6 courses of maintenance chemotherapy (doxorubicin combined with fluorouracil and cyclophosphamide) *versus* 7.8 months for the observation group (12). Because of these results, the classic attitude is currently to continue chemotherapy until toxicity or progression, but as a result, problem of cumulative toxicities becomes important.

OV use was spread throughout therapeutic lines. Single-agent OV was prescribed more frequently in later treatment lines, as expected and recommended in guidelines (2). When given in combination OV was mainly associated with capecitabine (79.0%) in HER2-negative disease (60.8% of

patients). In HER2-positive disease (15.3% of patients), OV was mainly associated with anti-HER2 (88.2%).

In the overall study population, median PFS following administration of OV was 3.3 months (95% CI=3.1-3.4). For those patients who received OV as a single agent median PFS was 2.9 months (95% CI=2.7-3.3), compared with 3.6 months (95% CI=3.3-4.2) when given in combination; median PFS was 4.2 months (95% CI=3.6-4.9) when OV was combined with capecitabine. Very little published data is available regarding the efficacy of single agent OV. Two randomised phase III trials have evaluated the efficacy of IV vinorelbine in MBC (13). These studies in pre-treated MBC patients reported a PFS ranging from 2.8 to 4.0 months and OS ranging from 8.7 to 16.4 months following vinorelbine treatment (14, 15). Other studies have compared IV and oral formulation of vinorelbine focusing on bioavailability. Equivalence of the oral and IV formulations has been demonstrated in pharmacokinetic studies (16). Our results are in line with these early descriptions. Regarding combination therapy, oral combinations of vinorelbine and capecitabine have been investigated in Phase I and II studies, with median PFS ranging from 6 to 10.5 months and median OS from 10 to 48 months (17-19). When this oral combination is used in first line setting, a PFS of 8.4 months and an OS ranging from 25.8 to 29.2 months were reported (18, 20). A more recent study of OV plus capecitabine in HER2/Neu-negative MBC demonstrated a time-to-disease progression of 8.6 months and a median survival time of 27.2 months (21) in first line, whereas in case of MBC patients previously preated with anthracycline or taxane-based regimens, a study including 55 patients demonstrate a median progression-free survival of 3.7 months and a median overall survival of 10 months (22). The efficacy of OV treatment seen in our retrospective study is globally consistent with that previously reported in clinical trials. The PFS of single-agent OV was lower than previously reported. Single agent OV is not a standard in first line therapy; however, limited efficacy in this setting may be related to the preferential prescription of this OV monotherapy in treating later stage disease after multiple prior therapies, possibly in a palliative setting. In the HER2 positive MBC, our data are consistent with the few publications using OV in combination with trastuzumab or lapatinib (23-25).

Concerning the prognostic factors for PFS reported in this study, namely histological grade, hormone receptor and HER2 status, as well as the presence of visceral metastases, have been previously described as prognostic factors in breast cancer (26, 27). These are traditional risk factors can be predicted the clinical outcome of metastatic breast cancer (28). A limitation of our results, as in most retrospective and real-world cohort studies, is the lack of information regarding, dose and administration schedule of OV, treatment-related toxicity and patient quality of life. Moreover, performance status and geriatric evaluations were not available and it would have been of interest to understand how they influenced treatment choices.

Conclusion

Real-world data allow analysis of the current use and reappraisal of the therapeutic outcomes of drugs that have been on the market for many years. In this French multicentre ESME MBC cohort, OV was prescribed to a small subset of MBC patients, as recommended after anthracyclines and taxanes. OV was mainly given as single agent in patients with heavily pre-treated MBC or less commonly in earlier lines in combination regimens co-administered with capecitabine, or anti-HER2 for HER2-positive patients. PFS was modest but in line with previous reports. This study shows that the actual data offer complementary results to the data from traditional clinical trials but that they concern a much larger population. It is therefore very important to continue promoting this type of scientific research.

Conflicts of Interest

P.H. reports grants, person-al fees and nonfinancial support from Astrazeneca; personal fees and nonfinancial support from Novartis; personal fees and non-financial support from Pfizer. S.D. reports personal fees and non-financial support from Roche/Genentech; grants, person-al fees and nonfinancial support from Pfizer; personal fees and nonfinancial support from Puma; grants, personal fees and non-financial support from AstraZeneca; grants, personal fees and non-financial support from Novartis; personal fees and non-financial support from Amgen. E.B reports personal fees from Pfizer, Roche, Mylan, BMS, Clinigen, TLC Pharma Chem, G1 therapeutics, Samsung and non-financial support from Roche, Pierre Fabre, Novartis, Astra-Zeneca, Pfizer. M-A.M-R reports other from Novartis, Lilly, Pfizer, Roche, Pierre Fabre, MSD. A.G. reports non-financial support from Roche, Novartis, AstraZeneca and Pfizer. M.R. reports other from Roche, Astra Zeneca, MSD, Pfizer, Daiichi Sankyo, Lilly. D. Perol has received a stipend from Pierre Fabre for expert analysis, and reports non financial support + personal fees from AstraZeneca, personal fees, BMS, Lilly, IPSEN, Roche, Novartis, Pierre Fabre, MSD+ Grant from MSD. The other Authors declare that they have no conflict of interest to disclose.

Authors' Contributions

All Authors participated in the different aspects of the study. Overall design of the study: P. Heudel, S. Delaloge, D. Parent and D.Pérol. Operational aspects of the study: M. Robain and G.Simon. Statistical analysis plan and statistical analysis: G. Chenuc, P. Heudel, S. Delaloge, D. Parent, D.Pérol and G. Simon. Interpretation of the results: all authors. Study report first and last draft: G. Chenuc and G. Simon. All Authors reviewed and amended the study manuscript repeatedly and approved the final version.

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