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Metronomic (mCHT) vs standard (sCHT) chemotherapy as first-line treatment in HR+/HER2- Metastatic Breast Cancer (MBC) patients following failure of endocrine treatments. The matched control VICTOR-15 study

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Abstract

Background HR+/HER2- MBC patients often receive chemotherapy (CHT) following endocrine therapy (ET); however, treatment-related toxicities remain a significant limitation. Metronomic chemotherapy (mCHT) involves the administration of low-dose chemotherapeutic agents at regular intervals without extended breaks. The VICTOR-15 study is a retrospective, matched controlled study designed to compare mCHT with standard chemotherapy (sCHT) in HR+/HER2- metastatic breast cancer (MBC) patients after ET failure.

Methods We identified consecutive patients treated with mCHT or sCHT between 2015 and 2024. Each mCHT patient was matched with a variable number of women treated with sCHT based on multiple clinical and demographic factors. The primary endpoint was real world progression-free suvival (rwPFS). Secondary endpoints included Overall Survival (OS)), Overall Response Rate (ORR) and Clinical Benefit Rate (CBR). rwPFS and OS were estimated by a weighted Kaplan-Meyer to account for variable matching.

Results The final analysis included 27 patients treated with mCHT and 52 with sCHT patients after matching (min = 1, max = 5). The median age at treatment initiation was 60.9 years for the mCHT group and 60.3 years for the sCHT group. Prior CDK4/6 inhibitor therapy was reported in 51.9% of mCHT patients and 48.1% of sCHT patients. Visceral metastases were present in 70.4% of mCHT patients and 69.2% of sCHT patients. CBR and ORR were higher in the mCHT group compared to the sCHT group (CBR: 66.7% vs. 61.5%; ORR: 37.0% vs. 28.8%).
Median rwPFS was 7.0 (95%CI=4.1-12.6) and 5.4 months (95%CI=3.9-7.0) for mCHT and sCHT. Median OS was 29.3 months (95%CI=22.4-44.9) for mCHT and15.3 months, (95%CI: 9.2-26.9) for sCHT. A higher proportion

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of patients in the sCHT group did not initiate a subsequent treatment compared to the mCHT group (23.1% vs 11.1%).

Conclusion mCHT demonstrated promising efficacy compared to sCHT following failure of ET±CDK 4/6i. This finding, combined with the generally favourable toxicity profile, supports the rationale for further randomized studies to better evaluate this therapeutic strategy.

Introduction

Breast cancer (BC) remains the leading cause of cancer death among women worldwide [1]. In Italy, approximately 55,000 new cases are diagnosed annually, with around 13,000 deaths attributed to the disease [2]. Despite significant advances in knowledge and the development of new therapies, approximately 30% of BC patients eventually progress to distant metastases and finally result in death [3]. The clinical course of metastatic breast cancer (MBC) is highly heterogeneous, varying in terms of growth rate and response to systemic therapies, which remains palliative in nature. There is no universally accepted chemotherapy strategy for Hormone Receptor-positive (HR+)/Human Epidermal growth factor Receptor 2 (HER2)-ve tumors, which account for 80–85% of all BC cases, despite the availability of newer agents, such as cycline-dependent kinase 4/6 (CDK 4/6) inhibitors [4–6] and targeted therapies, like Selective Estrogen Receptor Degrader (SERDs) [7]. HR+/HER2- MBC patients are typically treated with standard-dose chemotherapy (sCHT) following failure of multiple lines of endocrine therapies (ET) [8]. According to ESMO guidelines [8], when chemotherapy is indicated, single agents are generally preferred over combination strategies due to Quality of Life (QoL) considerations, except in cases requiring a rapid response due to high disease burden. Taxanes and anthracyclines are recommended, particularly for patients who have not previously received these agents. Other options such as Capecitabine, Eribulin, Vinorelbine, Platinum salts or other agents should be discussed with patients as potential treatments. Although guidelines recommend continuing chemotherapy until disease progression, treatment-related toxicities often limit this approach. Therefore, strategies that offer proven efficacy with reduced toxicity are needed, to enable continuous treatment while preserving QoL. Most of the aforementioned drugs are administered intravenously, with the exception of capecitabine and Vinorelbine, which are also available in oral formulations. Standard CHT typically refers to agents administered at predetermined doses that target dividing cells or damage the genetic material within tumor cells [9]. This type of treatment generally requires intervals between administrations to allow bone marrow recovery.

Metronomic chemotherapy (mCHT) refers to continuous administration of low-dose, chemotherapeutic agents with no, or short, regular treatment-free intervals. In metronomic regimens, drugs are typically administered orally, which improves patients' compliance and may also offer cost-saving benefits for healthcare systems.

Preclinical studies have demonstrated the potential efficacy of metronomic schedules in targeting angiogenesis. Due to the slower rate of cell division, endothelial cells replication is only minimally affected by the intermittent dosing of standard chemotherapy protocols. In contrast, the routine administration of cytotoxic drugs can effectively target slowly proliferating tumor endothelial cells and suppress their ability to repair and recover during the typical rest periods. Studies in mice with subcutaneous tumors have shown that metronomic dosing regimens may have clinical value [10]. Several clinical studies have investigated the role of mCHT in HR+/HER2- MBC patients [11–14], although only one has been designed as a randomized controlled trial, limiting broader clinical adoption of mCHT. To date, the only prospective randomized study comparing mCHT vs. sCHT is the METEORA II study [13] which aimed to determine whether the metronomic combination of Vinorelbine-Capecitabine-Cyclophosphamide (VEX) was superior to standard weekly paclitaxel in patients with ER+/ERBB2 – MBC requiring chemotherapy. The VICTOR-15 study is a retrospective, matched-controlled study designed to compare standard vs. metronomic chemotherapy as first-line treatment in HR+/HER2- MBC patients following failure of prior endocrine treatments, focusing on disease outcomes.

Patients and methods

Patients

As the primary objective of the study was the to compare mCHT vs. sCHT as first-line chemotherapy following failure of ET in HR+/HER2- MBC patients, we first identified all consecutive patients treated with mCHT (Vinorelbine alone or in combination with Capecitabine ± Cyclophosphamide) or sCHT (paclitaxel, nab-paclitaxel, or eribulin) between January 2015 and January 2024 at the Oncology and Phase 1 Research Units of Fondazione IRCCS San Gerardo dei Tintori. Inclusion criteria were histologically confirmed HR+/HER2- MBC, with available radiological evaluation; availability of data on age at relapse, number and type of previous endocrine treatment with or without CDK 4/6 inhibitors and Disease Free Interval. For each patient, data were collected on personal clinical history, date of primary tumor

diagnosis and first relapse, start and end date of first-line treatment, type and number of previous treatments, Performance Status (ECOG scale), sites of metastatic disease, outcomes (i.e. progression and death with corresponding dates) and treatment received after progression on mCHT or sCHT. The study was approved by the regional Ethical Committee (CET Lombardia 3, on 12 March 2025).

Methods

This retrospective study was based on a matched design in which each patient who received mCHT was matched to all the available patients treated with sCHT to gather as much information as possible. Selection bias is a potential concern, as treatment decisions are often influenced by patient preferences and clinical judgment based on individual risk profiles. To minimize this bias, we employed matching on prognostic factors to identify a comparable group of mCHT patients for accurate comparison with sCHT patients. Furthermore, since the sCHT group is larger, it is often possible to find more than one suitable match among sCHT patients for each mCHT patient. This rationale supports the use of a variable ratio matching approach. In our study, matching was done based on selected criteria usually considered clinically important for disease outcomes interpretation, with the aim of creating homogenous strata of patients that can be considered comparable: age at first-line treatment start (grouped into 5 decades 30–39, 40–49, 50–59, 60–69, ≥ 70 years), sites of metastatic disease (visceral vs. non visceral), previous treatment with CDK 4/6 inhibitors (yes vs. no), number of previous lines of therapy (0–1 vs. ≥ 2), disease free interval (DFI), defined as the time between primary tumor diagnosis and first relapse (≤ 5 vs. > 5 years).

As outside of randomized clinical trials, patient assessments are not precisely timed, uniformly documented, or manually curated at scale, posing challenges to obtain information on disease progression using real-world data [15], ESMO defined a uniform way to report outcomes parameters in the context of real-world [16]. Considering the retrospective design of our study, to describe the main outcome, we decided to adopt real-world Progression Free Survival (rwPFS), defined as the time from initiation of a certain cancer therapy until identified progression or death, whichever came first. Secondary endpoint was Overall Survival (OS), defined as the time from the date of mCHT or sCHT start to the date of death. For both the endpoints, patients were censored at the last recorded clinical activity, i.e. lost to follow-up or end of study, if there was no evidence of event. Follow-up was updated as of March 2025. Additional secondary endpoints were: Overall Response Rate (ORR, defined as the percentage of patients who achieved Complete (CR) and Partial Response (PR), and Clinical Benefit Rate (CBR), defined as the proportion of patients who achieved CR, PR or stable disease (SD) for more than 24 weeks.

Statistical analysis

Median (min-max) and absolute/relative frequency were used for the description of continuous and categorical variables, respectively. The standard Kaplan–Meier (KM) approach was used to estimate the rwPFS and OS curves for patients treated with mCHT, while a weighted version of this estimator was considered for the sCHT group. This approach was needed because, given the different number of sCHT patients for each mCHT woman, the distribution of the matching variables in the two groups could be rather different and the contribution of individuals belonging to largest sets of sCHT patients needed to be down-weighted (i.e. weights were the reciprocal of the number of controls) [17]. KM estimates were reported at various time points along with their 95% Confidence Intervals (CIs), which were build using the Greenwood's and the bootstrap standard error for mCHT and sCHT, respectively. Comparisons of rwPFS and OS in the two treatment groups that accounts for matching was done resorting to a multivariate permutation testing approach applied to all the observed event times included between the 20th and the 90th percentiles of the overall event distribution [17] ORR and CBR were reported in terms proportions with the corresponding 95%CIs. All the tests were two-sided and the significance level was fixed at 5%. The analyses were performed using R (version 4.4.3).

Results

Between January 2015 and January 2024, 56 patients were treated with mCHT and 89 with sCHT, meeting the inclusion/exclusion criteria of this study. Figure 1 describes the initial population and the one obtained after matching.

The characteristics of the 145 enrolled patients are reported in Supplementary Table 1.

Twenty-seven patients treated with mCHT were matched to 52 women treated with sCHT using a variable ratio, ranging from 1 to 5 (median = 1). At the time of mCHT/sCHT initiation, the overall median age was 60.4 years (30.2–78.8). Most of the patients had an ECOG PS of 0 (83.5%), presented with visceral metastases (69.6%) and had received CDK 4/6 inhibitors as first-line treatment (49.4%). Details on patients' and tumor characteristics overall and in both groups are reported in Table 1.

The median age at second-line treatment was approximately 60 years in both groups. In the mCHT group, all patients received Vinorelbine, either alone ($n = 7$, 25.9%) or in combination with Capecitabine, with or without Cyclophosphamide at the dose of 50 mg/day ($n = 13$, 48.1%). Vinorelbine was administered at at a

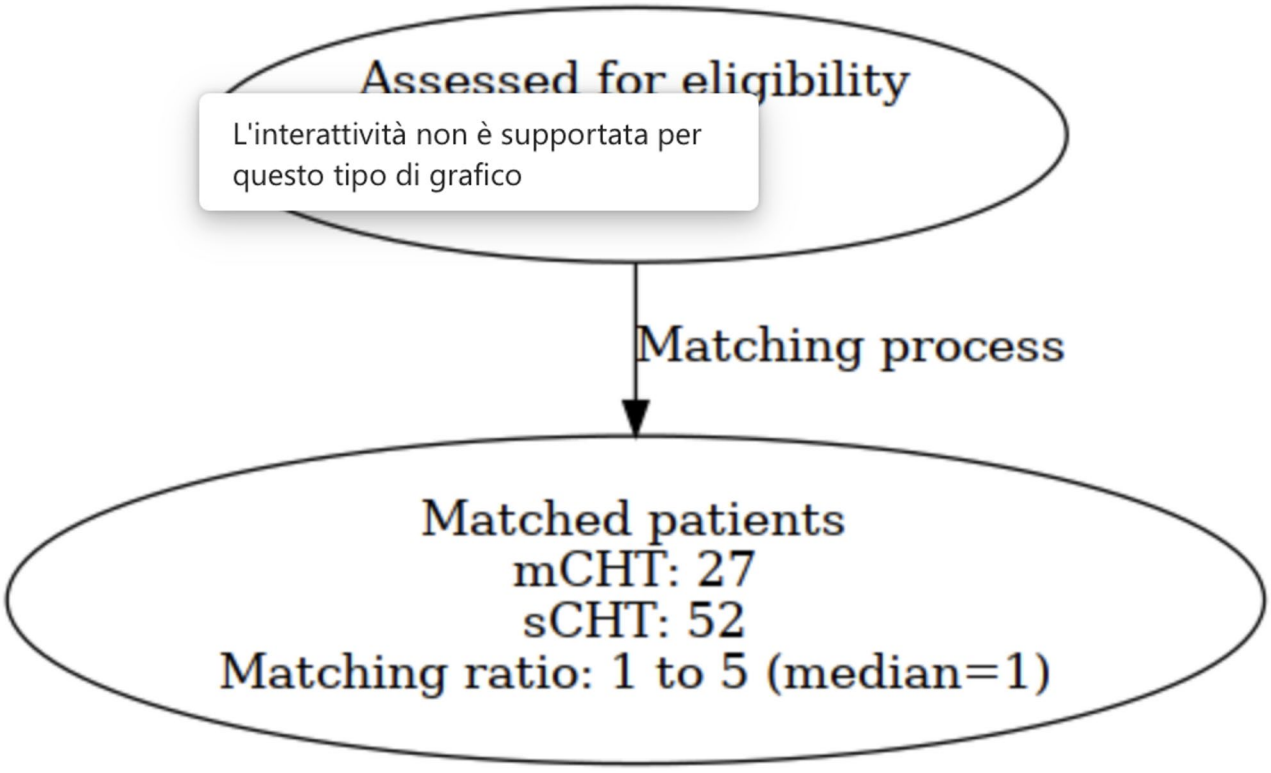

Fig. 1 CONSORT flow chart

dose of 50 mg (as single agent) or 40 mg (in combination regimens) three times per week; Capecitabine was administered at the dose of 500 mg three times per day, continuously. In the sCHT group, most patients received Paclitaxel, ($n=20$, 38.5%), or nab-paclitaxel ($n=18$, 34.6%) as single agents. Others received paclitaxel in combination with bevacizumab ($n=3$), carboplatin ($n=2$) or gemcitabine ($n=1$). Additional regimens included CMF ($n=1$), carboplatin plus gemcitabine ($n=1$), andsingle agents, such as epirubicin ($n=5$), or Eribulin ($n=1$).

After a median follow-up of 32 months, the 1-year rwPFS was 29.6% (95%CI = 16.6–53.0%) for mCHT and 12.6% (95%CI = 5.0-29.3%) for sCHT ($p=0.272$). Median rwPFS was 7.0 months (95%CI = 4.1–12.6) for mCHT and 5.4 months (95%CI = 3.9-7.0) for sCHT, (Fig. 2). The 1- and 3-year OS estimates were 81.5% (95%CI = 68.1–97.5%) and 46.9% (95%CI = 30.2–72.9%) in the mCHT and 53.1% (95%CI = 39.5–71.5%) and 20% (95%CI = 9.3–43.2%) in the sCHT group ($p=0.087$). Median OS was 29.3 months (95% CI = 22.4–44.9) for mCHT and 15.3 months (95% CI = 9.2–26.9) for sCHT (Fig. 3).

ORRs were 37% (95%CI = 19.4–57.6%) in the mCHT group and 28.8% (95%CI = 17.1–43.1%) in the sCHT group; CBR was 66.7% (95%CI = 46.0-83.5%) in mCHT patients and 61.5% (95%CI = 47.0-83.5) in those treated with a sCHT. Patients received various lines of treatment after mCHT/sCHT failure and details are reported in Table 2. Notably, a higher percentage of patients in the sCHT group did not receive further treatment in comparison to mCHT group (23.1% vs. 11.1%).

Discussion

The retrospective, matched VICTOR-15 study compares mCHT and sCHT as first-line treatment after endocrine therapy +/- CDK 4/6i failure in HR+/HER2- MBC patients. Both median rwPFS and OS were longer in patients treated with mCHT compared to those treated with sCHT, with an absolute difference of 1.6 months (7.0 months, 95%CI = 4.1–12.6 vs. 5.4 months, 95%CI = 3.9-7.0) for rwPFS and of 14 months (29.3 months, 95%CI = 22.4–44.9 vs. 15.3 months, 95%CI = 9.2–26.9) for OS.

To date, the only randomized study comparing mCHT vs. sCHT is the METEORA II study [13] The study randomized 140 patients, previously treated with no more than one CHT regimen and two lines of endocrine therapies, to prospectively receive either the metronomic VEX regimen or intravenous weekly paclitaxel. The primary endpoint was Time to Treatment Failure (TTF), defined as the interval from randomization to the end-of-treatment; secondary endpoints included PFS, disease control rate (DCR) and OS. TTF was 8.3 (95%CI = 5.6–11.1) months for metronomic VEX regimen versus 5.7 (95%CI = 4.1–6.1) months for Paclitaxel. The median PFS was

Table 1 Patients' and tumor characteristics of the matched mCHT and sCHT women. Results are reported as median (min-max) and n (%)

Characteristic	mCHT (*n* = 27)		sCHT (*n* = 52)		Total (*n* = 79)	
ECOG Performance Status						
0	21	(77.8)	45	(86.5)	66	(83.5)
1	5	(18.5)	7	(13.5)	12	(15.2)
2	1	(3.7)	0	(0)	1	(1.3)
Age at primary tumor (year)	52.6 (29.9–65.4)		54 (27.2–72.6)		53.2 (27.2–72.6)	
< 55	17	(63)	30	(57.7)	47	(59.5)
55–69	10	(37)	21	(40.4)	31	(39.2)
≥ 70	0	(0)	1	(1.9)	1	(1.3)
Age at first relapse (year)	58.7 (30.0-73.8)		58.4 (30.7–78.3)		58.6 (30.0-78.3)	
< 55	7	(25.9)	14	(26.9)	21	(26.6)
55–69	15	(55.6)	31	(59.6)	46	(58.2)
≥ 70	5	(18.5)	7	(13.5)	12	(15.2)
Age at mCHT/sCHT start (year)	60.9 (30.2–77.8)		60.3 (30.7–78.8)		60.4 (30.2–78.8)	
< 55	6	(22.2)	14	(26.9)	20	(25.3)
55–69	15	(55.6)	30	(57.7)	45	(57)
≥ 70	6	(22.2)	8	(15.4)	14	(17.7)
DFI (years)	6.8 (0–26)		3.5 (0.17.1)		8.7 (0–26)	
≤ 5	12	(44.4)	29	(55.8)	41	(51.9)
> 5	15	(55.6)	23	(44.2)	38	(48.1)
ER status						
ER+ / PR +	24	(88.9)	41	(78.8)	65	(82.3)
ER+ / PR -	3	(11.1)	11	(21.2)	14	(17.7)
Previous CDK4/6 inhibitors						
Yes	14	(51.9)	25	(48.1)	39	(49.4)
No	13	(48.1)	27	(51.9)	40	(50.6)
N. of therapy lines at study entry						
≤ 1	18	(66.7)	35	(67.3)	53	(67.1)
> 1	9	(33.3)	17	(32.7)	26	(32.9)
Categories of metastatic sites						
Visceral (liver & lung)	19	(70.4)	36	(69.2)	55	(69.6)
Non visceral	8	(29.6)	16	(30.8)	24	(30.4)
Site of metastases						
Bone	21	(77.8)	40	(76.9)	61	(77.2)
Lymph nodes	16	(59.3)	23	(44.2)	39	(49.4)
Liver	13	(48.1)	25	(48.1)	38	(48.1)
Lung	9	(33.3)	12	(23.1)	21	(26.6)
Other	12	(44.4)	15	(28.8)	27	(34.2)

Legend: *DFI* Disease Free Interval

11.1 (8.3–13.8) for VEX and 6.9 (5.4–10.1) for Paclitaxel,. OS was similar between the two groups: 29.5 (95% CI, 19.4- not estimable) months for VEX versus 33.7 (95%CI = 20.0-not estimable) months for paclitaxel (HR = 0.98; 95%CI = 0.59–1.63; p = 0.90). Our results, although based on a limited sample size, are consistent with those reported in the METEORA study. The rwPFS observed in our study for mCHT is slightly lower that that reported in the METEORA trial, which may be attributed to the use of three-drug combination (VEX regimen) in the latter. This difference could also be explained by the higher proportion of patients who did not receive further treatments after first-line sCHT (23.1% vs. 11.1% in the mCHT group) or by the fact that more than 50% of the patients treated with mCHT subsequently received Taxanes (paclitaxel or nab-paclitaxel) as second-line chemotherapy.

One important difference between mCHT and sCHT is the lower rate of side effects associated with mCHT, primarily due to its unique mode of administration, as described in different articles [12, 13, 18]. The reduced incidence of Grade 2 or greater of neutropenia and nausea/vomiting, and fatigue, may be critical in preventing deterioration of patients' PS, which can ultimately lead

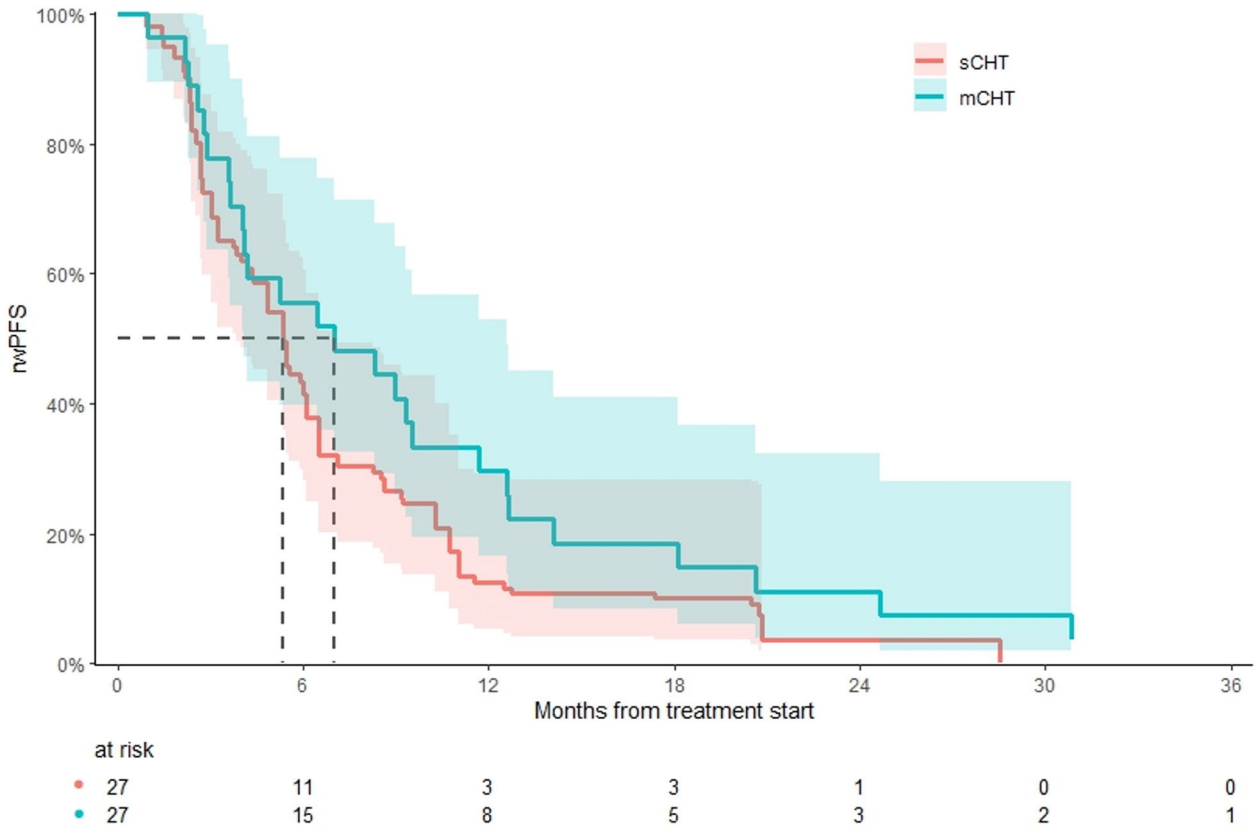

Fig. 2 Real-world progression free survival in the 2 matched groups. Patients at risk in the sCHT group are reported in a weighted version

to delays in second-line treatment or refusal to continue chemotherapy. Other studies [19, 20] have compared intravenous vs. oral administration of chemotherapy agents, showing similar efficacy; however, these trials were conducted over a decade ago and included heterogeneous populations. Several randomized phase II or III studies [21] have reported median PFS ranging from 6.0 to 7.9 months with first-line single-agent capecitabine in HER2- MBC patients, further supporting the results of our matched study.

More recently, the TEMPO Breast trial [22] reported a head-to-head comparison of the same agent, Vinorelbine, administered orally at either standard or metronomic doses, focusing on in disease control rate. The Authors found that the standard weekly vinorelbine regimen resulted in longer PFS (5.6 vs. 4.0 months) and OS (26.7 vs. 22.3 months) compared to metronomic vinorelbine, but was associated with a higher incidence of adverse events. As formal comparison between the two regimens was not permitted due to the study design, the Authors concluded that, following failure of endocrine therapy plus CDK 4/6 inhibitors, oral Vinorelbine may be a viable option with either schedule.

Considering the results of METEORA II and TEMPO Breast trials, it remains uncertain whether combinations of different oral agents (Vinorelbine + Capecitabine w/o Cyclophosphamide) are more effective than single agent strategies. in the absence of randomized trials addressing this question, real-world data become particularly valuable. In the VICTOR-6 trial [12], a real-life analysis involving more than 500 h+/HER2- MBC patients in Italy treated with various metronomic regimens, the longest PFS duration were observed in Vinorelbine-based combination regimens (9.6 months, 95%CI = 8.8–11.3) compared to single agent treatments.

The main limitations of our study include the small sample size obtained after matching, since approximately half of the initially identified patients were excluded due to lack of matching criteria and the relative heterogeneity of treatments in both groups. Although 73.1% of patients received Taxanes (paclitaxel or nab-paclitaxel) and that the type of treatment in these patients remained consistent over the time, we acknowledge this point as one limitation of our study. Additionally, the absence of toxicity or quality-of-life data represents another limitation. Prospective, larger, and confirmatory studies are needed to better establish the role of mCHT following ET failure.

For a long time, despite its widespread use in the clinical practice across various Countries, mCHT has been considered a palliative therapy, typically reserved for later

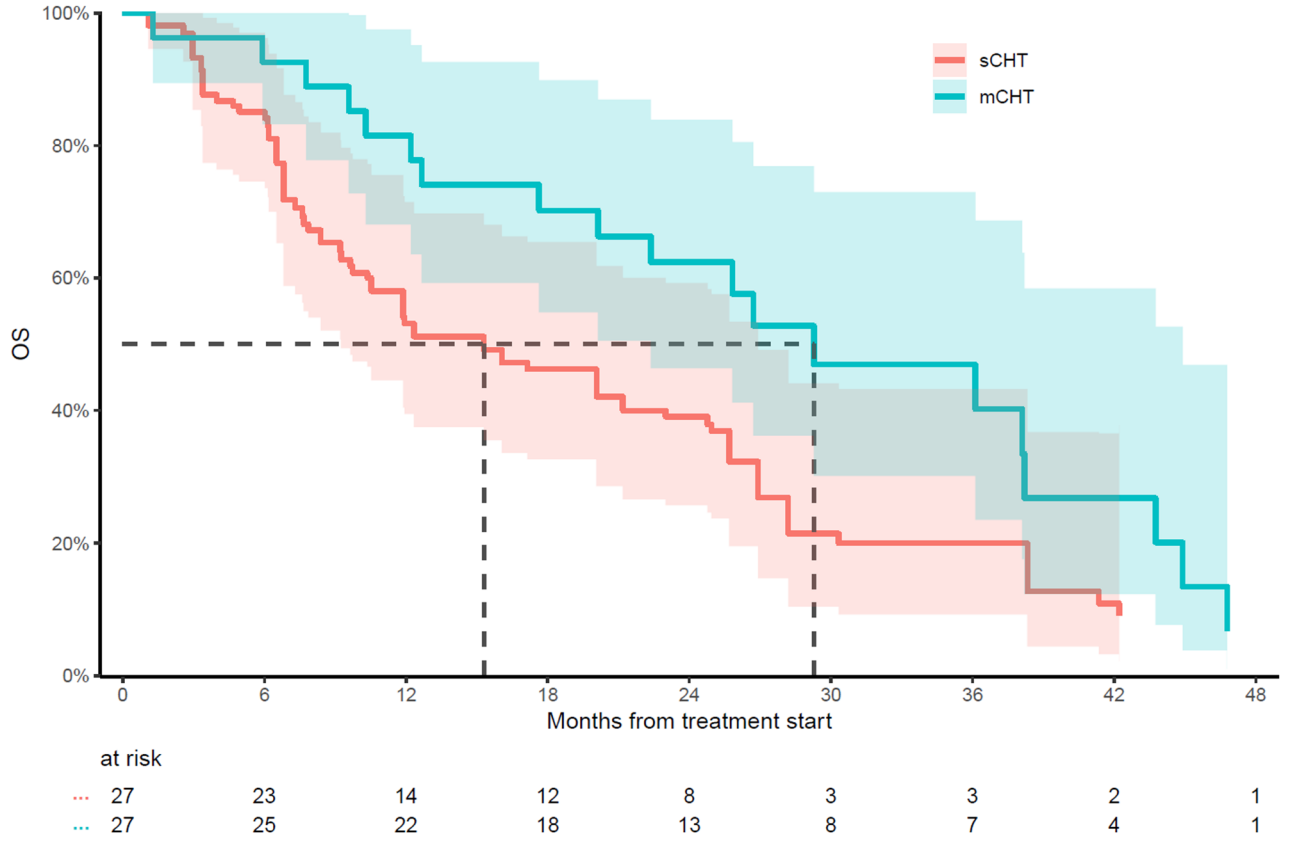

Fig. 3 Overall survival in the 2 matched groups. Patients at risk in the sCHT group are reported in a weighted version

Table 2 – Type of treatment received after mCHT/CHT. Results are reported as *n* (%)

Second line treatment	mCHT (*n* = 27)		sCHT (*n* = 52)		Total (*n* = 79)	
Nab-paclitaxel	7	(25.9)	0	(0)	7	(8.9)
Paclitaxel	6	(22.2)	0	(0)	6	(7.6)
Everolimus + exemestane	5	(18.5)	0	(0)	5	(6.3)
Eribuline	2	(7.4)	7	(13.5)	9	(11.4)
CDK 4/6i + ET	1	(3.7)	5	(9.6)	6	(7.6)
Vinorelbine (non mCHT)	1	(3.7)	4	(7.7)	5	(6.3)
Carboplatin + Paclitaxel	1	(3.7)	0	(0)	1	(1.3)
Capecitabine (non mCHT)	1	(3.7)	0	(0)	1	(1.3)
Epirubicin	0	(0)	8	(15.4)	8	(10.1)
Vinorelbine-based mCHT	0	(0)	5	(9.6)	5	(6.3)
Lyposomal doxorubicin	0	(0)	3	(5.8)	3	(3.8)
Carboplatin/cisplatin + Gemcitabine	0	(0)	2	(3.8)	2	(2.5)
Sacituzumab Govitecan	0	(0)	2	(3.8)	2	(2.5)
Talazoparib	0	(0)	2	(3.8)	2	(2.5)
Gemcitabine	0	(0)	1	(1.9)	1	(1.3)
Vinorelbine + Capecitabine (mCHT)	0	(0)	1	(1.9)	1	(1.3)
No further treatment	3	(11.1)	12	(23.1)	15	(19.0)

lines of treatment and preferentially to frail, old or highly pretreated patients. In our opinion, this positioning has largely been due, in our opinion, to the lack of randomized studies directly comparing mCHT with standard regimens, such as paclitaxel, nab-paclitaxel or Eribulin. However, the present findings may at least partially help to overcome this limitation.

Finally, another important aspect to consider is the cost of treatment. The rising expenses associated with cancer care have led to significant - and in some case persistent

- inequities. In this context, the availability of low-cost regimens, such as the combination of Vinorelbine and Capecitabine, with or without Cyclophosphamide, may offer a more affordable yet effective treatment for both high-income and low- and middle-income countries. As recommended by Battaiotto et al. in their recent review [23], the use of metronomic chemotherapy in breast cancer - to improve tolerability, reduce treatment-related complications and associate costs and enhance sustainability of cancer care - should not be viewed as a universal solution, for all breast cancer settings. However, our findings demonstrated for the first time that mCHT is not inferior to standard regimens such as paclitaxel or nab-paclitaxel. A pharmacoeconomic evaluation comparing the two regimens is currently ongoing.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12885-025-15482-1.

Supplementary Material 1.

Acknowledgements
Not applicable.

Authors' contributions
M.E.C. and S.G. designed the study, performed the statistical analyses and wrote the main manuscript text. F.F.P., V.C. and F.S. enrolled patients. F.S. was responsible for data collection. All authors reviewed the manuscript.

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None.

Data availability
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request. Data supporting the reported results can be found at Fondazione IRCCS San Gerardo.

Declarations

Ethics approval and consent to participate
The study was conducted in accordance with the guidelines of the Declaration of Helsinki and approved by the Comitato Etico Regionale Lombardia 3 on March 12, 2025. Informed consent was obtained from all alive subjects involved in the study. For those who died, or could not be located, consent was not required, in accordance with the General Authorization to Process Personal data for Scientific Research Purposes (1 March 2012) issued by the Guarantor for the protection of Personal data.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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