Efficacy and Safety of Vinorelbine Plus Cisplatin *vs.* Gemcitabine Plus Cisplatin for Treatment of Metastatic Triple-Negative Breast Cancer After Failure with Anthracyclines and Taxanes

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Source of support: This study was supported by a grant from the National Natural Science Foundation of China (grant no. 81402514) and the Natural Science Research Project of Anhui Provincial Higher School (grant no. KJ2015B118by)

Background: This study aimed to compare the efficacy and safety of vinorelbine plus cisplatin (NP regimen) *vs.* gemcitabine plus cisplatin (GP regimen) for treatment of metastatic TNBC after failure with anthracyclines and taxanes.

Material/Methods: A total of 48 patients with metastatic TNBC that failed in anthracyclines and taxanes treatment were enrolled and randomly grouped. Patients in the NP group (*n*=22) were given 25 mg/m² vinorelbine on days 1 and 8 and 25 mg/m² cisplatin on days 2–4 of each 21-day cycle, while subjects in the GP group (*n*=26) were administered 1000 mg/m² gemcitabine on days 1 and 8 and 25 mg/m² cisplatin on days 2–4 of each 21-day cycle. The treatment response and adverse events were compared between the 2 groups every 2 cycles.

Results: The ORR, DCR, and median TTP were 45.5%, 77.3%, and 5 months in the NP group, and 46.2%, 80.8%, and 5.2 months in the GP group, and no significant differences were observed in ORR, DCR, and median TTP between the 2 groups (*P*>0.05). The major adverse events included grade I–II bone marrow inhibition, gastrointestinal reactions, and phlebitis, and a lower incidence of thrombocytopenia and rash and a higher incidence of phlebitis was found in the NP group than in the GP group (*P*<0.05).

Conclusions: Either NP or GP regimen is active and tolerated in treatment of metastatic TNBC with anthracyclines and/or taxanes resistance, which may be used as a salvage treatment for metastatic TNBC.

MeSH Keywords: **Chemical Safety • Comparative Study • Treatment Outcome • Triple Negative Breast Neoplasms**

Full-text PDF: https://www.medscimonit.com/abstract/index/idArt/905300

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Background

Triple-negative breast cancer (TNBC), an aggressive form of breast cancer that is negative for estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2), is characterized by high invasiveness, high metastatic spread, high recurrence, and poor prognosis [1–3]. TNBC, which is relatively highly prevalent in young women, is estimated to account for 10% to 25% of all breast cancers, and the global incidence appears to be increasing [4–6]. In China, a sharp increase is reported in the incidence of both breast cancer and TNBC [7].

To date, there has been no effective therapy for TNBC [8], and the standard treatment still depends on surgery and adjuvant chemotherapy and radiotherapy [9–11]. In general, TNBC exhibits an elevated chemosensitivity relative to other forms of breast cancers [12]. Anthracyclines and taxanes are active against TNBC, and the addition of anthracyclines or taxanes to the chemotherapy regimen has been shown to remarkably improve the clinical outcomes [13–17]. However, there is an increasing number of patients with anthracyclines- and taxanes-resistant TNBC following extensive use of these agents [18–20]. There is still no consensus on the standard therapy of TNBC with resistance to anthracyclines and taxane, and empirical therapy remains the major treatment. Finding effective regimens without cross-resistance to anthracyclines and taxanes is of great importance for the treatment of recurrent and metastatic TNBC.

Vinorelbine, a semi-synthesized vinca alkaloid belonging to the *Catharanthus* alkaloid group, is a cell cycle-specific agent that exhibits cytotoxicity through binding to tubulin, thereby disrupting microtubule formation during mitosis [21]. Vinorelbine has no cross-resistance to anthracyclines and taxanes, and is an effective agent for the treatment of recurrent and metastatic TNBC [22]. Vinorelbine and cisplatin, which act on various targets, exhibit a synergistic anti-cancer activity and have shown a relatively high efficacy against TNBC [23,24].

Gemcitabine, an antimetabolite, is also a cell cycle-specific agent, which primarily kills cells that are undergoing DNA synthesis (S phase), blocks the cell cycle transition from G1 phase to S phase, and suppresses DNA synthesis, thereby inhibiting cancer cell growth [25,26]. It has been demonstrated that gemcitabine is active for advanced breast cancers, and may serve as an option for the treatment of patients with metastatic breast cancer who failed anthracyclines and/or taxanes treatment [27–29]. Gemcitabine monotherapy was reported to achieve less than 20% response rate (RR) in the treatment of metastatic breast cancer with resistance to anthracyclines and/or taxanes [30,31], and gemcitabine combination chemotherapy has been used for the treatment of many cancers [32,33]. Although multiple chemotherapy regimens have

been tested for their efficacies and toxicities against breast cancer, there is still no standard regimen for the treatment of metastatic TNBC.

The purpose of this study was to evaluate and compare the efficacy and safety of vinorelbine plus cisplatin (NP regimen) *vs.* gemcitabine plus cisplatin (GP regimen) for the treatment of metastatic TNBC after failure with anthracyclines and taxanes.

Material and Methods

Ethics statements

This study was approved by the Ethics Review Committee of the First Affiliated Hospital of Bengbu Medical College (permission no. BYFY20110297). Signed informed consent was obtained all participants following a detailed description of the purpose of this study.

Subjects and grouping

The clinical records of 48 female TNBC patients admitted to the Department of Oncology, the First Affiliated Hospital of Bengbu Medical College (Bengbu, China) during the period from July 2011 through June 2014, were retrospectively reviewed. All patients were definitively diagnosed with breast cancer using pathologic examinations, and immunohistochemistry revealed that all breast cancers were negative for ER, PR, and HER-2. The patients had a median age of 49 years (range, 33 to 77 years), and the 48 cases included 41 cases with infiltrating duct carcinoma, 5 cases with infiltrating lobular carcinoma, and 2 cases with basal-like breast carcinoma. There were 47 cases undergoing radical or modified radical surgery, and all patients had a history of neoadjuvant therapy, adjuvant therapy, or palliative chemotherapy with anthracyclines and taxanes; however, none of the patients received treatment with gemcitabine or vinorelbine. Physical examinations, imaging examinations, or biopsy revealed TNBC recurrence and metastasis, and CT or MRI scanning displayed at least 1 measurable target tumor focus. All patients were identified with stage IV breast cancer [34], and had Eastern Cooperative Oncology Group (ECOG) performance status scores of 0 to 2 [35]. The subjects had a predicted survival of over 3 months, and did not receive any anti-cancer therapy within the latest month prior to the enrollment. All subjects had nearly normal functions of vital organs, which did not affect chemotherapy.

The patients were assigned into the NP regimen group (*n*=22) or the GP regimen group (*n*=26). Patients in the NP regimen group had a median age of 48 years (range, 35 to 74 years), while subjects in the GP regimen group had a median age of 49 years (range, 33 to 77 years).

Treatment protocol

Patients in the NP regimen group were administered an intravenous infusion with vinorelbine at a dose of 25 mg/m^2 on days 1 and 8 and cisplatin at a dose of 25 mg/m^2 on days 2–4 of each 21-day cycle, while subjects in the GP regimen group were intravenously infused with gemcitabine at a dose of 1000 mg/m^2 on days 1 and 8 and cisplatin at a dose of 25 mg/m^2 on days 2–4 of each 21-day cycle. If patients developed bone metastasis, zoledronic acid was given by intravenous infusion at a single dose of 4 mg administered once every 3 to 4 weeks. All patients underwent 2 to 6 cycles of chemotherapy, and antiemetic therapy with 5-HT3 receptor antagonists during the chemotherapy. Routine blood test, liver and kidney function tests, and electrocardiogram were performed 1 week prior to, during, and 1 week after chemotherapy, and CT and MRI scans were conducted after 2 cycles of chemotherapy. Prophylactic leukocyte-elevated treatment was not given during the chemotherapy, and granulocyte colony-stimulating factor (G-CSF) and granulocyte-macrophage colony-stimulating factor (GM-CSF) or IL-11 were administered to enhance leukocyte and platelet levels pre- and post-chemotherapy based on analysis of bone marrow inhibition. If grade III or IV chemotherapy-related toxicity occurred [36], the dose of chemotherapeutic agents was reduced. The response to chemotherapy was assessed once every 2 cycles, and chemotherapy-related toxicity was evaluated once each cycle. The chemotherapy regimen was continued for 6 cycles if the patients had improvements in disease severity or stable disease, and chemotherapy was terminated or the chemotherapy regimen was changed if patients had disease progression or were intolerant to chemotherapy-related toxicity.

Assessing the response to chemotherapy

The response to the NP and GP regimens was assessed using the Response Evaluation Criteria in Solid Tumors version 1.1 [37], including complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD). RR was calculated as the proportion of patients with CR + PR in all patients, and the disease control rate (DCR) was described as the proportion of patients with CR + PR +SD in all cases. TTP was defined as the length of time from the beginning of chemotherapy to disease progression.

Assessment of chemotherapy-related toxicity

The adverse events caused by chemotherapy were recorded after each cycle of chemotherapy, and the adverse events were classified into grade 0 to IV according to the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.0 [36].

Statistical analysis

All statistical analyses were performed using the statistical software SPSS version 16.0 (SPSS, Inc.; Chicago, IL, USA). Differences in proportions were tested for statistical significance with the chi-square test or Fisher's exact test, and survival analysis was performed with the Kaplan-Meier method. A *P* value <0.05 was considered statistically significant.

Results

Response to the NP and GP regimens

The baseline demographic and clinical characteristics were comparable between the NP and GP regimen groups (*P*>0.05) (Table 1). All 48 patients were subjected to the evaluation of the response to the chemotherapy. A total of 100 cycles of chemotherapy were administered in the NP regimen group, with a mean of 4.5 cycles given to each subject, and a 45.5% ORR and 77.3% DCR were achieved. In the GP regimen group, a total of 116 cycles of chemotherapy were performed, with a mean of 4.5 cycles given to each patient, and a 46.2% ORR and 80.8% DCR were observed. There were no significant differences detected in the ORR or DCR between the NP and GP regimen groups (*P*>0.05) (Table 2). A better response to either the NP regimen or the GP regimen was seen in the postmenopausal patients, patients with first-line treatment, patients with local and lymph node metastases, and patients with single metastatic lesion compared to the premenopausal patients, patients with second-line treatment, patients with visceral metastasis, and patients with multiple metastatic lesions (*P*>0.05) (Table 3).

TTP

Complete follow-up was available for all 48 subjects enrolled in the study. The subjects in the NP regimen group had TTP of 2 to 18 months, with median TTP of 5 months (95% *CI*: 3.28 to 6.72 months), and patients in the GP regimen group had TTP of 1.8 to 18.5 months, with median TTP of 5.2 months (95% *CI*: 3.33 to 7.07 months). There was no significant difference in the median TTP between the NP and GP regimen groups (*P*>0.05) (Figure 1).

Chemotherapy-related toxicity

Bone marrow inhibition, gastrointestinal reactions, and phlebitis were the predominant chemotherapy-induced toxicities, which were mainly identified as grade I and II, and grade III and IV adverse events, mainly leucopenia, thrombopenia, nausea, vomiting, loss of appetite, and phlebitis. A higher incidence of thrombopenia and skin rash was detected in the GP regimen

Table 1. Comparison of the baseline demographic and clinical characteristics between the NP and GP regimen groups.

Demographic and clinical feature		NP regimen group (*n*=22)	GP regimen group (*n*=26)	*P*
Age (years)	≤45	5	7	0.738
	> 45	17	19	
Menses	Pre-menopause	11	14	0.790
	Post-menopause	11	12	
ECOG performance status score	0–1	15	18	0.938
	2	7	8	
Treatment	First-line treatment	14	17	0.9
	Second-line treatment	8	9	
Metastatic site	Lymph lode or soft tissues	8	10	0.881
	Chest wall	3	4	0.864
	Lung	12	13	0.753
	Liver	5	7	0.738
	Bone	8	11	0.675
	Brain	1	0	1.000
No. metastatic foci	Single	8	11	0.675
	Multiple	14	15	

Table 2. Comparison of the response to the NP and GP regimens in TNBC patients with failure in treatment with anthracyclines and taxanes.

Group	No. patients with CR	No. patients with PR	No. patients with SD	No. patient with PD	ORR (%)	χ^2	*P*
NP regimen group (*n*=22)	1	9	7	5	45.5	0.305	0.959
GP regimen group (*n*=26)	2	10	9	5	46.2		

CR – complete response; PR – partial response; SD – stable disease; PD – progressive disease, ORR – overall response rate.

Table 3. Response to the NP and GP regimens in TNBC patients with various clinical characterisitcs.

| Characteristics		NP regimen group (*n*=22)				GP regimen group (*n*=26)			
		No. of patients	CR + PR	ORR (%)	*P* value	No. of patients	CR + PR	ORR (%)	*P* value
Menstruation	Premenopause	11	4	36.4	0.392	14	5	35.7	0.249
	Postmenopause	11	6	54.5		12	7	58.3	
Treatment	First-line	14	7	50.00	0.571	17	9	52.9	0.126
	Second-line	8	3	37.5		9	3	33.3	
Metastatic site	Local + lymph node	11	5	45.5	0.337	14	7	50.00	0.133
	Viscera	18	5	27.8		20	5	25	
No. of metastatic lesions	Single	8	5	62.5	0.225	11	7	63.6	0.126
	Multiple	14	5	35.7		15	5	33.3	
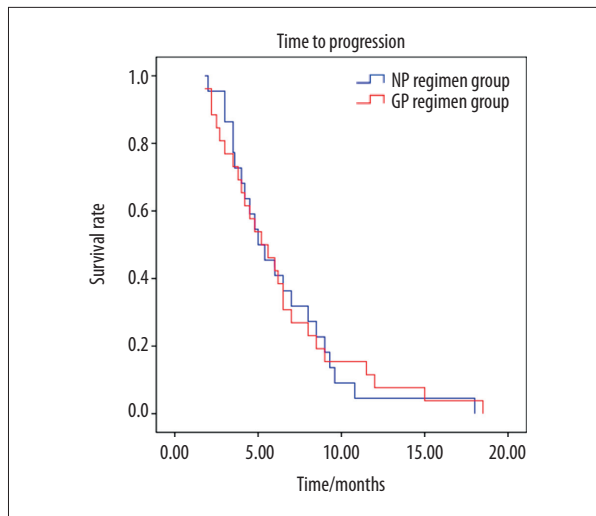
Figure 1. TPP in metastatic TNBC patients with failure in anthracyclines and taxanes treatment.

group than in the NP regimen group (*P*<0.05), and a higher incidence of phlebitis was seen in the NP regimen group than in the GP regimen group (*P*<0.05). Other common chemotherapy-induced adverse events included mild constipation, anemia, and hepatorenal dysfunction, which did not affect chemotherapy after active treatment (Table 4).

Discussion

Breast cancer is a highly heterogeneous malignancy [38–41], and TNBC is a specific heterogeneous subgroup of breast cancer [2]. The clinico-pathological characteristics and biological behaviors of TNBC are characterized by high invasiveness, poor prognosis, early onset of disease, high recurrence, and early metastasis [2]. Currently, the standard therapy for TNBC is surgery with adjuvant chemotherapy and radiotherapy [9–11]. However, it is reported that most of the TNBC patients develop recurrence and metastasis 2 to 3 years after surgery [42]; adjuvant therapy is thus necessary for TNBC patients, which may improve patient survival and prognosis [43]. Since TNBC has no specific targets and is negative for hormone receptors, the TNBC patients are not susceptible to endocrine therapy or targeted therapy [44–46]. Chemotherapy remains the major approach for the systemic treatment of recurrent and metastatic TNBC [47]; however, to date there is no consensus on the chemotherapy regimens for the treatment of recurrent and metastatic TNBC [20].

To date, anthracyclines and taxanes remain important agents for TNBC [13–17], and adding an anthracycline or taxane to the chemotherapy has been found to substantially improve the treatment outcomes [15]. However, anthracyclines- and

Table 4. Adverse events caused by the chemotherapy with NP and GP regimens.

Adverse events	NP regimen group (*n*=22)						GP regimen group (*n*=26)						*P* value
	Grade 0	Grade I	Grade II	Grade III	Grade IV	Incidence of grade III and IV adverse events (%)	Grade 0	Grade I	Grade II	Grade III	Grade IV	Incidence of grade III and IV adverse events (%)	
Leucopenia	1	6	9	4	2	27.3	0	8	11	5	2	26.9	0.866
Thrombopenia	11	6	4	1	0	4.5	3	9	8	4	2	23.1	0.04
Anemia	13	6	3	0	0	0	15	7	4	0	0	0	0.985
Nausea and vomiting	12	5	3	2	0	9.1	13	6	5	2	0	7.7	0.96
Loss of appetite	3	4	8	5	2	31.8	2	6	9	6	3	34.6	0.961
Constipation	14	5	3	0	0	0	15	6	5	0	0	0	0.863
Skin rash	22	0	0	0	0	0	19	5	2	0	0	0	0.031
Phlebitis	13	5	3	1	0	4.5	24	2	0	0	0	0	0.041
Neurotoxicity	15	4	3	0	0	0	23	3	0	0	0	0	0.104
Hair loss	17	4	1	0	0	0	18	6	2	0	0	0	0.806
Hepatic dysfunction	16	4	2	0	0	0	19	5	2	0	0	0	0.975
Renal dysfunction	18	3	1	0	0	0	19	6	1	0	0	0	0.705

taxanes-resistant TNBC increasingly emerges following extensive use of the agents [18–20]. Currently, gemcitabine, vinorelbine, capecitabine, and platinum agents are common drugs used for the treatment of advanced TNBCs that fail in anthracycline and taxane treatments [48]. It has been shown that TNBC is sensitive to platinum agents, which is mainly attributed to BRCA1 mutations [49–51], and BRCA1 mutations are strongly associated with the occurrence of TNBC [52]. Cisplatin, a cell cycle non-specific antineoplastic drug, acts on the DNA of proliferating cells and binds to the bases in cells to allow DNA interstrand and interstrand cross-linking, thereby resulting in loss of DNA replication [53]. Since TNBC is highly sensitive to platinum agents, the selection of the combination regimens containing platinum drugs merit further investigations [51]. Previous findings from clinical and experimental studies have shown that the efficacy of the combination chemotherapy is superior to monochemotherapy, and agents with various mechanisms of actions and synergistic effect and without superposition of chemotherapy-related toxicities are generally used in the combination chemotherapy [54]. However, to date there is no standard scheme for the treatment of TNBC with failure in anthracyclines and taxane therapy.

Cisplatin combination chemotherapy is the cornerstone of treatment of multiple cancers. In the present study, we used the NP and GP regimens for treatment of TNBC that failed in anthracycline and taxane treatment. These 2 regimens combined the use of cell cycle-specific and non-specific agents, which facilitated the improvements of chemotherapy efficacy and allowed tolerable chemotherapy-related toxicity.

It has been shown that the vinorelbine and cisplatin combination chemotherapy achieves satisfactory survival duration and acceptable chemotherapy-associated toxicities for treatment of human cancers, including breast cancer [23,24,55]. It was reported that the vinorelbine-cisplatin combination yielded 46% to 62% RRs for the treatment of advanced breast cancer [56,57]. In metastatic breast cancer patients previously treated with anthracyclines and docetaxel, the vinorelbine-cisplatin combination was reported to achieve a 47.2% ORR, and median TPP of 16 weeks [58]. In addition, the combination of vinorelbine and cisplatin achieved a 43.9% ORR and median TTP of 6 months in 41 patients with TNBC, and the major chemotherapy-induced toxicity were bone marrow inhibition, gastrointestinal reactions, and phlebitis [59].

It was hypothesized that gemcitabine combination therapy may achieve a better efficacy in breast cancer patients that tolerated the treatment. *In vitro* assay showed the synergistic anti-cancer activity of the gemcitabine-cisplatin combination [60]. In anthracycline-pretreated patients with metastatic breast cancer, chemotherapy consisted of gemcitabine 1 mg/m^2 plus cisplatin 30 mg/m^2 on days 1 and 8, achieving a 47.7% ORR, median progression-free survival of 6.9 months, and median survival time of 13 months [61]. In addition, the gemcitabine and cisplatin combination chemotherapy was reported to achieve a 41.2% ORR and median TTP of 5.2 months in anthracycline-resistant, metastatic TNBC patients, and the adverse events mainly included bone marrow inhibition and gastrointestinal reactions, with no chemotherapy-related deaths [62]. Previous studies have examined the efficacy and safety of multiple gemcitabine-based chemotherapy regimens for breast cancer; however, there has been consensus on the chemotherapy regimen for the treatment of TNBC with failure in anthracyclines and taxane treatment until now.

In the present study, a 45.5% ORR and 77.3% DCR were achieved in the NP regimen group undergoing vinorelbine 25 mg/m^2 on days 1 and 8 plus cisplatin 25 mg/m^2 on days 2–4, and a 46.2% ORR and 80.8% DCR were observed in the GP regimen group receiving gemcitabine 1000 mg/m^2 on days 1 and 8 plus cisplatin 25 mg/m^2 on days 2–4, which was similar to previous findings [59,61–63]. Subgroup analyses showed a better response to either the NP regimen or the GP regimen in the postmenopausal patients, patients with first-line treatment, patients with local and lymph node metastases, and patients with single metastatic lesion than in the premenopausal patients, patients with second-line treatment, patients with visceral metastasis, and patients with multiple metastatic lesions; however, no significant differences were seen between the 2 groups (*P*>0.05). In addition, there were no significant differences detected in the ORR, DCR, or TTP between the NP and GP regimen groups (*P*>0.05).

In this study, we observed bone marrow inhibition, gastrointestinal reactions, and phlebitis as the predominant chemotherapy-induced toxicities, which were mainly identified as grade I and II, and only 1 case had grade III phlebitis, which may have been caused by peripherally inserted central venous catheterization [64].

Conclusions

In summary, the results of the present study demonstrate that either vinorelbine plus cisplatin or gemcitabine plus cisplatin is active and tolerated in metastatic TNBC with resistance to anthracyclines and/or taxanes, which may be used a salvage treatment for metastatic TNBC.

Statements

The funders had no role in the study design, data collection and analysis, or preparation of the manuscript.

Conflict of interests

None.

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