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Original article

Metronomic chemotherapy for advanced breast cancer patients in the real world practice: Final results of the VICTOR-6 study

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ABSTRACT

Metronomic chemotherapy (mCHT) refers to the minimum biologically effective dose of a chemotherapy agent given as a continuous dosing regimen, with no prolonged drug-free breaks, that leads to antitumor activity. Aim of the present study is to describe the use of mCHT in a retrospective cohort of metastatic breast cancer (MBC) patients in order to collect data regarding the different types and regimens of drugs employed, their efficacy and safety. Between January 2011 and December 2016, data of 584 metastatic breast cancer patients treated with mCHT were collected. The use of VRL-based regimens increased during the time of observation (2011: 16.8% - 2016: 29.8%), as well as CTX-based ones (2011: 17.1% - 2016: 25.6%), whereas CAPE-based and MTX-based regimens remained stable. In the 1st-line setting, the highest ORR and DCR were observed for VRL-based regimens (single agent: 44% and 88%; combination: 36.7% and 82.4%, respectively).

Assuming VRL-single agent as the referee treatment (median PFS: 7.2 months, 95% CI: 5.3–10.3), the longest median PFS were observed in VRL-combination regimens (9.5, 95%CI 88.8–11.3, HR = 0.72) and in CAPE-single agent (10.7, 95%CI 8.3–15.8, HR = 0.70). The VICTOR-6 study provides new data coming from the real-life setting, by adding new information regarding the use of mCHT as an option of treatment for MBC patients.

1. Introduction

Metastatic breast cancer (MBC) is an incurable disease and patients are expected to have a different life expectancy according to the different expression of hormone receptors and Human Epidermal Growth Factor Receptor 2 (HER2).

The Luminal A-like subtype usually show the best outcome in terms of Overall Survival (OS), whereas the triple negative subtype has the worst outcome [1].

Different strategies can be efficaciously used to reach disease control, such as chemotherapy, endocrine therapy and more recently therapy with target agents.

Nevertheless, despite the unequivocal improvement in overall survival (OS) observed in the last decades, mainly related to the contributions of various therapies rather than to a single drug or regimen, metastatic disease remains the primary cause of death in the majority of patients with breast cancer.

In the past few years, clinicians and researchers focused on approaches to prolong disease control, which ultimately translates into an improvement in overall survival[2].

Metronomic chemotherapy (mCHT) refers to the minimum biologically effective dose of a chemotherapy agent given as a continuous dosing regimen with no prolonged drug-free breaks that leads to antitumor activity [3]. A great number of Phase II studies have been published starting from mid-2000s, showing an increasing interest of clinicians on this topic [4]. The authors identified 107 treatment regimens with at least one metronomic drug, being Cyclophosphamide (CTX), Capecitabine (CAPE), etoposide and Vinorelbine (VRL) the most frequently used. The mean Response Rate (RR) of the pooled treatment regimens was 26%, with a mean Disease Control Rate (DCR) of 56.3%. Median duration of response was 4.6 months on average.

Moreover, toxicity associated to mCHT is very low (<10%) and could be safely administered to a wide variety of breast cancer patients.

Aim of the present study is to describe the use of mCHT in a retrospective cohort of MBC patients in order to collect data regarding the different type and regimens of drugs employed, their efficacy and safety.

2. Patients and methods

2.1. Study design

This is a multicentre retrospective cohort study, which collected data of MBC patients who received mCHT between January 2011 and December 2016 in 43 Italian Oncology sites. The centres selected usually treat more than 150 new cases of breast cancer per year, and can be considered representative of the national population as a whole.

The interval of time chosen for observation was determined by the following factors:

- First literature results of mCHT regimens including drugs different from Cyclophosphamide + Methotrexate (CTX + MTX - CM) combination appeared in 2011
- The end of observation was established considering that the median Time to progression (TTP) for mCHT is approximately 5 months and 18 months of follow up were considered sufficient to capture the efficacy and safety of new regimens

The study obtained the approval of all the Ethical Committees of the participating sites. All patients provided written informed consent, if still alive at the moment of data collection. Data regarding patients died before protocol starting have been collected according to Italian regulatory aspects. Data were collected via electronic database. Baseline information included patient's age at metastatic diagnosis, breast cancer biological information, (histology, HR and HER status), date and site of first relapse, type of medical treatment for first metastasis, number and type of treatments received before mCHT number and sites of metastases at mCHT administration. For each patient, physicians were requested to provide a fully comprehensive description of the type (endocrine/chemotherapy) and number of treatments performed prior to mCHT therapy.

[1] The authors from the VICTOR Study Group are listed in Appendix.

2.2. Patients

The eligible patients were female, > 18 years, with documented locally advanced or MBC, previously treated or not with other drugs for the metastatic disease, for whom mCHT was chosen by the physician, according to the clinical situation of the patient. All patients who received at least one dose of mCHT were considered eligible. Other inclusion criteria were HER2-negative disease (IHC 0–1 or IHC 2, confirmed as FISH negative), measurable or evaluable lesions and availability of all requested data. Data collection started when each centre received the approval of its own local Ethical Committee. Data retrieval included disease characteristics, hormone receptor and HER2 status, sites of metastases and tumour biology, as well as previous therapies received both in the metastatic setting.

2.3. Treatment plan

Considering the study design, no treatment plan was provided a priori.

Physicians were asked to identify all consecutive patients who met the pre-specified criteria of the study and to collect patients' data from the clinical records in an electronic case-report-form (CRF) dedicated to the trial.

Each regimen which comprised CTX, MTX, VRL and CAPE, administered alone, in combination with biological agents, or with other mCHT schedules was accepted.

Considering the available literature on mCHT, which defines regimens on the basis of one of the drugs contained in the administration, we decided to define:

VRL-based, as those which include VRL, alone or in combination with CAPE ± CTX, (VRL 40–50 mg 3 times per week; CAPE 500 mg 3 times per day, CTX 50 mg per day).

CAPE-based, as those including the CAPE alone, in combination with CTX (CAPE 500 mg 3 times per day, CTX 50 mg per day).

CTX-based, as those in which CTX has been administered alone (50–100 mg per day), in combination with MTX (2.5 mg per day, 2 times per week) or other drugs different from those mentioned above (etoposide 50–100 mg per day), and MTX-based (2.5 mg per day 2 times per week) all the other regimens.

Every regimen has been contested only in the respective group of membership

2.4. Clinical outcomes

All measures of clinical outcomes were based on the physician's evaluation. The primary end-point of this retrospective study was to describe patients' characteristics treated with mCHT. Secondary end points were: overall response rate (ORR) and disease control rate (DCR), defined as the sum of Complete + Partial Responses + Stable Disease, according to the type of mCHT, Time to Treatment Failure (TTF), Survival Post Progression (SPP), Overall Survival (OS) and toxicity.

Patients who had not progressed, or had died were censored at the data cut-off date (October 2017).

2.5. Statistical considerations

Demographic data, patients' baseline characteristics and disease, plus treatment information were summarized with standard summary statistics (mean SD and range for continuous data, relative and absolute frequencies for categorical data). Relationship of these variable with response were analysed by mead of a Mantel-Haenzel. Time to event analysis was described by Kaplan Meier approach and association with baseline characteristic was analysed by stratified log-rank test and proportional hazard model.

Univariate and multivariate logistic analyses were used for estimating the association of selected basal characteristics and treatment with response. Odds ratio and relative 95% confidence interval (CI) were used as summary statistics. The number of patients was calculated in order to obtain a quite precise description of chosen statistics and a good fit with the Cox model.

The data were statistically analysed using SAS version 8 (SAS Institute Inc, Cary, NC).

3. Results

3.1. Patient and tumour characteristics

Between January 2011 and December 2016, we retrospectively retrieved clinical data of 597 metastatic breast cancer patients treated with mCHT. Data of 13 records did not satisfy the pre-specified criteria and were excluded from the analysis. (Fig. 1).

At primary diagnosis, main tumour characteristics were ductal histology (84.5%), pT2 stage (41.4%), pN1 stage (34.6%), ER+/PgR+ (64.0%).

Median follow up time was 39.9 months (36.1–43.7). Median age at the time of diagnosis was 63 years (30–98). Median DFI was 38 months (0–667); At the beginning of mCHT, most patients had an ECOG PS of 0 (59.3%) or 1 (32.6%). Almost half of the patients had 2 metastatic sites (40.7%); major sites of metastases were bone (67.8%), liver (39.2%) and lung (31.2%). Prior to mCHT, 40% of the patients had already received more than 3 lines of therapy.

Metronomic CHT was used as first-line therapy in 111 patients (19.0%) and in 143 (24.3%) previously treated with only endocrine agents.

None of the patients received CDK 4/6 inhibitors.

One-hundred thirty-three patients (22.8%) had already received VRL or CAPE at standard schedules and doses. Details are summarized in Table 1.

3.2. Clinical activity

The vast majority of patients (463, 79.3%) received mCHT as single-agent, regardless of the drug: VRL (202, 34.6%), CAPE (130, 22.3%) and CTX (121, 20.7%); the use of MTX was negligible. The use of VRL-based regimens increased during the time observed (2011: 16.8% - 2016: 29.8%), as well as CTX-based ones (2011: 17.1% - 2016: 25.6%), whereas CAPE-based and MTX-based regimens remained stable.

mCHT was the 1st chemotherapy line in 229 patients (39.2%), with or without previous endocrine treatments: 136 (59.8%) received VRL-combination regimens (VEX: VRL + CAPE + CTX or VRL + CAPE). Among single-agents, CAPE was the most used (53, 23.1%).

Fig. 2 summarizes data regarding type of mCHT.

Details regarding the clinical activity of the mCHT drugs is available for 578 patients.

Overall Response Rate (ORR) of mCHT ranged from 33.8% in first-line to 8.8% in fourth-line setting; similarly, DCR was 74.4%, ranging from 81.5% to 54.4%, according to the line of treatment.

In the 1st-line setting, the highest ORR and DCR were observed for VRL-based regimens (single agent: 44% and 88%; combination: 36.7% and 82.4%, respectively). Notably, the ORR in 2nd-line setting of VRL-combination strategies was 23.6%. Table 2 summarizes ORR and DCR according to the settings and the drugs.

At the multivariate analysis, no clinical or tumor characteristic (PS, Hormone Receptor status, number of metastatic sites) was associated with ORR, nor was the type of mCHT.

Median TTF was 6.28 months (95% CI: 5.63–7.01), regardless of

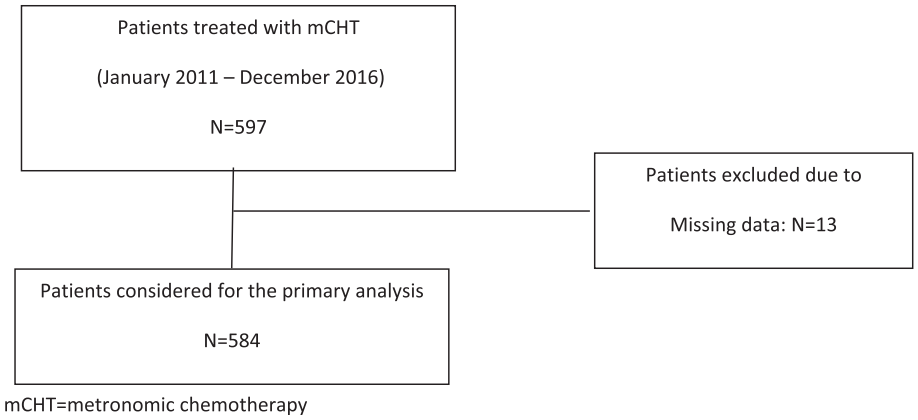


Fig. 1. CONSORT flow chart.

Table 1
Patients and tumour characteristics at mCHT start.

Characteristic	N (%)
Median age (range), years 65	(30–98)
PS	(frequency missing = 2)
0345	(59.3)
1190	(32.6)
2 42	(7.2)
3 5	(0.9)
HR status	
ER+/PgR+	374 (64.0)
ER+/PgR-	113 (19.3)
TNBC	97 (16.6)
Metastatic sites	
- Bone	396 (67.8)
- Liver	229 (39.2)
- Lung	182 (31.2)
- Soft	tissue 110 (18.7)
- CNS	24 (4.1)
- Other	192 (32.9)
Number of metastatic sites (frequency missing = 10)	
- ≥ 3	130 (22.1)
- 2	238 (40.7)
- 1	206 (35.3)
Number of treatments before mCHT[a]	
- 0	111 (19.0)
- 1	117 (20.0)
- 2	123 (21.1)
- ≥	3233 (40.0)
Typology of treatments prior to mCHT	
- No CHT, and NO ET (naive)	111 (19.0)
- ET only (1st line)	143 (24.3)
- CHT only	106 (18.2)
- CHT and ET	224 (38.4)
Key prior CHT	
- Taxane-based	218 (37.3)
- Anthra-based	103 (17.5)
- VRL-CAPE based	133 (22.8)
Key prior endocrine treatments	
AIs	307 (52.3)
TAM	51 (8.7)
Everolimus	49 (8.3)

mCHT = metronomic chemotherapy; ET = Endocrine therapy; CHT= Chemo therapy; VRL=Vinorelbine; CAPE = capecitabine; AIs = aromatase inhibitors; TAM = tamoxifen.
[a] both ET and CHT.

the drug used.

Main reason for drug interruption was progression of the metastatic disease (74.3%). At the multivariate analysis, no variable was associated with TTF.

At the moment of data cut-off date 71 patients (11.9%) were still on treatment without progression and 214 were alive (35.8%). Median SPP was 12.0 months (95% CI: 10.4–15.6).

Median PFS was 7.2 months (95%CI: 5.3–10.3) for VRL-single agent. Assuming this latter as the referee regimen, median PFS were 9.5 (95%CI 88.8–11.3, HR = 0.72), 10.7 (95%CI 8.3–15.8, HR = 0.70) and 4.4 months (95%CI 2.6–9.8, HR = 1.91) for VRL-combinations, CAPE and CTX-single agents, respectively.

Median OS was 22.7 months (95%CI 13.0–43.5) in the referee treatment (VRL-single agent) and 30.0 (95%CI 26.2–34.7, HR = 0.67), 28.8 (95%CI 23.1–37.0, HR = 0.71) and 14.2 (95%CI 9.9-NE, HR = 1.55) for VRL-combination regimens, CAPE and CTX single-agent, respectively. Details are summarized in Fig. 3.

3.3. Safety

The main toxicity was haematological (Grade 3–4: 5.8%), followed by skin reactions (Grade 3–4: 2.6%) and nausea/vomiting (Grade 3–4: 2.1%). Severe diarrhea was observed in 1.0% of the patients. Table 3 summarizes type of toxicity of all mCHT regimens. Discontinuation due to adverse events was observed in only 51 patients (8.7%).

4. Discussion

VICTOR-6 is an observational, retrospective study regarding the use of mCHT in the strategy of treatment of advanced breast cancer patients.

To our knowledge, this is the largest study reporting data from real world. Real world studies are becoming more and more important in the last years, because they provide information regarding the real efficacy of a treatment in an unselected population of patients and can serve as confirmatory studies with respect to toxicity.

In the past few years, clinicians and researchers focused on approaches to prolong disease control, which ultimately translates into an improvement in overall survival [2]. In this context, mCHT could represent one of the most promising strategies to reach this goal, considering that the main peculiarity of this treatment is the use of doses well below the Maximum Tolerated Dose (MTD) of drugs, without significant bone marrow toxicity and for this reason the ideal therapy to be administered for a long period of time.

The most favourite compounds for metronomic administration are those administered orally, due to the potential long-term use of this treatment. In this context, the most studied drugs for metronomic chemotherapy in advanced breast cancer are CTX, MTX, CAPE and oral VRL (Marina Elena [5]. mCHT is now recommended

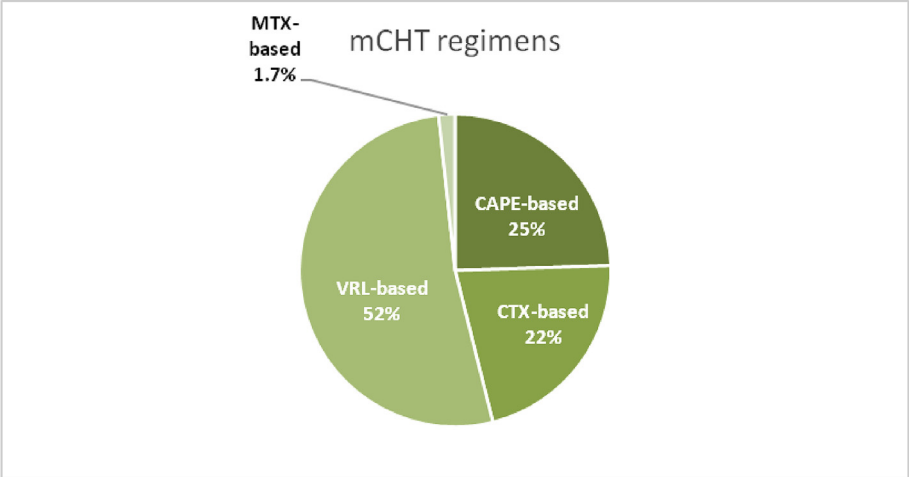


Fig. 2. mCHT regimens.

by international guidelines as a possible option of treatment for advanced breast cancer patients [6].

A great number of Phase II studies have been published starting from the mid-2000s, showing an increasing interest of clinicians on this topic [4,13]. Among the 80 publications selected for the systematic literature analysis by Lien and colleagues, 21 trials covered the topic of breast cancer involving 1135 patients. The authors identified 107 treatment regimens with at least one metronomic drug, being CTX, CAPE, etoposide and VNR the most frequently used.

The mean Response Rate (RR) of the pooled treatment regimens was 26%, with a mean Disease Control Rate (DCR) of 56.3%. Median duration of response was 4.6 months on average.

Our results in terms of drug choice are similar to those described by Lien et Al: the vast majority of patients (463, 79.3%) received mCHT as single-agent, regardless of the drug. The use of VRL-based regimens increased during the time observed (2011: 16.8% - 2016: 29.8%), as well as CTX-based ones (2011: 17.1% - 2016: 25.6%), whereas CAPE-based and MTX-based regimens remained stable.

This observation is closely related to the increased amount of publications regarding mCHT data, especially in the field of breast cancer, but also to a better understanding of the mechanisms of action of the different mCHT therapies.

In their review, Lien et Al [4]. reported that 38 regimens used a pure mCHT regimen, both as single-agent strategy (monotherapy: 24, 63.2%; doublet therapy: 14, 36.8%). Our findings are similar to those observed by these Authors: the vast majority of patients (463, 79.2%) received mCHT as single-agent, regardless of the drug taken: VRL (202, 34.6%), CAPE (130, 22.3%) and CTX (121, 20.7%).

The choice for sequential single-agent therapies is strongly recommended in all international guidelines, starting from the hypothesis that adding a drug to another one doesn't translate into efficacy improvement compared to a potential increase in toxicity.

Our results are aligned with guide lines, considering that most of the patients have been treated with metronomic single agents.

However, if the axiom “more agents translates into more toxicities” is true for combinations using drugs at the their MTD, the same cannot be assumed for mCHT combinations.

Some recent in-vitro data [7] clearly demonstrated that drug concentrations used in combination treatments are superimposable to those used in single-agent strategy and a significant antiproliferative activity was observed in cells treated with metronomic vs STD administration of 5FU or VNR alone. However, combination of the two drugs showed an additive inhibitor effect on cell growth in both cell lines. Moreover, after exposure of cells to 5FU and VNR under mCHT or conventional schedule of administration the Authors also observed a downregulation of chemo-resistance factor Bcl-2, changes in pro-apoptotic protein Bax and in cleaved effector caspase-3 and increased expression of LC3A/B autophagy protein, suggesting that the combination of 5FU + VRL could be better than each single agent, even administered in a metronomic way.

In VICTOR-6, the high percentages of patients treated with single-agent strategy could also be related to the lack of prospective randomized, even phase II trial results in the observation period: the release of data of the two most important studies in this setting [8,9] were published subsequently to the main enrollment period.

Regarding major end points, Overall Response Rate (ORR), PFS and safety assessment are the most frequent primary end-points reported in mCHT trials.

Our results in an unselected population of advanced breast cancer patients showed that ORR of mCHT as a whole was 25.8% and ranged from 33.8%% in first-line to 8.8% in fourth-line setting; similarly, DCR was 74.4%, ranging from 81.5% to 54.4%, according to the line of treatment.

Liu et Al [10] conducted a meta-analysis which consisted of 22 clinical trials with 1360 advanced breast cancer patients treated with mCHT. The pooled ORR and clinical benefit rate (CBR) of mCHT were 34.1% (95% CI 27.4–41.5) and 55.6% (95% CI 49.2–61.9), respectively.

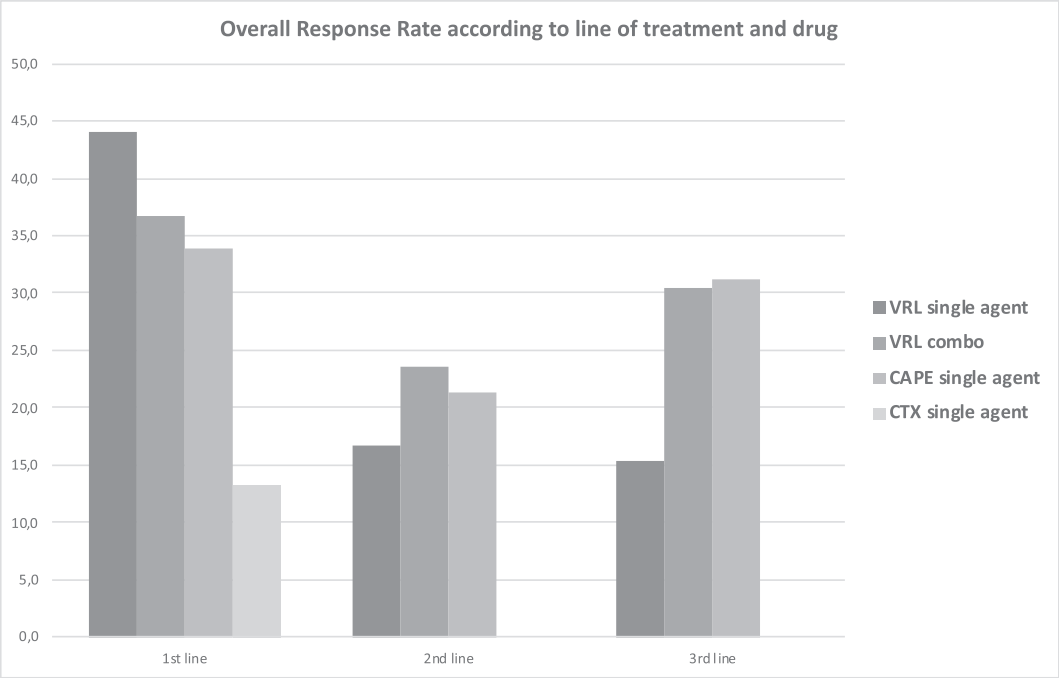
As the findings described by these Authors, we didn't find any significant associations between ORR, DCR and patient characteristics, or the type of drug(s).

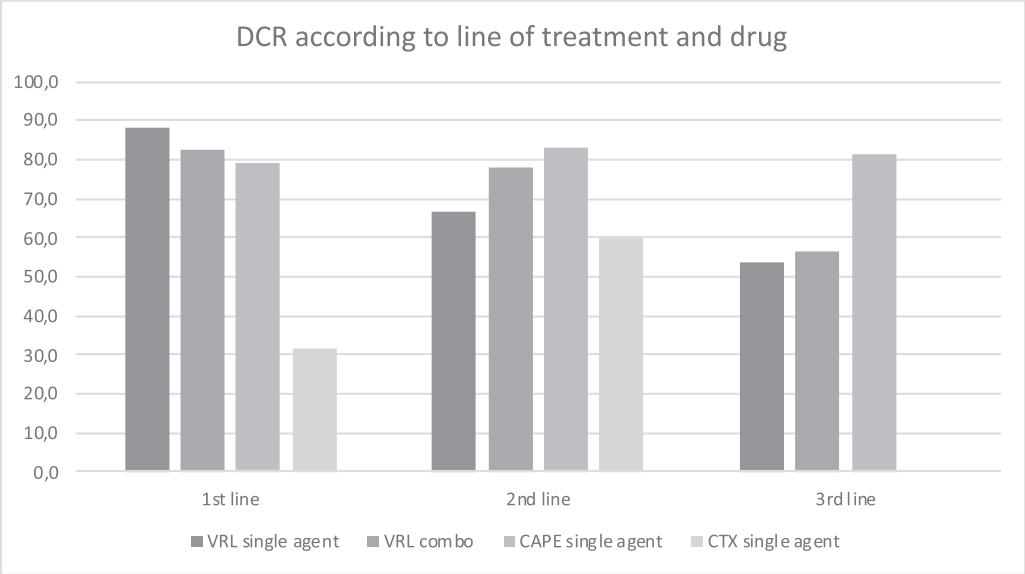
In the VICTOR-6 trial, median PFS was 6.28 months (96% CI: 5.63–7.01), regardless of the drug used. The longest PFS intervals were observed for CAPE single agent (10.7 months, 95% CI:8.3–15.8) and for VRL-based regimens (9.2 months, 95% CI: 7.6–13.9) and for treatments administered in 1st-line setting (10.0 months, 95%CI: 8.7–11.9).

In the abovementioned meta-analysis, the overall PFS-6 rate (PFS rate at 6 months) was 56.8% (95% CI 48.3–64.9) as determined by the random effects model (heterogeneity analysis: $Q = 54.1$, $P < 0.001$, $I2 = 77.8$). There was no statistically significant difference in the PFS rate at 6 months between mCHT alone and the combination regimens (61.6% vs. 54.0%, $P = 0.513$). Without stratification for tumor type, the median reported PFS was 4.6 months (Supplementary Fig. 1S).

Liu et Al also performed a subgroup analysis among CTX + MTX

Table 2
Clinical activity of the main mCHT regimens.

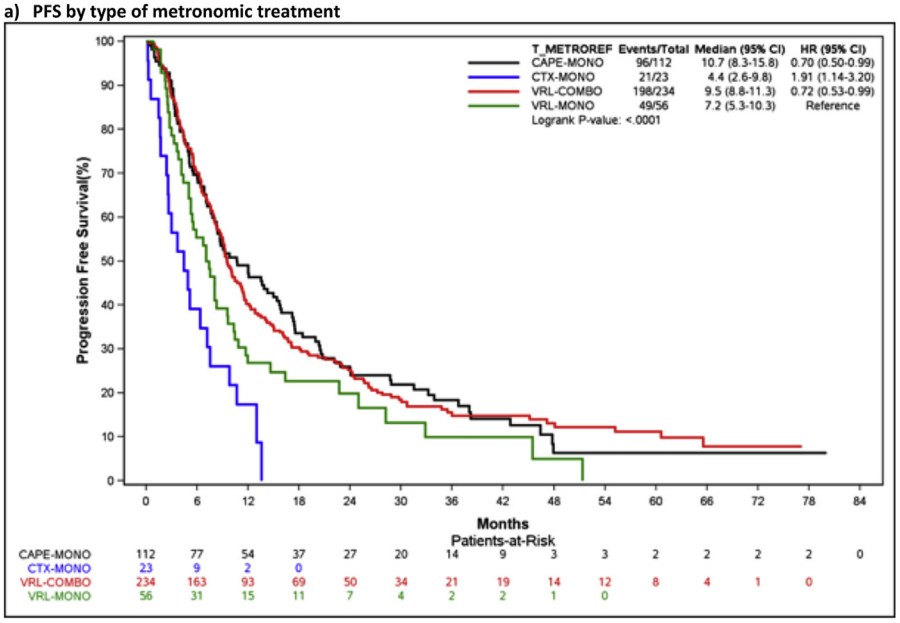




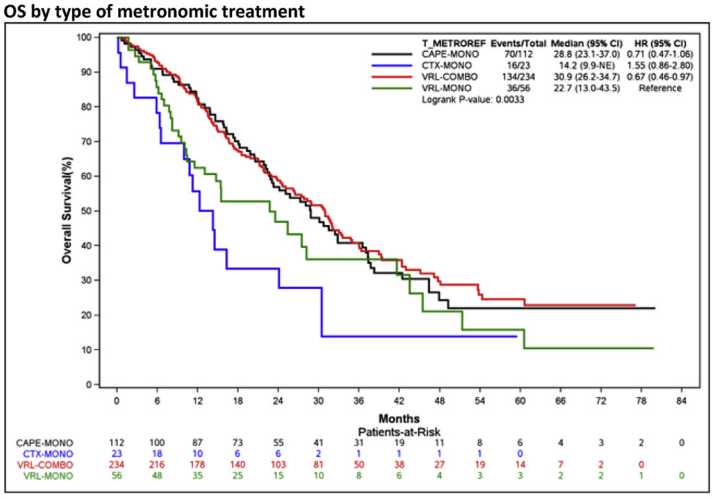
Clinical Efficacy End Point°,	n/N	%
Overall Response rate	149/578	25.8
- 1st-line	88/260	33.8
- 2nd-line	39/173	22.5
- 3rd-line	16/77	20.8
- 4th-line	6/68	8.8
Disease Control Rate	430/578	74.4
- 1st-line	212/260	81.5
- 2nd-line	135/173	78.0
- 3rd-line	46/77	59.7
- 4th-line	37/68	54.4

°Not evaluable for efficacy: N = 6

a) PFS by type of metronomic treatment



b) OS by type of metronomic treatment



c) PFS according to line of treatment

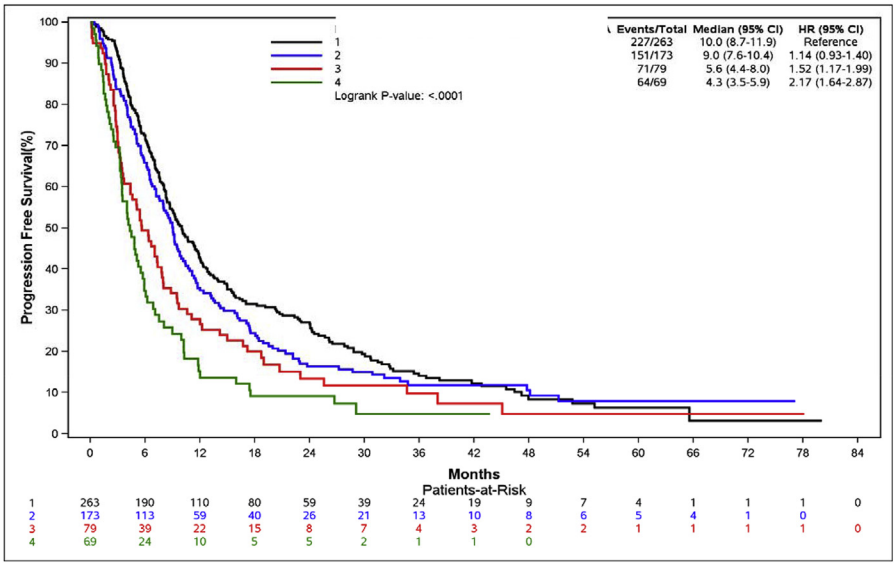
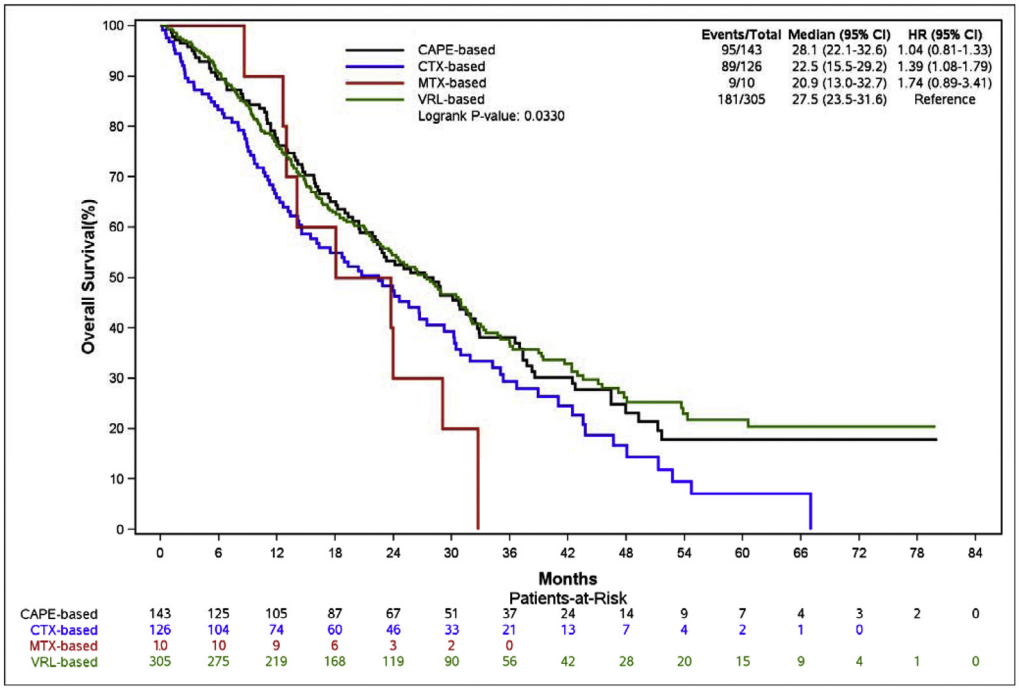


Figure 3. mCHT regimens: time to events.

d) OS according to the type of mCHT



e) OS according to the line of treatment

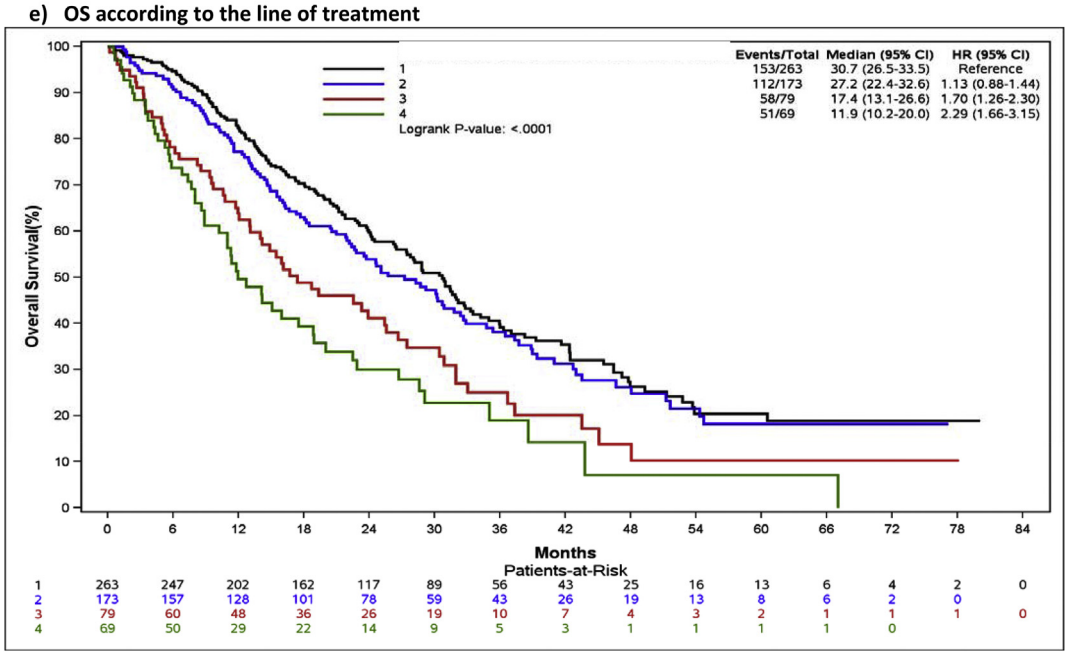


Figure 3. (*continued*).

(CM), CAPE, and other drug based regimens, but no statistically significant difference was found. Meta-regression with univariate models did not show statistical associations between DCR and Relative-Dose-Intensity ($p = 0.68$), regimen type ($p = 0.73$), or metronomic drug(s) used ($p = 0.37$). The multivariable mixed-effect model, taking into account all the factors above, did not reveal any statistical associations between DCR with any of the above factors adjusting for the rest of the factors.

In VICTOR-6 study, ORRs and DCRs obtained by different single agents as well as VRL-combination strategy are quite similar for VRL and CAPE as single-agents and for VRL-combination regimen; on the contrary, CTX-single agent ORR is lower in comparison to the other metronomic strategies, suggesting that this agent should not be used at least in first-line treatment.

Similar differences have been noted in terms of PFS and OS, suggesting again that the choice for a metronomic treatment should be limited to VRL, alone or in combination and CAPE.

Low toxicity was historically one of the greatest benefits of

Table 3
Safety.

Toxicity	Grade 1–2 n (%)	Grade 3–4 n (%)	Any Grade
Hematologic	82 (14.0)	34 (5.8)	116 (19.9)
Nausea/Vomiting	90 (15.4)	12 (2.1)	102 (17.5)
Diarrhea	70 (12.0)	6 (1.0)	76 (13.0)
Skin 54	(9.2)	15 (2.6)	69 (11.8)
Fatigue	60 (10.3)	5 (0.9)	65 (11.1)
Hepatic	34 (5.8)	8 (1.4)	42 (7.2)
Other toxicity	62 (10.6)	9 (1.5)	71 (12.2)

mCHT treatment.

As already reported in VICTOR-2 and VEX prospective trials, adverse events rates were very low and close to those reported in VICTOR-6: severe toxicity was observed in 89 patients (15.2%), mainly hematologic one (34 out of 89, 38.2%). No toxic deaths were recorded. Our data are quite similar to those reported in the meta-analysis by Liu et Al, where 24 regimens did not result in any severe hematological side-effects, while non-hematological toxicities were prevalent in more than 5% of patients. Furthermore, in 17 regimens no grade 3 or 4 toxicities were detected. No toxicity affected more than 6% of all pooled patients. Overall, 15 treatment related deaths were recorded (0.4%).

Despite the increasing use of mCHT in patients with MBC and the endorsement of mCHT in guidelines, no consensus exists about which patients may substantially benefit from mCHT, which agents can be recommended, and in which treatment setting mCHT is the most appropriate choice.

In October 2017, ten international experts in the management of breast cancer convened to develop a report (PENELOPE Consensus Meeting) describing the current status of the use of mCHT for the treatment of advanced breast cancer, based not only on available literature at that moment, but also on their opinion (Marina E [11]. A full consensus was reached concerning the acknowledgement that mCHT is not simply a different way of administering chemotherapy but a truly new treatment option. The best-known effect of mCHT is on the angiogenesis inhibition, but exciting new data are imminent, regarding the potential activity on immune system activation. The experts strongly suggested that the ideal patients for mCHT are those with hormone receptor (HR)-positive tumors. The majority of the trials investigating mCHT have enrolled HR + ve patients. While the inclusion of HR + ve patients in mCHT trials was mainly due to the frequent presence of indolent disease, there is also a strong rationale for including these patients in clinical trials given that cytotoxic drugs directly suppress ovarian function, causing a decline in plasma estrogens and a corresponding increase in gonadotropins [12].

Regardless of HR status, mCHT could be an advantageous option for elderly patients, who are often under-treated simply because of their age [14].

All of the experts participating in the PENELOPE Meeting agreed that mCHT is a therapeutic option for metastatic breast cancer patients and that, even though no formal comparisons are available, it has a better tolerability profile compared with classical MTD regimens. However, the results of large phase III trials designed with the metronomic concept in mind will be reported within the next few years [www.clinicaltrials.gov].

In conclusion, the VICTOR-6 study provided new data coming from the real-life setting, so far adding a significant contribution to the field of mCHT: it is our opinion that the large amount of pre-clinical, clinical and real-world data for mCHT is now sufficient to consider this kind of therapy as a treatment option in patients with metastatic breast cancer.

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Compliance with ethical standards

Conflict of interest

The authors have declared no conflicts of interest.

Informed consent

The study was conducted in accordance with the 1987 Declaration of Helsinki and adhered to Good Clinical Practice guidelines. Approval of the protocol was obtained from the local ethics committee for each participating centre; all patients were required to give written informed consent before enrolment and to comply with the protocol for the duration of the study.

Disclosures

Author Dr Cazzaniga has a role as consultant/advisory role for: Pierre-Fabre, Roche; Novartis; Lilly; Celgene. Author Dr Pinotti declares that she has no conflict of interest; Author Dr Montagna declares that she has no conflict of interest; Author Dr Amoroso declares that he has no conflict of interest; Author Dr Berardi declares that she has no conflict of interest; Author Dr Butera declares that she has no conflict of interest; Author Dr Cagossi declares that she has no conflict of interest; Author Dr Cavanna has a role as consultant/advisory role for: Astra Zeneca; Author Dr Ciccarese declares that she has no conflict of interest; , Author Dr Cinieri has a role as consultant/advisory role for: Ely Lilly, Author Dr Cretella declares that she has no conflict of interest, Author Dr De Conciliis declares that he has no conflict of interest, Author Dr Febbraro declares that he has no conflict of interest, Author Dr Ferraù declares that he has no conflict of interest, Author Dr Ferzi declares that she has no conflict of interest, Author Dr Fiorentini declares that he has no conflict of interest, Author Dr Fontana declares that he has no conflict of interest, Author Dr Gambaro declares that she has no conflict of interest, Author Dr Garrone declares that she has no conflict of interest, Author Dr Gebbia declares that he has no conflict of interest, Author Dr Generali has received a remuneration of 5.000 € and had a role as consultant/advisory role for: Novartis, FMI, Istituto Gentili, Roche, Pfizer, Ely Lilly, Author Dr Gianni declares that he has no conflict of interest, Author Dr Giovanardi declares that he has no conflict of interest, Author Dr Grassadonia declares that he has no conflict of interest, Author Dr Leonardi declares that she has no conflict of interest, Author Dr Marchetti declares that he has no conflict of interest, Author Dr Melegari declares that she has no conflict of interest, Author Dr Musolino remuneration acting as consultant/advisory role for: Novartis, Roche, Ely Lilly and funding from EISAI, Author Dr Nicolini declares that he has no conflict of interest, Author Dr Putzu declares that he has no conflict of interest, Author Dr Riccardi declares that he has no conflict of interest, Author Dr Santini declares that he has no conflict of interest, Author Dr Saracchini declares that she has no conflict of interest, Author Dr Sarobba declares that she has no conflict of interest, Author Dr Schintu declares that she has no conflict of interest, Author Dr Scognamiglio declares that he has no conflict of interest, Author Dr Spadaro declares that he has no conflict of interest, Author Dr Taverniti declares that he has no conflict of interest, Author Dr Toniolo declares that he has no conflict of interest, Author Dr Tralongo declares that he has no

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.breast.2019.07.006.

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