

Vinorelbine thiotepa in metastatic breast cancer: a large real-life retrospective study

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Background

Breast cancer (BC) ranks as both the most prevalent and deadliest form of malignancy among women worldwide [1]. In metastatic breast cancer (MBC), survival hinges on critical prognostic factors, including tumor subtype, performance status, age, metastatic-free interval, and the presence of visceral metastasis or high tumor burden [2–4]. The occurrence of cerebral and/or leptomeningeal tumor spread is a frequent phenomenon [4–6], significantly impacting prognosis [6,7]. This is, in part, a result of the blood–brain barrier (BBB), which restricts the entry of most antineoplastic drugs into the central nervous system (CNS), rendering them less effective against CNS metastases [8,9].

Although promising novel drugs such as cdk 4/6 inhibitor [10], antibody–drug conjugates (ADCs) [11–13] or immunotherapy [14] have disrupted the standard of care over the last decade, cytotoxic chemotherapy remains the cornerstone in subsequent lines of salvage therapy. The first treatment lines reach consensus [15]. Subsequent therapeutic options with lower objective response rates (ORRs) are not clearly defined. The use of several classes of chemotherapy in the perioperative setting makes treatment selection challenging in case of metastatic relapse. Guidelines typically recommend a sequential approach of cytotoxic monotherapy for MBC, which often proves sufficient to attain a satisfactory disease control rate. The goal of polychemotherapy is to increase the ORR and improve disease control in aggressive forms of cancer. The improvements in survival duration for MBC patients have led to a growing incidence of secondary cerebral and/or meningeal tumor spread, presenting a significant management challenge [16].

Vinorelbine is widely used for the management of MBC. As a single-agent chemotherapy, it has demonstrated comparable efficacy to standard agents like anthracyclines, with an overall response rate (ORR) of approximately 50% when

used as a first-line treatment [17]. A systematic review has confirmed its activity as a second-line treatment in MBC pre-treated with anthracyclines and taxanes, reaching an ORR of approximately 15–20% [18]. Several vinorelbine-based combinations have shown to be effective [19]. Thiotepa is used in several tumor types and has shown an acceptable safety profile [20]. Its lipophilic structure allows penetration through the BBB, improving its bioavailability in the brain and meninges [21]. This agent has demonstrated its effectiveness, in patients with meningeal carcinomatosis [22], and in hematologic diseases like CNS lymphomas [23]. Furthermore, thiotepa has demonstrated efficacy in patients with cerebral metastases and carcinomatous meningitis in cases of MBC, with studies reporting positive outcomes from both intravenous infusions [24] and intrathecal injections [25].

The combination of intravenous vinorelbine and thiotepa for the treatment of MBC is not frequently used in clinical practice, and there are limited data available on its efficacy and safety in the existing literature. The only study available is a phase II trial [26] published by Fabi et al., reporting an ORR of 28% [95% CI 12–44] and a median progression-free survival (mPFS) of 6 months [95% CI 1–20] in second-line treatment in 32 patients with MBC. This combination holds promise in the treatment of MBC patients, particularly those with cerebral and/or leptomeningeal metastasis.

We conducted an observational retrospective monocentric cohort study to assess the efficacy and safety of the association of vinorelbine and thiotepa in patients with MBC.

Materials and methods

Study design and patients

Data were retrospectively collected from all consecutive patients with MBC, who received vinorelbine and thiotepa during a 10-year period, between 13 January 2011 and

30 April 2021, in the Breast Cancer Department of Saint Louis Hospital, a University Hospital in Paris, France.

Patients with histologically confirmed MBC treated with intravenous vinorelbine and thiotepa were considered for inclusion. Other eligibility criteria were: ≥ 18 year-old, at least one prior chemotherapy line with anthracycline or taxane received in neoadjuvant, adjuvant, or metastatic setting and at least one fully administered cycle of vinorelbine–thiotepa. Exclusion criteria were concomitant treatment for another neoplasm and vinorelbine–thiotepa received as a local recurrence treatment.

Study treatment

Vinorelbine was administered at a dose of 30 mg/m², and thiotepa at a dose of 12 mg/m², intravenously, on day 1 and 8, every 3 weeks. Premedication consisted of 80 mg intravenous methylprednisolone and 8 mg ondansetron. Treatment was discontinued upon disease progression, unacceptable toxicity, altered performance status, or physician decision. Patients with brain metastasis or meningeal carcinomatosis could receive iterative or concomitant intrathecal perfusion of methotrexate and local radiotherapy or surgery.

Endpoints

The primary endpoint was progression-free survival (PFS) in the overall population and among patients with CNS metastasis. PFS was defined as the time between the introduction of vinorelbine–thiotepa and disease progression (RECIST or not-RECIST progressive disease: according to physician choice evaluation) or death. Secondary endpoints were OS in the overall population, OS in patients with CNS metastasis, and safety profile. OS was defined as the time between the introduction of vinorelbine–thiotepa and death. Subgroup analyses included PFS in highly pretreated patients (≥ 3 lines of treatment at the metastatic stage) and in triple-negative breast cancer (TNBC) population. For the safety evaluation, adverse events were retrospectively collected and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0.

Statistical analysis

Univariate descriptive data analysis was performed. The PFS, OS, and the follow-up time data were analyzed using Kaplan–Meier's curves. The follow-up time was calculated using the reverse Kaplan–Meier's method. Statistical analyses were performed using the R software (Version 4.0.2) (R Foundation for Statistical Computing, Vienna, Austria) and R studio software (Version 1.2.1335) (Boston, MA).

Results

Patient characteristics

A total of 144 patients with BC treated with vinorelbine–thiotepa were identified through a local database. Three patients did not meet eligibility criteria ($n = 1$ without histologically

confirmed BC and $n = 2$ did not receive a full cycle of vinorelbine thiotepa) and four patients presented exclusion criteria ($n = 2$ with local recurrence without metastatic disease and $n = 2$ with concomitant treatment for another neoplasm). A total of 137 patients were included in the final analysis (flowchart, [Supplementary Figure S1](#)).

The median age was 57 years (range 31–86). A large majority of the patients (99.3%; $n = 136/137$) were women. The most frequent histological type was invasive ductal carcinoma (83.2%; $n = 114/137$). Over two-thirds of the patients (73.7%; $n = 101/137$) had hormone-positive BC, and approximately one quarter (24.1%; $n = 33/137$) had a TNBC. The patients characteristics are detailed in [Table 1](#).

One hundred and nine patients (79.6%) experienced metastatic relapse after local treatment. Among this population, the majority have received a neoadjuvant/adjuvant chemotherapy (94.5%; $n = 103/109$). Among patients with hormone-positive BC, most of them (74.7%; $n = 59/79$) have received an endocrine therapy at early BC stage.

Before vinorelbine–thiotepa regimen, patients have received a median of 2 [0–8] previous systemic therapeutic lines for MBC. All enrolled patients had received prior taxanes and/or anthracyclines. Twenty-two patients treated for a hormone receptor positive-BC were previously treated by an endocrine therapy associated with a cdk4/6 inhibitor ($n = 22/101$; 21.8%).

At the initiation of vinorelbine–thiotepa treatment, more than half of the patients (56.2%; $n = 77/137$) had at least three different metastatic sites. Cerebral-meningeal involvement affected over a third of the patients (34.3%; $n = 47/137$): 45/47 patients (95.7%) had brain metastasis, 17/47 patients (36.2%) had leptomeningeal carcinomatosis including 15/47 patients (31.9%) with both metastatic sites. Majority of them (74.5%; $n = 35/47$) were treated with concurrent encephalic radiotherapy treatment (whole brain radiation therapy or stereotaxic radiotherapy). A small proportion of patients underwent cerebral surgery and post-operative radiotherapy (13.3%; $n = 6/45$). Fourteen patients (82.4%; $n = 14/17$) have been treated with intrathecal chemotherapy in case of leptomeningeal carcinomatosis in combination with intravenous vinorelbine–thiotepa.

Efficacy

Median follow-up was 4.7 years (interquartile range (IQR), 3.8; NR). The median PFS was 4.4 months [95% CI, 3.7–5.1] in the overall populations ([Figure 1\(A\)](#)) and 3.6 months [95% CI, 2.6–5.2] in the CNS-metastasis population ([Figure 1\(B\)](#)). The median OS was 12.7 months [95% CI, 10.7–15.6] in the overall population and 10.3 months [95% CI 6.9–13.4] in the CNS-metastasis population ([Supplementary Figure S2A and S2B](#)).

The median PFS in highly pretreated patients ($n = 49$), who had received at least three previous lines of systemic therapy at the metastatic stage, was 3.5 months [95% CI, 3.0–4.6]. The median PFS in patients with metastatic-TNBC ($n = 33$) was 4.5 months [95% CI, 2.4–6.4].

Table 1. Patients' characteristics.

	N (%) Overall population n = 137	N (%) Population with CNS-metastasis n = 47
Age, years, median (range)	57 (31–86)	57 (31–86)
Female	136 (99.3)	47 (100)
Histology ^a		
Invasive ductal carcinoma	114 (83.2)	39 (83)
Invasive lobular carcinoma	17 (12.4)	6 (12.8)
Other	6 (4.4)	2 (4.2)
Hormone-receptor status ^a		
Hormone-receptor positive ^b	101 (73.7)	30 (63.8)
Triple-negative breast cancer ^c	33 (24.1)	16 (34)
Missing/other	3 (2.2)	1 (2.1)
Early breast cancer treatment	109 (79.6)	39 (83)
Chemotherapy	103 (94.5)	39 (100)
Radiotherapy	95 (87.1)	37 (94.9)
Surgery	107 (98.2)	39 (100)
Endocrine therapy	59 (74.7)	26 (86.7)
Prior taxane or anthracycline therapy	137 (100)	47 (100)
Metastatic disease at diagnosis	28 (20.4)	8 (17)
Metastatic sites (excluding CNS)		
Bone only	14 (10.2)	1 (2.1)
Visceral only ^d	42 (30.6)	15 (31.9)
Bone and visceral	81 (59.1)	31 (66)
Number of metastatic sites		
<3 sites	60 (43.8)	11 (23.4)
≥3 sites	77 (56.2)	36 (76.6)
CNS metastasis		
Cerebral metastasis	45 (32.8)	45 (95.7)
Leptomeningeal carcinomatosis	17 (12.4)	17 (36.2)
Both	15 (10.9)	15 (31.9)
Number of cerebral metastasis		
1	7 (5.1)	7 (15.5)
2–5	12 (8.8)	12 (26.7)
>5	26 (19.0)	26 (57.8)
Concurrent cerebral-meningeal treatments		
Intrathecal chemotherapy	14 (10.2)	14 (29.8)
Radiotherapy	35 (25.5)	35 (74.5)
Surgery and radiotherapy	6 (4.4)	6 (12.8)
No. of prior systemic therapies at metastatic stage, median (range)		
0	24 (17.5)	17 (36.2)
1–2	64 (46.7)	23 (48.9)
≥3	49 (35.8)	7 (14.9)
Prior endocrine therapy with a Cdk4/6 inhibitor	22 (21.8)	6 (12.8)

CNS: central nervous system.

^aHistology of the primitive tumor.

^bHormone-receptor status was defined by local immunohistochemistry results.

^cTriple-negative breast cancer was defined as estrogen-receptor and progesterone-receptor and HER2 negative, as defined by local test results. HER2 denotes human epidermal growth factor 2.

^dIncluding skin and lymph nodes metastasis.

Safety

All patients were included in the safety analysis ($n = 137$, Table 2). Grade 3 or 4 adverse events occurred in 48/137 (35.0%) patients. The most common grade ≥ 3 adverse event was hematotoxicity. Adverse events led to dose reduction in 50/137 (36.5%) patients and to discontinuation in 7/137 (5.1%) patients. Twenty-three (16.8%) of these dose reductions were due to hematotoxicity. No adverse event lead to death.

Discussion

This retrospective study was conducted to evaluate the efficacy and the safety profile of the vinorelbine–thiotepa chemotherapy regimen in MBC. In this large real-life cohort, the combination of vinorelbine and thiotepa demonstrated

efficacy in terms of PFS and OS for MBC but was also associated with significant toxicity.

Despite vinorelbine has failed to show superiority compared to other single-agent chemotherapy in patients with previously treated MBC [18], its efficacy was found to be closed to eribulin's in a phase III randomized trial from Yuan et al. in heavily pretreated patients [28]. Median PFS and OS observed in our study was numerically longer than what was reported in the phase III trial (2.8 and 12.5 months, respectively) [28]. Dual chemotherapy regimens containing vinorelbine have shown activity in the treatment of MBC [17–19,29]. Thiotepa's lipophilic structure enables it to readily penetrate the BBB [21]. As a result, it holds great promise for treating MBC with CNS metastases. Thiotepa and vinorelbine combination has been studied in a phase II trial [26] including only 32 patients mainly pretreated with anthracyclines, which reported a median PFS of six months [95% CI 1–20] and an

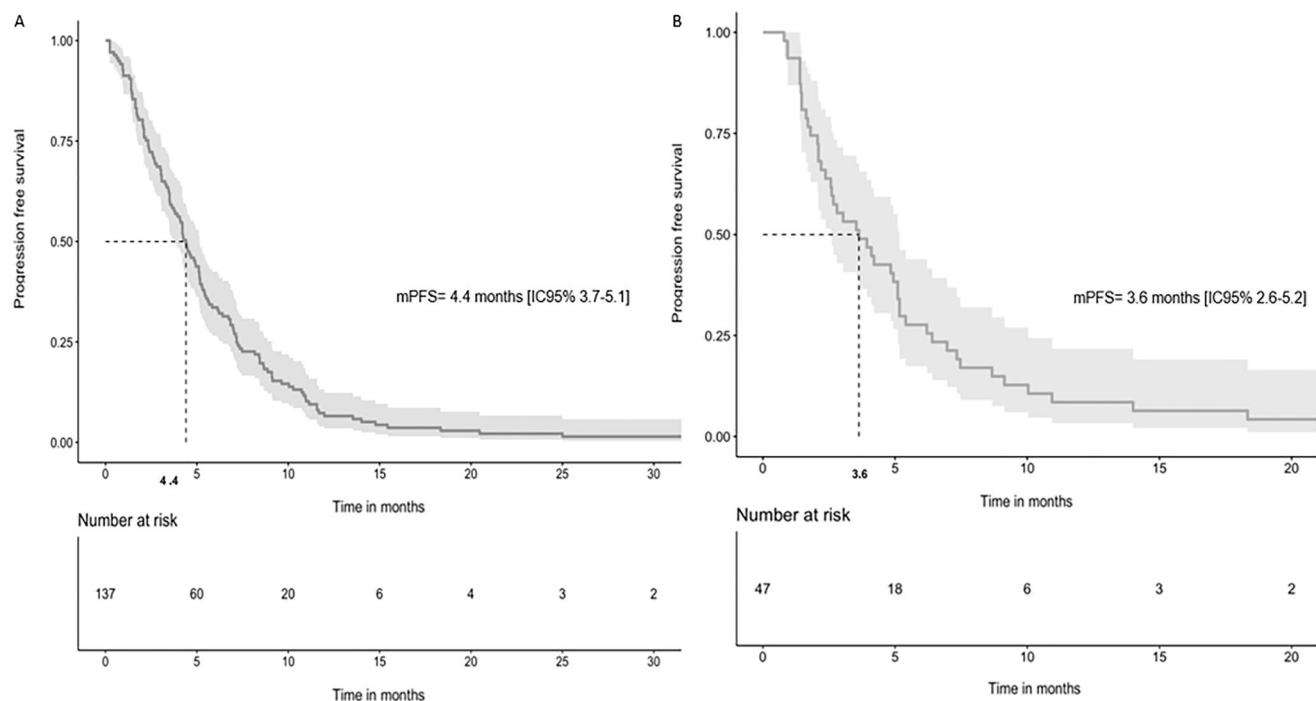


Figure 1. (A) Progression-free survival in the overall population. (B) Progression-free survival in patients with central nervous system metastasis.

Table 2. Safety profile.

	Grade ≥3 (n = 137)
Any event	48 (35)
Hematotoxicity	36 (26.3)
Perineural neuropathy	7 (5.1)
Digestive toxicity	9 (6.6)
Dose reduction	50 (36.5)
Causes of dose reduction	
Hematotoxicity	23 (16.8)
Perineural neuropathy	8 (5.8)
Digestive toxicity	7 (5.1)
Unknown	14 (10.2)
Discontinuation due to toxicity	7 (5.1)

Grade according to Common Terminology Criteria for Adverse Events (CTCAE) V5.0.

overall ORR of 28% [95% CI 12–44]. This led our center to adopt vinorelbine thiotepa as a treatment option for MBC patients, particularly those with CNS metastases.

In this extensive real-world retrospective cohort, we included unselected patients with several unfavorable prognostic factors and a history of multiple prior lines of therapy.

While performance status data were unavailable, it appears that this cohort encompassed a more vulnerable and heavily pretreated patient population compared to the one in the phase II study [26]. This difference in patient characteristics could account for the comparatively modest outcomes in terms of PFS. In this setting, a median PFS of 4.4 months and OS of 12.7 months are noteworthy. Of note, in CNS-metastatic patients, the median PFS and median OS achieved 3.6 months and 10.3 months. These findings suggest that this chemotherapy regimen may demonstrate efficacy in treating MBC with CNS metastasis. In the subgroup of metastatic-TNBC, the median PFS was 4.5 months, which is comparable to the PFS achieved with capecitabine [30].

Intravenous and oral vinorelbine have similar efficacy but different safety profiles [31]. In this study, the treatment was

administered intravenously, but it could be administered orally without anticipated variance in efficacy. However, the safety profile of the vinorelbine and thiotepa combination exhibited notable toxicity, with 35% of the patients experiencing grade ≥3 adverse events.

Our study is subject to several limitations, primarily stemming from its retrospective design and single-center setting. Due to significant heterogeneity in radiological evaluation methods and a substantial amount of missing data, we were unable to assess the radiological ORR reliably. Considerable heterogeneity between patients was also observed in terms of prior chemotherapy regimens administered and tumor types. Besides given the extensive inclusion period, it is important to note that the study sample may not fully represent a typical patient with MBC. Indeed only 21.8% of the patients with a hormone positive BC received cdk 4/6 inhibitor associated with endocrine therapy in the metastatic stage, which is currently the standard of treatment. The recent introduction of novel therapies, such as immune checkpoint inhibitors [14] and PARP inhibitors [32], to the therapeutic toolkit for addressing MBC, further complicates the interpretation of these findings. Another limitation is the potential for confusion bias caused by the administration of other concurrent local treatments such as intrathecal chemotherapy, surgery, and/or radiotherapy in the population with CNS metastases. Consequently, while the results in this subgroup are remarkable, it would be challenging to draw conclusions regarding the benefits of thiotepa for patients with CNS metastases.

As vinorelbine has been shown to be effective in treating MBC [16], the observed antitumor effect may be solely attributed to vinorelbine, and the contribution of adding thiotepa to the treatment is uncertain. The true benefits of this combination therapy can only be established through a

prospective randomized clinical trial involving a cohort of pre-treated MBC patients who are randomly assigned to receive either vinorelbine and thiotepa or vinorelbine and a placebo.

To the best of our knowledge, this study represents the first report demonstrating the clinical benefits of vinorelbine thiotepa in a substantial real-life cohort of patients with MBC. This study suggests that vinorelbine thiotepa might be effective in this setting and especially in patient with CNS metastasis. Nonetheless, we recognize the limitations inherent in our study, and we emphasize the need for future prospective and comparative studies to comprehensively evaluate the potential of this treatment approach.

Ethics statement

All alive patients received written information and provided their oral consent for data collection. Patients' clinical charts were retrospectively collected from electronic files using a de-identified form. This study was approved by the Ethical Review Board of the French College of Gynecologists and Obstetricians (2022-GYN-0304). In accordance with the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines, we have structured the reporting of our study to ensure comprehensive and transparent presentation of our research methodology and findings (STROBE checklist: cohort studies, Supplementary Table S1).

Author contributions

Rebecca Loison: conceptualization, data curation, formal analysis, investigation, methodology, resources, visualization, writing original draft, and writing review and editing. Baptiste Abbar: formal analysis, data curation, methodology, visualization, and writing review and editing. Leonor Drouin, Charlotte Bonnet-Bensimon, Caroline Cuvier, Sylvie Giacchetti, and Marc Espie: resources and writing review and editing. Luis Teixeira: conceptualization, investigation, methodology, project administration, resources, supervision, validation, visualization, and writing review and editing. Victoire De Castelbajac: conceptualization, investigation, methodology, project administration, resources, supervision, validation, visualization, and writing review and editing.

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Data availability statement

The data that support the findings of this study are available from the corresponding author, BA, upon reasonable request.

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