Research article

DOI: 10.59715/pntjmp.4.2.4

Evaluation of the outcome of oral vinorelbine plus trastuzumab in metastatic breast cancer

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Abstract

Background/Objectives: In the COVID-19 era, switching from an intravenous chemotherapy regimen to an oral regimen reduces the frequency of in-person contact and the duration of infusion. In the HERTANA trial, the vinorelbine plus trastuzumab regimen was considered equivalent to docetaxel plus trastuzumab. We conducted this study to evaluate the outcome of oral vinorelbine plus trastuzumab in metastatic breast cancer.

Methods: This is a retrospective study of 74 cases of HER2-positive breast cancer, either de novo or recurrent metastatic breast cancer, treated with oral vinorelbine in combination with trastuzumab at HCM City Oncology Hospital from June 14, 2021, to June 14, 2023.

Aims: The primary endpoint is the overall response rate (ORR). Secondary endpoints include progression-free survival (PFS), median overall survival (mOS), and adverse events (AEs).

Results: The median progression-free survival was 6.5 months, and the median overall survival was 21.1 months. The response rates at 3 and 6 months were 25.7% and 12.2%, respectively.

Conclusions: The vinorelbine–trastuzumab regimen is a viable alternative to docetaxel–trastuzumab as a first-line treatment for patients who refuse infusion therapy or are intolerant to docetaxel.

Keywords: Vinorelbine, Trastuzumab, Breast Cancer

Received: 20/11/2024
Revised: 20/3/2025
Accepted: 20/4/2025

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1. INTRODUCTION

Breast cancer accounts for the second most common malignancy in the world, with more than 2.2 million cases in 2022. Its mortality rate ranks fourth after lung, colorectal, and liver cancer, with 666,103 cases, according to GLOBOCAN 2022 [2].

In Vietnam, in 2022, breast cancer was the leading cause of new cancer cases, with 24,563 new cases, and its mortality rate ranked fourth.

Metastatic breast cancer remains an incurable disease, with an overall survival (OS) of approximately three years and a 5-year survival rate of 25%. The goal of treatment for metastatic breast cancer is to prolong progression-free survival (PFS), improve quality of life, and control symptoms.

Currently, the choice of systemic therapy is crucial, based on patient characteristics (menopausal status, age, ECOG), pathological status (clinical features, disease progression, spread, site and number of metastases, response to prior systemic treatment), and biological characteristics (hormone receptors, HER2 status, BRCA gene mutation, PIK3CA).

The first-line treatment selection for advanced metastatic breast cancer mainly depends on the breast cancer subtype. The majority of subtypes, after progressing following first-line treatment or in cases of rapidly progressing disease, require

intervention with chemotherapy.

In the context of the COVID-19 pandemic in 2020, treatment strategies shifted toward protocols that reduce direct contact and shorten infusion times for outpatients.

Vinorelbine can be used as monotherapy or in combination therapy, for patients diagnosed with advanced, metastatic, or relapsed breast cancer following previous treatment failure. The effectiveness of vinorelbine is reflected in its ability to prolong survival time with low toxicity during treatment.

Trastuzumab was previously approved for patients with HER2-positive breast cancer.

According to previous data, the disease control rate is about 71–83%, and the median progression-free survival (PFS) is approximately 9.7 months in the first line and 6.6 months in the second line (1, 2, 3, 4, 5). Moreover, due to its low toxicity, vinorelbine is well tolerated and improves patients' quality of life. Therefore, vinorelbine is often the preferred choice.

In addition, the convenience of the oral formulation, combined with its good tolerability, allows patients to receive treatment for an extended period.

2. METHODOLOGY

2.1 Patient selection

2.1.1 Population:

Patients from 18 years of age diagnosed with HER2(+)/FISH(+) metastatic breast cancer

2.1.2 Selection criteria:

- Patients diagnosed with HER2(+)/ FISH(+) metastatic breast cancer treated with Vinorelbin in combination with Trastuzumab
- The histopathological diagnosis of primary breast tumor is invasive epithelial carcinoma
- result in any ER, any PR, any Ki67, but HER2 positive, , or FISH 3+
- Assessment of the patient's overall condition according to the ECOG scale = 0.1.2

2.1.3 Exclusion Criteria:

- Patients who have used Vinorelbine ≤ 2 cycles
- Patients with other concomitant cancers that are not stably controlled

2.2 Research methods

2.2.1 Research Methodology

- Description of the case series
- Data collection period: from June 14, 2021, to June 14, 2023
- Location: Department of Mammography – Gastroenterology – Hepato-Urology, Oncology Hospital, Ho Chi Minh City
- Treatment regimen: Vinorelbine 60–80 mg/m² on Days 1 and 8, and Trastuzumab 600 mg (subcutaneous injection on Day 1) or 8 mg/kg in Cycle 1 and 6 mg/kg from Cycle 2. Each cycle consists of 21 days.
- Patients would start with a dose of Vinorelbine 60 mg/m² on Day 1 of the cycle. After 1 week, the granulocyte count would be checked to determine whether to increase the dose to 80 mg/m² on Day 8.
- The patient would continue to be monitored for granulocyte count weekly during the first two cycles.
- Treatment duration: Until disease progression or grade 3–4 toxicity develops (except in cases of grade 4 granulocytopenia).
- In cases of grade 4 granulocytopenia, the patient would be treated according to current guidelines and the dose of Vinorelbine would be reduced by 20 mg/m² in the next cycle after recovery. Alternatively, the regimen would be changed if life-threatening symptoms occur.

2.3 Responsive Assessment

- Tumor and lymph node size measurements on clinical breast examination, ultrasound, mammography, and CT scan/MRI, assessed every 3 months based on

RECIST 1.1 criteria.

- Evaluation criteria for total clinical response (ORR) = complete response (CR) + partial response (PR) (WHO standard).
- Progression-free survival: calculated from the time the patient starts treatment with Vinorelbin – Trastuzumab until clinical or radiological progression,
- Average overall survival: the mean time from the time the patient starts treatment with the Vinorelbin – Trastuzumab regimen until death.
- Related side effects: Toxicity (leukopenia, granulocytopenia, hypothrombocytopenia, thrombocytopenia, nausea/ vomiting, diarrhea, hand, foot syndrome, peripheral neuropathy, alopecia, oral mucositis, liver enzymes, creatinine)

3. RESULTS

The study collected data from patients treated at Ho Chi Minh City Oncology Hospital in 12 months for the following results:

3.1 Demographic characteristics:

The total number of diseases that meet the criteria ts is 74 patients, of which 19 (25.7%) patients metastasize at the beginning, the remaining 55 patients at relapse, accounting for 74.3%.

The average age is 51 years old, 52.7% of patients are menopause. The percentage of patients with positive endocrine receptors is 58.1%, and the remaining 41.9% of patients have negative endocrine receptors.

The Vin – Tras treatment regimen was used to treat patients from line 1, line 2, and line 3 at 6.8%, 70.2% and 23%, respectively.

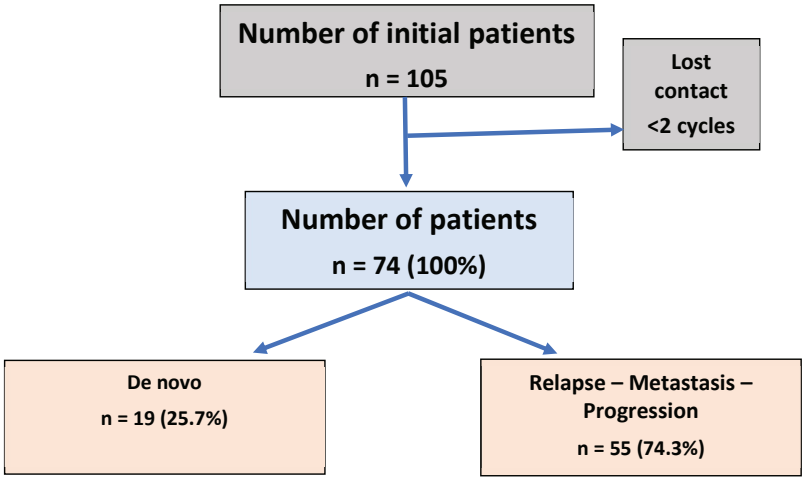

Table 1 – Demographics and clinical characteristics of all patients		
Age		
Mean age	51.0	
Range	24-73	
Menstrual status		
Menopause	39	(52.7%)
Not yet menopausal	35	(47.3%)
Endocrinology		
Negative	31	(41.9%)
Positive	43	(58.1%)
Initial condition		
De novo	19	(25.7%)

Develop	55	(74.3%)
Condition Her-2/neu		
FISH+	10	(13.5%)
IHC 3+	64	(86.5%)
Treatment lines		
Line 1	5	(6.8%)
Line 2	52	(70.3%)
From line 3	17	(23.0%)
Number of metastases		
1	15	(20%)
2	25	(34%)
>3	34	(46%)
Metastasis characteristics		
Viscera	55	(74%)
Bone	11	(15%)
In the region/in the region	8	(11%)
Metastasis location		
Bone	33	(29%)
Liver	27	(24%)
Lung	33	(29%)
Brain	4	(4%)
Other locations	15	(13%)
Histopathology		
UTBM Intrusive Tube	73	(99%)
Papillae	1	(1%)
Histology		
Grade I	0	(0%)
Grade II	56	(76%)
Grade III	18	(24%)
Endocrine treatment		
Have	26	(35%)
Not	48	(65%)
Trastuzumab in adjuvant phase		
Have	27	(36%)
Not	47	(64%)

The number of patients with organ metastases accounted for 74%, bone metastases accounted for 15% and the remaining 11% were local recurrences in the region.

99% of patients have tubular histological bodies, and histology II accounts for the highest at 76%.

Only 36% of patients received Trastuzumab during the support period.

3.2 Overall survival and survival until disease progression

The average time to survival to disease progression (PFS) is 4.5 months, ranging from 1.4 to 28.4 months. (Fig. 1)

The average survival time was 21.1 months, of which the shortest was 4 months and the longest was 45 months. (Fig. 2)

Patients receiving Vin – Tras treatment from line 2 for the longest average PFS duration is 7.2 months.

Patients receiving Vin – Tras treatment at lines 1 and 3 are 5.0 and 4.6 months, respectively (Table 2)

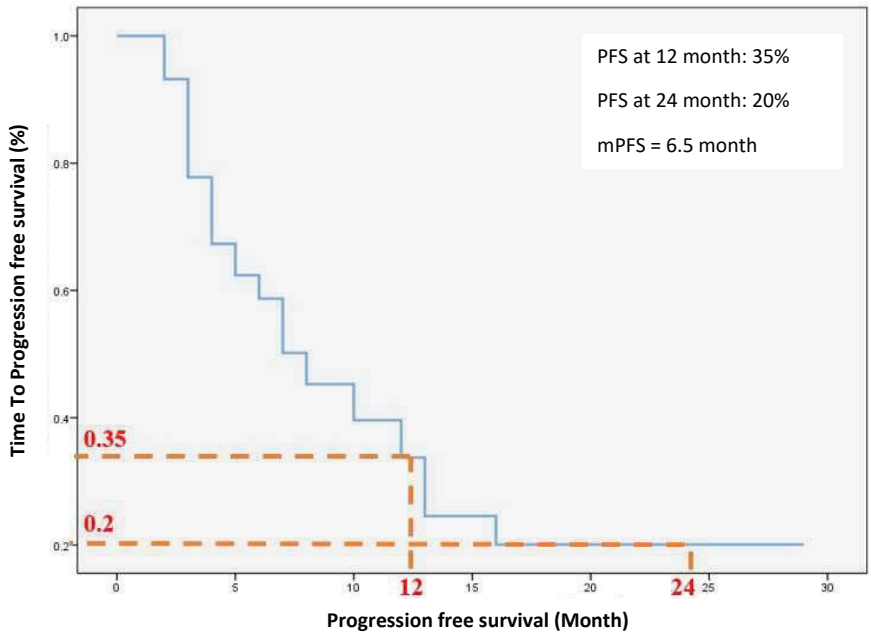

Fig 1. Progression free survival (Overall)

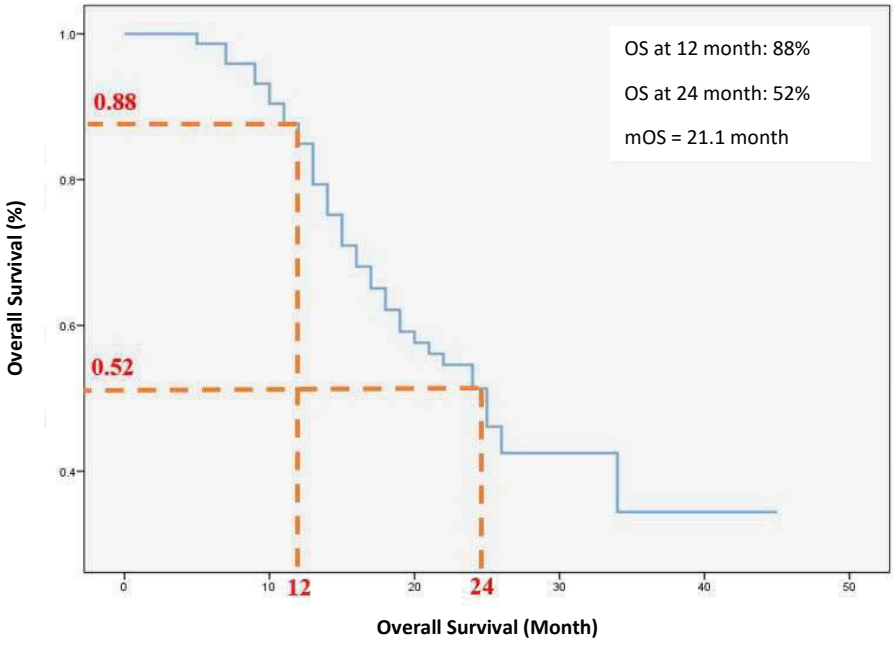

Fig 2. Overall Survival

Table 2 - Median survival time according to treatment line		
Treatment lines	**Survival time without disease progression (month)**	**Overall Survival Time (months)**
Line 1	5.0	23.6
Line 2	7.2	20.8
Line >3	4.6	21.3

3.3 Disease response rate (total and partial response rate)

The response rate after 3 months and 6 months was highest in the relapsed population, which progressed higher than that of the Denovo group at 17.6% compared to 8.1% and 9.5% compared to 2.7%, respectively with a p-< of 0.05, statistically minded (p = 0.035 and 0.023) (Table 3)

Table 3 – Overall Response Rate

Character		Evaluation of response after treatment 3 months (Entity)	Evaluation of response after treatment 6 months (Entity)
		N=19	N=9
RR	De novo	6 (8.1%)	2 (2.7%)
	Relapse	13 (17.6%)	7 (9.5%)
	p value	*0.035*	*0.023*

The group of patients in the endocrinal positive had a higher clinical response rate than the group of patients with endocrinal receptor negative at 3 months of 7.6% and 8.1% with a p=0.035. (Table 4)

Stage 4 - Response rate according to disease characteristics

Character	Responsive Assessment After Treatment 3 months	*p Value*	Responsive Assessment After Treatment 6 months	*p Value*
Negative endocrine status	6 (8.1%)	*0.035*	5 (10.9%)	*0.008*
Positive endocrine status	13 (17.6%)		4 (8.7%)	

3.4 Toxicity

The most common toxicity is vomiting and nausea, accounting for 44%. (fig. 3)

The most common toxicity rate of grade 3.4 is thrombocytopenia (Table 5)

The rate of delay in Vinorelbin doses is up to 24.3%, which is commonly caused by granulocytopenia and increased liver enzymes. The rate of dose reduction is 1.4%, and the mortality rate is 1.4% due to granulocytopenia. (Table 6)

None of the patients recorded a > 10% change in cardiac ejection fraction. (Table 7)

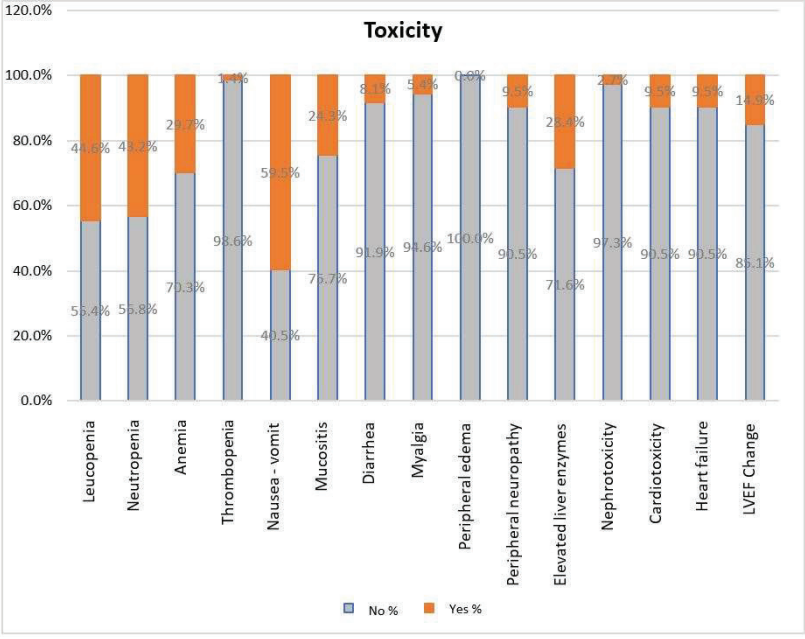

Fig 3. Toxicity

Table 5 – Toxicity			
Degree	**Neutrophilic polyleukopenia**	**Vomiting, nausea**	**Increase liver enzymes**
	N=26	**N=6**	**N=14**
Level 3	7 (9.5%)	3 (4.1%)	5 (6.8%)
Degree 4	6 (8.1%)	0 (0.0%)	2 (2.7%)
Level 3, 4	13 (17.6%)	3 (4.1%)	7 (9.5%)

Table 6 – Effects of chemotherapy toxicity	
	N=20
Delay chemotherapy	18 (24.3%)
Reducing the dose of chemotherapy	1 (1.4%)
Death	1 (1.4%)

Table 7 – Change in LVEF from the original	
	N=74
Not	63 (85.1%)
<10% off	11 (14.9%)

4. DISCUSSION

During the two-year period from June 14, 2021, to June 14, 2023, we received 105 patients with breast cancer treated with the Vin–Tras regimen. However, due to the general impact of the COVID-19 epidemic and intermittent drug supply, our report only collected 76 patients who met the inclusion and exclusion criteria. The median reported age of patients was 51, ranging from 24 to 73 years. The average progression-free survival was 6.5 months, ranging from 1.4 to 28.4 months.

There were 70.3% of patients receiving Vin – Tras treatment at line 2 and 23% from line 3 onwards.

The longest overall survival time is 45 months and the lowest is 4 months.

Overall survival time is comparable when using the Vinorelbin – Trastuzumab regimen in lines 1, 2 or 3.

The group of patients who relapsed and progressed had a higher response rate in that of Denovo. This may be due to the strict follow – up plane after adjuvant phase, hence, recurrence is early detected and may be due to that the relapse group have been treated with anthracyclin, taxane and/or Trastuzumab agents for adiuvant purpose.

The mean PFS duration tends to be higher in patients treated with the Vin-Tras regimen at line 2. In our study highlights that the time to progression free survival and, overall survival is lower and so does the response rates in comparision to the above studies. The reasons are that the majority of patients who received Vinorelbin – Trastuzumab treatment from line 2, the rate of organ metastases accounted for 74%, the majority of patients did not receive adjuvant treatment with trastuzumab in the adjuvant phase (64%), and also recorded cases of Denovo, who had not been exposed to anthracycline and taxane chemotherapy. (Table 8).

At 6 months, the group of patients with receptor negative status had a response rate of 10.9% compared to 8.7% in the group of patients with positive status, with p = 0.008. (Table 4). However, the number of patients who responded completely in the negative endocrine receptor group was less (1 patient) than in the group of endocrine receptor positive patients (7 fewer patients), which suggests a more sustainable clinical response in the endocrine receptor negative patient .

Toxicity related to treatment

Table 8 - Comparison with other studies						
		RR	mPFS	Mos	Side effects	
					Anemia	Neutrophilic polyleukopenia
Vietnam	Our Research	25.7%	6.5	21.1	29.7%	43.2%
	Le Thi Yen et al. [3] (8)	57.5%			50.0%	50.0%
	Vu Thi Trang and fortifications [4] (7)	63.2%	8.4		60.1%	57.2%
World	HERNATA (Vin-Tras Branch) (2)	59.1%	15.3	38.8		
	Harold J. Burstein [5] (3)	51%	5.8	8.5		
	Farhat (Oral Vin-Tras) [6] (4)	56%	6.7	27.9		

The most common toxicity is vomiting and nausea, accounting for 44%. The most common toxicity rate of grade 3.4 is thrombocytopenia. Most of these toxicities have been anticipated with the chemotherapy agent Vinorelbine and there are specific treatment guidelines. The most difficult to manage toxicity is largely due to patients not complying with the follow-up visits requested by the treating physician or not understanding how to use the drug one day per week

5. CONCLUSION

- Overall survival time is equivalent when using the Vinorelbine–Trastuzumab regimen in lines 1, 2, or 3.
- The group of patients who relapsed and progressed had a higher response rate than the de novo group.
- The mean PFS tends to be higher in patients treated with the Vin–Tras regimen at line 2.

6. REFERENCES

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