

METRONOMIC CHEMOTHERAPY WITH ORAL NAVELBINE PRODUCES CLINICAL BENEFIT AND LOW TOXICITY IN METASTATIC BREAST CANCER IN K HOSPITAL

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ABSTRACT

Background: The metronomic concept emerged more than 20 years ago, however, a significant development in various solid tumors was noticed in the past 10 years. There are potentially several mechanisms of action against tumor cells including inhibition of angiogenesis. This study aims to assess the efficacy and the safety of a metronomic schedule of oral Vinorelbine (Navelbine) in treatment of metastatic breast cancer.

Methods: For the duration from January 2020 to June 2021 there were 30 metastatic breast cancer patients at the median age of 53 years (range 34 - 72), were treated with a metronomic schedule of oral Vinorelbine (VNR).

Oral VNR was administered 40 mg three times weekly, continuously. Patients took oral VNR continuously on days 1, 3 and 5 of the week until the disease progression or unacceptable side effects. The difference between before and after 9 weeks treatment was conducted via the matched t - tests to discern the quality - of - life indicator ($p < 0.05$ was considered significant).

Progression - free survival analysis was performed using Kaplan Meier.

Results: All 30 patients received at least 9 weeks of therapy and were evaluated. 7 achieved partial responses (23.3%) and 13 achieved stable disease responses (43.4%). Median progression - free survival entailed 6.9 months. The quality of life was notified significantly. A good result was found in our metastatic breast cancer patients, who were given with a Metronomic Vinorelbine (mVNR) administration.

Conclusions: As a result of our latest study indicated that the metronomic vinorelbine might become a potential treatment for metastatic breast cancer patients via the reduction of adverse effects and improvement of life quality and sets the stage for future extensive clinical trials.

Keywords: Metastatic breast cancer, oral Vinorelbine (Navelbine), Metronomic.

I. INTRODUCTION

Nowadays, patients with metastatic breast cancer differ substantially from patients 10 - 20 years ago and are much more difficult to treat because they have usually received very potent adjuvant therapies. Trials published since 2012,

particularly in HER2 - positive disease, have shown not just prolongation of progression - free survival, but also overall survival. These results indicate that the concept of metastatic breast cancer as a chronic disease controlled by sequential therapies over a

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long period is realistic, atleast for certainsubgroups. Therapeutic goals inmetastatic breast cancer are maintenance of the quality of lifeand palliation of symptoms [1].

Combination chemotherapy is indicated in metastatic breast cancer if rapid response is needed in life - threatening situation or in highly symptomatic patients, and patients in good condition. Unless patient symptoms require combination chemotherapy, sequentialmonochemotherapies are recommended, as combinationchemotherapy does not prolong survival. Monochemotherapy can be given until progression orintolerable toxic effects, whereas because of toxicity, combination chemotherapy is usually given untilbest response [1]. Vinorelbine, a third - generation microtubuletargeting agent, was approved in the treatment of metastatic breastcancer alone or in combination. The mainmechanism of action consists of inhibiting tubulin polymerization during mitosis leading to cell death. Oral VNR was assessed at a starting dose of 60 mg/m²/week for thefirst three administrations and then increased to 80 mg/m²/week in the absence of severe hematological toxicity. Infirst - line treatment of metastatic breast cancer, oral VNR showed a good efficacy and safety profile, even in elderly patientswith response rates ranging from 19 to 53%, prolonging progression - free survival from 5.2 to 9.7 months with low toxicity, helping to improve quality of life, alleviate symptoms for patients [2 - 4].

Metronomic chemotherapy schedule is defined asfrequently close or continuous administration of a low doseof a drug and its use was made easier with the advent of oral form. In clinical studies conducted in patientswith metastatic breast cancer, oral metronomic Vinorelbine (mVNR) appeared overall effective and well - tolerated asmonotherapy and within combination regimens. Due to its good safety profile, the possibility ofan oral administration and its anticancer efficacy, treatment with oral mVNR may represent a suitable treatment strategy in patients withbreast cancer, especially in thosewho are morefrail (e.g., elderly). Vinorelbine, a microtubuleinhibiting agent, could be an ideal drug for a metronomic schedule due to its enhancement of

angiogenesis inhibition and immunity stimulation. Importantly, it is the onlyorally available microtubule - targeting agent. Angiogenesis inhibition could be of great valuein the maintenance setting, especially whenactive and strong cancercontrol is needed foraggressive subtypes of cancer, such as triplenegative breast cancer [3, 5, 6].

In clinical practicein K Hospital and other hospitals in Vietnam shows that metronomic oral VNR brings good results in terms of survival as well as the patient's quality of life. However, there are not any studies to document these results in Vietnam. This study is aimed to assess themetronomic schedule of oral VNR's efficacy, safety in treatment of metastatic breast cancer and improvement their life quality in K hospital.

II. PATIENTS AND METHODS

2.1. Patients

30 patients with advanced breast cancer were treated with the metronomic schedule of oral VNRin K hospital from January 2020 to June 2021. The patient had failed previous treatment regimens or is unfit or refuse to be treated with intravenous chemotherapy regimens, not eligible for anti - Her - 2/neu treatment in case of Her - 2/neu is positive.

2.2. Methods

The methodology of this study is descriptive, prospective, convenient& using purposeful sampling.

2.3. Research process

Patients with advanced breast cancer were eligible for selection.

Oral Vinorelbine was administered 40 mg three times weekly, continuously. Patients received oral Vinorelbine on days 1, 3 and 5 of each week continuouslyuntil disease progression or unacceptable side effects.

Toxicity information(hematological, gastrointestinal, neurological) was collected every 3 weeks.

Therapy response was assessed by RECIST.

The progression - free survival was evaluated according to Kaplan Maier.

The comparative quality of life before and after 9 weeks of treatment was evaluated according to QoL EORTC 30.

III. RESULTS

Table 1 presents the general characteristics of the study group. The lowest age is 34, the highest is 72 (53 ± 10.9). The rate of metastatic lung was the highest, accounting for 53.3%. Up to 60% of patients had metastases from 2 or more sites, and up to 3 patients with brain metastases accounted for 10%. The percentage of patients with Her - 2 neu positive status was the highest, accounting for 53.4%, the hormone receptor- positive and the negative - triple was 23.3%.

Table 1: General characteristics of the study group

Characteristics	N	%
Average age	53 ± 10.9	
Features of metastasis		
Lung	16	53.3
Bone	13	43.3
Liver	9	30
Node	6	20
Brain	3	10
Number of sites with metastasis		
One site	12	40
Two or more site	18	60
Biological characteristics		
Her - 2neu positive	16	53.4
Hormone receptor positive	7	23.3
Triple negative	7	23.3

The result of treatment is showed in Table 2. The partial response rate was 23.3% (7/30), the stable disease rate was 43.4% (13/30), the remaining 33.3% was progressive disease, no patient had a complete response. The results of this study showed that the mean PFS was 6.9 ± 4.2 months (2.8 - 18 months) (**Figure 1**).

Table 2: Response to treatment after 3 cycles

Response	N	Rate (%)
Complete response	0	0
Partial response	7	23.3
Stable disease	13	43.4
Progressive disease	10	33.3
Total	30	100

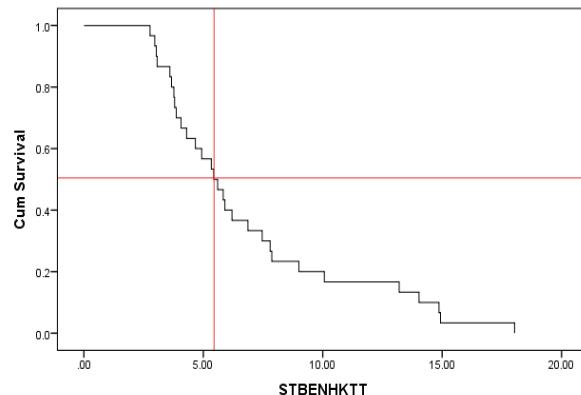


Figure 1: Progression - free survival (PFS)

When analyzing the relationship between PFS and endocrine receptor status and Her - 2 neu expression level, the survival time of the positive endocrine receptor status seems to be higher, but the difference is not significant (**Table 3 and Figure 1**).

Table 3: Biological characteristics associated with PFS

Biological characteristics	n	Mean \pm SD
Her - 2neu positive	7	9.4 ± 4.6
Hormone - receptor positive	16	5.7 ± 3.1
Triple negative	7	6.9 ± 5.2
Total	30	6.9 ± 4.2

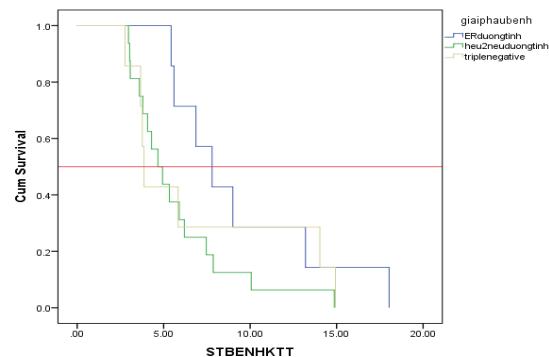


Figure 2: PFS according to biological characteristics.

The rate of undesirable effects is very low, almost not encountered, only the highest rate of grade 1 Neutropenia is 13.3%, the rate of grade 2 and 3 Neutropenia and liver enzyme lowering is only 6.7%. None of the patients had adverse effects on thrombocytopenia as well as on the kidneys (**Table 4**).

Table 4: Undesirable effects on the hematopoietic system and liver function

Toxicity	Degree 1		Degree 2		Degree 3	
	n	%	N	%	N	%
Neutropenia	4	13.3	2	6.7	1	3.3
Hematocrit	2	6.7	0	0	0	0
Liver function	2	6.7	0	0	0	0

The results showed a marked improvement: increase in physical function, activity after treatment (the difference was statistically significant with $p < 0.05$). In terms of social function after treatment, it decreased from 54.4 ± 14.5 to 50 ± 26.2 . However, the improved emotional function after treatment was not different from before. After 3 cycles of treatment, the financial problems had not improved significantly. Evaluation of pain and other symptoms in the group of patients before and after treatment showed significant improvement with statistical significance, respectively 23.8 ± 16.4 and 19.8 ± 9.8 compared with the previous treatment, with 20 ± 10.3 and 16.8 ± 9.5 . For the general condition, the patient's quality of life before and after treatment was improved, making a statistically significant difference (Table 5).

Table 5: Improving quality of life

Functions	Before treatment Mean \pm SD	After 3 cycles Mean \pm SD	P
Physical function	63.6 ± 15.1	69.3 ± 19	<0.01
Emotion function	75 ± 13.2	84.1 ± 12.6	0.6
Cognitive function	72.8 ± 13.4	78.3 ± 13.9	0.02
Social function	54.4 ± 14.5	50 ± 26.2	0.08
Financial problems	77.8 ± 16	70 ± 23.7	0.03
Global health status	45 ± 19.6	53.6 ± 14.8	<0.01
Pain	23.8 ± 16.4	20 ± 10.3	0.03
Other symptoms	19.8 ± 9.8	16.8 ± 9.5	0.01

IV. DISCUSSION

4.1. General features

Data of 30 patients, the mean age was 53 ± 10.9 . The rate of lung metastasis was the highest, accounting for 53.3%, followed by bone at 43.3%, and less common were liver, lymph nodes and brain at 30%, 20% and 10%, respectively (Table 1). Up to 60% of patients had metastases from 2 or more sites, and up to 3 patients with brain metastases accounted for 10%. This result shows that this group of patients has a higher rate of metastasis, and the overall condition is weaker than the results of other authors. Duc LT (2013) showed that the rate of metastasis recurrence from 2 or more sites accounted for 50.1% [4]. And the research of Huong NT is indicating that the rate is 70.3% [7].

The percentage of patients with Her - 2 neu positive status was the highest (53.4%), hormone receptor - positive and negative triple was 23.3%. This result is different from some other results, which is the highest proportion of the group with positive hormone receptor status, which can be explained by the better prognosis of endocrine receptor breast cancer, the ability to respond to hormones is higher and breast cancer with overexpression of Her - 2 neu has a worse prognosis, the patients in this study group are not eligible for anti - Her - 2 neu treatment. Oral drug according to VNR Metronomic regimen as the therapy of the last choice for patients.

4.2. Treatment results

Response rate

The study results showed that the partial response rate was 23.3% (7/30), the stable disease rate was 43.4% (13/30), the remaining 33.3% was progressive disease, No patient had a complete response (Table 2).

Comparison of response rates of some other studies (Table 6): the results are similar, but no patient has a complete response, which can be explained as this group of patients has undergone many previous treatment regimens, weaker and higher Her - 2 neu overexpression rate.

Table 6: Response rate of other authors

Author	Year	n	Response rate (%)	References
Addeo	2010	34	38	[8]
DeLulilis	2015	32	68.7	[9]
Duc LT	2013	37	40.4	[4]
Huyen PT	2016	71	40.8	[10]
Huong NT	2018	37	81.1	[7]

Progression - free survival (PFS) (**Figure 1**).

The results of this study showed that the mean PFS was 6.9 ± 4.2 months (2.8 - 18 months). According to Addeo and De Luliis, patients using Vinorebine Metronomic for PFS were 7.7 months and 9.2 months was higher than our study, the reason may be: patients of this author group used the drug at an earlier step, possibly better condition. According to the results of some domestic authors, patients taking Vinorebine by the week also had an average progression - free survival time equivalent to our study.

The relationship between PFS with endocrine receptor status and Heu 2 neu overexpression level

There was no association between PFS and endocrine receptor status and Heu 2 neu overexpression, although the PFS of hormone receptor - positive status appeared to be higher, but the difference was not statistically significant with $p = 0.153$ (**Table 3 and figure 2**). The research results of L.T. Duc also did not see this association.

Undesirable effects (**Table 4**).

The rate of undesirable effects is very low, almost not encountered, only the highest rate of grade 1 neutropenia is 13.3%, the rate of grade 2 and 3 neutropenia and liver enzyme lowering is only 6, 7%. There were no patients with thrombocytopenia nor renal side effects

When compared with domestic authors such as Duc LT, Huyen PT, and Huong NT on patients with metastatic recurrent breast cancer who took Vinorebine weekly, the rate of undesirable effects was higher (range 20 - 60%).

This may be because the patient group in our study is in weaker condition, through many previous treatment steps, up to 10% of patients with

brain metastasis but using Vinorebine metronomic regimen are well tolerated. Side effects are much lower than in the study of the above authors using Navelbine weekly regimen.

Quality of life

The results in **Table 5** show a clear improvement: increase in physical function, activity before treatment is 63.6 ± 15.1 and 72.8 ± 13.4 compared to 69.3 ± 19 after treatment and 78.3 ± 13.9 (the difference is statistically significant with $p < 0.05$).

Social function after treatment decreased from 54.4 ± 14.5 to 50 ± 26.2 . This can explain that although the regimen in the study is effective, patients with late stage breast cancer, many metastatic lesions, have improved health but are still not confident enough to participate in the integration activities or social activities.

However, improved emotional function after treatment was not different from before treatment: 75 ± 13.2 and 84.1 ± 12.6 (with $p = 0.6$). This may be because patients with late - stage cancer have undergone many treatment courses, the later the psychological burden is worse, so after 9 weeks of treatment, their emotional function is not adversely affected, is a precious thing.

After 3 cycles of treatment, financial status did not improve significantly, decreasing from 77.8 ± 16 to 70 ± 23.7 (with $p = 0.03$). This we find that the group of patients in the study is entitled to health insurance, they can take medicine at home, so they do not have to pay for drugs, do not have to stay in inpatient treatment to receive chemotherapy. However, the results reflect an objective reality that late - stage breast cancer patients undergo a long process, many treatment courses, so it is also a financial burden on their families and themselves.

Evaluation of pain and other symptoms in the group of patients before and after treatment showed significant improvement with statistical significance, respectively 23.8 ± 16.4 and 19.8 ± 9.8 compared with the previous treatment with 20 ± 10.3 and 16.8 ± 9.5 . This once again confirmed the effectiveness of the regimen on patients with advanced breast cancer in this study.

For the general health condition, the patient's quality of life before and after treatment improved, making a statistically significant difference, increasing from 45 ± 19.6 to 53.6 ± 14.8 . However, the average assessment

Patient life's quality in this study group is still low&some people still need the support from their relatives.

This improvement in quality of life is consistent

with the results of other domestic and foreign studies.

V. CONCLUSION

As a result of our latest study indicated that the metronomic vinorelbine might become a potential treatment for metastatic breast cancer patients via the reduction of adverse effects and improvement of life quality and sets the stage for future extensive clinical trials.

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