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Comparison of vinorelbine plus cisplatin with vinorelbine plus capecitabine in patients with anthracyclines- and taxanes-refractory advanced breast cancer*

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Abstract ***Objective:*** The aim of our study was to compare the efficacy and toxicities of vinorelbine plus cisplatin (NP) regimen with that of vinorelbine plus capecitabine (NX) regimen in the treatment of anthracycline- and taxane-refractory advanced breast cancer. ***Methods:*** Forty-six patients with anthracycline- and taxane-refractory advanced breast cancer were equally randomized into a NP group (n = 23) and a NX group (n = 23). Response rates and toxicities were evaluated after 2 cycles of chemotherapy. ***Results:*** The overall response rate were 48.0% in both groups. There were no significant differences in disease control rates (78.0% vs. 83%) or 1-year survival rates (54.6% vs. 55.9%). The main adverse events were bone marrow depression and gastrointestinal reaction, and no significant difference was found in toxicities between the groups. ***Conclusion:*** For anthracycline- and taxane-refractory advanced breast cancer, NP and NX regimens exerted similar curative effects with acceptable toxicity.

Key words capecitabine; vinorelbine; cisplatin; advanced breast cancer

Anthracycline and taxane are the cornerstone of drugs used in the first-line treatment of breast cancer. They have greatly improved survival of patients with advanced breast cancer. However, many patients inevitably develop resistance to these drugs and have to switch to second- or third-line therapy. Although many drugs are optional in the settings of second- or third-line therapy, still, there is no definite standard regimen for the treatment of anthracycline- and taxane-refractory advanced breast cancer [1]. This study was designed to compare the efficacy and toxicities of vinorelbine plus cisplatin (NP) regimen with that of vinorelbine plus capecitabine (NX) regimen.

Materials and methods

Clinical and biologic characteristics

From January 2010 to January 2012, a total of 46 cases of female patients with anthracycline- and taxane-refractory advanced breast cancer were enrolled in this study. All the patients were pathologically diagnosed with breast cancer, with a median age of 51 years (22 to 72 years). Thirty-nine patients underwent modified radical surgery and the other 7 patients received core biopsy. Thirteen patients developed bone and/or lymph node metastasis and 33 patients developed visceral metastases. There were 29 patients who presented with two or more metastatic sites. Thirty-four patients received second-line therapy and 12 patients received third-line therapy. Thirty-two patients were postmenopausal and 20 were premenopausal. No prior use of cisplatin, vinorelbine or capecitabine was allowed. All the eligible patients have measurable or evaluable disease, with an Eastern Cooperative Oncology Group (ECOG) performance status of 0 (19 cases) or 1 (26 cases); evidence of adequate organ function and > 3 months of expected survival.

Study design and treatment

Forty-six patients pretreated with anthracyclines and taxanes were equally randomized into a NP (n = 23) and a NX group (n = 23).

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Table 1 Short-term efficacy of the NP and NX groups

Group	*n*	CR	PR	SD	PD	RR (%)	*P* value	DCR (%)	*P* value
NP	23	2	9	7	5	48	1	78	0.65
NX	23	1	10	8	4	48		83	

NP: vinorelbine plus cisplatin; NX, vinorelbine plus capecitabine; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; RR, response rate; DCR, disease control rate

In the NP arm, vinorelbine (25 mg/m^2) was administrated intravenously on days 1 and 8; cisplatin (75 mg/m^2) was administrated intravenously on day 1 of a 3-week cycle. In the NP arm, vinorelbine (25 mg/m^2) was administrated intravenously on days 1 and 8; capecitabine (1250 mg/m^2 twice daily) was administrated orally on days 1 to 14 of a 3-week cycle. Treatment was continued until disease progression, unacceptable toxicities or patient refusal of further treatment. Patients were premedicated with tropisetron for prophylaxis of chemotherapy induced nausea and vomit. Subsequent chemotherapy was not specified.

Assessments

Tumor assessment was performed using CT or MRI at baseline and repeated every 2 cycles of treatment until documented disease progression. RECIST (version 1.1) was used to evaluate treatment responses.

The primary end point was progression-free survival (PFS), defined as time from random assignment to disease progression or death resulting from any cause. Secondary end points were overall survival (OS; 1 year), response rate (RR), disease control rate (DCR) and 1-year survival rate. Severity of all adverse events including laboratory abnormalities, were collected, recorded, and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 3.0.

Statistical analysis

All statistical analyses were performed with the SPSS 13.0 statistical software. $P < 0.05$ was considered significant. PFS was analyzed and estimated using the Kaplan-Meier method. Chi-square and Fisher's exact tests were used to assess the difference of RR, DCR and toxicities between the two study groups.

Results

Short-term efficacy

All the patients enrolled in this study received 2 or more cycles of chemotherapy and were evaluable for efficacy. The patients in the NP group received a total of 82 cycles of chemotherapy, with an average of 3.9 cycles. Responses in the 23 patients enrolled in the NP arm were complete response (CR) in 2, partial response (PR) in 9, stable disease (SD) in 7, progressive disease (PD) in 5, for an overall response rate (ORR) of 48.0% and a disease control rate (DCR) of 78.0%. The patients in the NX group received a total of 89 cycles of chemotherapy, with an average of 4.5 cycles. Responses in the 23 patients enrolled in the NX arm were CR in 1, PR in 10, SD in 8, PD in 4, for an ORR of 48.0% and DCR of 83.0%. There was no significant difference in RR and DCR between the two groups (Table 1; $P > 0.05$). No clinically defined subpopulation was found to have a statistically significant difference in RR between the two groups (Table 2).

Table 2 Subgroup analysis of response rate (RR) by prespecified baseline factors

Factor	*n*	RR		*P* value
		n	%	
Visceral metastasis	33	15	45.0	0.681
Non-visceral metastasis	13	7	54.0	
1 prior chemotherapy	34	16	50.0	0.892
> 1 prior chemotherapy	12	6	50.0	
Postmenopause	32	14	44.0	0.356
Premenopause	14	8	57.0	

Median survival and 1-year survival rate

In January 2013, after a follow-up period of 12–36 month, all the patients completed the study. For the primary end point of PFS, no statistically significant difference was observed between NP and NX groups. Median PFS was 5.7 months in the NP group and 5.9 months in the NX group ($P > 0.05$). Median OS was 13.9 months in the NP group and 14.1 months in the NX group ($P > 0.05$). 1-year survival rate was 54.6% in the NP group and 55.9% in the NX group ($P > 0.05$).

Safety

The toxicities observed in 46 patients during treatment and follow-up are shown in Table 3. The most common toxicities were myelosuppression and gastrointestinal side effect; both were mostly low grade (1 or 2) in serverity. The most frequently reported grade 3 or 4 adverse events were nausea and vomit. Patients in the NP group experienced a slightly higher incidence of hand-foot syndrome and a lower incidence of gastrointestinal side effects, but no statistically significant difference was detected (Table 3).

Table 3 Adverse events in the treatment arms

Adverse events	NP (*n* = 23)					NX (*n* = 23)					*P* value
	0	I	II	III	IV	0	I	II	III	IV	
Myelosuppression	1	7	11	3	1	2	7	10	4	0	0.931
Nausea and vomit	0	6	13	4	0	0	10	11	2	0	0.858
Hand-foot syndrome	14	7	2	0	0	9	8	5	1	0	0.051
Liver	22	1	0	0	0	19	2	2	0	0	0.789
Phlebitis	18	4	0	0	0	20	3	0	0	0	0.791

NP: vinorelbine plus cisplatin; NX, vinorelbine plus capecitabine

Discussion

Breast cancer is the leading cause of cancer death in the world. A substantial number of breast cancer patients eventually develop incurable metastasis. System chemotherapy is one of the main treatment options for patients with advanced breast cancer. Anthracycline and taxane are the mostly frequently used drugs for the treatment of advanced breast cancer in the setting of adjuvant or first-line chemotherapy. Unfortunately, many patients with advanced breast cancer will develop resistance to these drugs and have to switch to second and third line therapies. The efficacy of chemotherapy for anthracycline and taxane pretreated patients with advanced breast cancer remain at a low level of 33.0% to 38.3% [1]. Several toxical drugs such as vinorelbine, cisplatin, capecitabine and gemcitabine are recommended for the treatment of anthracyclines- and/or taxanes-refractory metastatic breast cancer, however, no optimal regimen by far has been proved to be more effective or less toxic than the others due to their different mechanisms of action and different toxicity profiles.

Vinorelbine is a semi-synthetic vinca alkaloids antineoplastic agent that can prevent the polymerization of tubulin and induce the depolymerization of microtubules. By stopping the cells in mitotic metaphase, it inhibits the growth of tumor and display no cross-resistance to anthracycline. Global data has proved vinorelbine-based regimens are effective for the treatment of patients with metastatic breast cancer. Capecitabine, an oral drug derivated from fluorouracil, is converted to 5-Fu by thymidine phosphorylase in liver and tumor tissues. Its relative selectivity for caner tissue both enhances the anti-tumor effects and reduces systemic toxicity [2]. Cisplatin is cell non-cycle specific drug, which acts in both mitotic phase and DNA synthetic phase of cancer cells. As an frequently used agent against a broad-spectrum of tumors, it shows strong antineoplastic effect and no cross-resistance to anthracyclines. Combination therapy are commonly recommended in the treatment of advanced breast cancer, therefore, vinorelbine plus cisplatin or capecitabine may provide a viable approach for the second- or third-line treatment of metastatic breast cancer.

In this study, we compared NP regimen with the NX regimen in the treatment of anthracycline- and taxanes-refratory advanced breast cancer. In consistence with previous trials, the ORR were identical in both treatment arms, DCR was similar [3–5]. The median time to progression was 5.7 months in NP group and 5.9 months in NX group, respectively. The median survival were 13.9 months and 14.1 months and the 1-year survival rates were 54.6% and 55.9% respectively. There was no significant difference between the two groups in terms of efficacy, the median time to progression, median survival, or 1-year survival rate.

No significant difference was found in the stratified analysis with respect to menopause, previous treatment and sites of metastasis. This was different from previous study. The inconsistence may possibly explained by the small number of patients enrolled in our study [6–7]. Further study needs to be conducted in a larger cohort of patients.

The main toxicities in both treatment groups were myelosuppression, gastrointestinal reactions, hand-foot syndrome and phlebitis. Although, patients in the NX group showed a slightly higher incidence of hand-foot syndrome and a lower incidence of gastrointestinal reaction, the differences were not statistically significant. Neutropenia was mostly reported myelosuppression, with a low grade (II–III) in severity, which was recovered by the administration of recombinant human granulocyte colony-stimulating factor. Phlebitis was also reported in both groups, this was probably because of the placement of central venous catheter in all patients enrolled.

In conclusion, no difference in PFS or RR between NP and NX groups was observed in this study. The potential differences in toxicity profile and treatment schedule between both treatments will help in choosing either NP or NX. Both regimens are considered reasonable second- or third-line treatment options for anthracyclines and taxanes-refractory advanced breast cancer.

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