Cisplatin plus Vinorelbine (PVn) as A Palliative Regimen Beyond Second Line for Advanced Breast Cancer–A Single Institute Experience

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Abstract

Objectives: The combination of cisplatin and vinorelbine has been proved to be effective and safe in the therapy of advanced breast cancer. We reported the experience of treating advanced breast cancer with combination of cisplatin and vinorelbine (PVn) as second line palliative regimen in Hualien Buddhist Tzu Chi General Hospital. Study design: Retrospectively, we analyzed thirty patients who underwent the regimen of PVn between Oct. 2002 and Sep. 2008. Patients received cisplatin (75mg/m2) on day 1 and vinorelbine (25mg/m2) on day 1 and 8 by intravenous infusion in every three weeks. Treatment was repeated for up to six cycles. The effectiveness and complications of the regimen were analyzed. Results: Among 30 patients, there were 21 patients with objective responses (70%), including 4 complete responses (13.3%) and 17 partial responses (56.7%). Time to progression was 7.79 months, and overall survival was 13.2 months. Grade 3 or 4 neutropenia was observed in 15 patients (63.3%), and neutropenic fever developed in 11 patients (36.7%). There was no treatment-related mortality. Conclusion: The combination of cisplatin and vinorelbine is effective and with modest toxicity as a palliative regimen in advanced breast cancer.(J Intern Med Taiwan 2011; 22: 344-351)

Key words: Chemotherapy, Cisplatin, Vinorelbine, Advanced breast cancer, Palliative

Introduction

Breast cancer is the most common malignancy in women. Many patients are treated with anthracycline-based or taxan-based regimens as first line in advanced breast cancer. If the front line therapy fails, it is important to identify active, well-tolerated, non-cross-resistant regimens as second or third line of palliative therapy[1].

By previous studies, cisplatin is not an active drug as single agent for previously treated advanced breast cancer. In previously untreated advanced

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breast cancer, a response rate of 47~54% can be achieved[2,3], but lower response, about 6%, is noted for previously treated patients[4]. Combinations of cisplatin with other antitumor drugs, including paclitaxel, docetaxel, gemcitabine, and vinorelbine, have been proved for improvement of the response rate[1,5-10]. Vinorelbine has been widely used as single agent for advanced breast cancer, and the response rate was about 41-50% as first line[5-10]. The rationale for combining cisplatin and vinorelbine (PVn) was based on their different mechanisms of action and the lack of overlapping toxicity, especially myelotoxicity[11]. The combination regimen of cisplatin and vinorelbine in first- and second-line treatment was reported first in 1994[12]. Subsequent investigations with the same or similar combinations have been reported[5-7,13-14]. These studies showed the response rate was between 25~73%, and time to progression was around 3~12.5 months. These data indicate this regimen is an effective treatment for advanced breast cancer.

In our hospital, taxane-based regimen is the first-line treatment for advanced breast cancer. If the disease progresses after the first line therapies, combination of cisplatin and vinorelbine is often used as the second line or third line regimen. The combination of cisplatin and vinorelbine is effective and with modest toxicity as a palliative regimen in advanced breast cancer in our hospital. Here, we reported the experience of the patients with advanced breast cancer who treated with combination of cisplatin and vinorelbine (PVn) as a palliative regimen in Hualien Buddhist Tzu Chi General Hospital.

Methods

Patient inclusion

Retrospectively, we analyzed the clinical data of patients who received the regimen of PVn after failure of the first line chemotherapy under the diagnosis of advanced breast cancer in Hualien Tzu-chi General Hospital during Oct. 2002 and Sep. 2008. We reviewed all the advanced breast cancer patients who were treated in our hospital from the database of oncologic department, and we collected the patients using the treatment regimen of PVn for this study. The advanced breast cancer included "Locally advanced", which means a tumor greater than 5 cm across, or a fixed lump in the axilla representing cancer, ulceration of the skin from cancer, or involvement of the deep chest muscles; and "Metastatic", which means the disease has spread to other areas of the body, such as the lung, liver, brain, skin or bone. By AJCC staging system of breast cancer revised in 2008 edition, we included N3 or M1 patients in this study. But we excluded patients with only one cycle treatment because the response could not be evaluated adequately.

Treatment protocol

Patients received cisplatin (75mg/m2) on day 1 and vinorelbine (25mg/m2) on day 1 and 8 by intravenous infusion. The dosage was adjusted by patient's condition and renal function. Treatment was repeated for up to six times every 3 weeks.

Criteria for response and toxicity evaluation

Physical examination, laboratory study, chest x-ray, computed tomography (CT) scan and bone scan were performed for evaluation of response. All the patients had a physical examination each month at least. The laboratory study, included complete blood count, alkaline phosphatase, calcium, blood urea nitrogen, and creatinine, were repeated before every course of treatment. The imaging study, included chest x-ray, CT, or bone scan, were performed depending on the patient's clinical condition or sites of metastatic condition, but at least after every three courses of chemotherapy. The definition of response is by standard RECIST criteria. Objective response (OR) is defined as percentage of patients who had complete response (CR) or partial response (PR).

For the response criteria in bone metastasis, there only were the following: CR, complete recalcification of all lytic lesions on X-ray; PR, recalcification of ~50% of all lytic lesions on X-ray (in both cases lasting > 3 months).

Toxicity was evaluated according to National Cancer Institute (NCI) criteria[16]. We collected the rate of neutropenia, neutropenic fever, nephrotoxicity, neurotoxicity, nausea and vomiting.

Statistical Analysis

The primary end point was time to progression, and the second end points included overall survival. Time to progression was defined as time from starting the combination treatment to tumor progression or last visit. Overall survival was defined as time from starting the combination treatment to death or last visit. Survival curves for time to progression and overall survival were estimated using the Kaplan-Meier method[17].

Results

Patient characteristics

Totally thirty-eight advanced breast cancer patients accepted the regimen of PVn during Oct. 2002 and Sep. 2008 (the number of 1st line and 2nd line). Eight patients were excluded for only one cycle of treatment and cannot be evaluated about the response to this chemotherapy. The data of the remaining 30 cases were analyzed. The patient characteristics are described in Table 1. Their mean age was 47.3 years (range, 28-73 years). Fourteen patients (46.6%) were premenopausal, 9 patients (30%) had positive estrogen receptor, 11 patients (36.6%) had positive progesterone receptor, and 9 patients (30%) had amplification of the HER2/neu oncogene by FISH study. Only two patients was locally advance stage, and the other twenty-eight patients had metastatic condition while including this study. All patients had been treated with palliative prior chemotherapy after advance breast cancer was diagnosed. All above patients accepted the first-line palliative prior chemotherapy (not included adjuvant), after lymph node or organ metastasis. The palliative regimens included 14 patients with Taxotere, 4 patients with Taxotere then Xeloda, 3 patients with Taxotere then UFUR, 3 patients with CEF (Cyclophosphamide, Epidoxorubicin and Fluorouracil), 2 patients with Taxotere then Taxol and Gemcitabine, and others (included Taxotere then CEF, AT, Taxol and Gemcitabine, and CEF then Taxol). They received 2.3 lines palliative chemotherapy (median: 2, range: 2-3) before PVn regimen. There were 23 patients (76.5%) who had received radiotherapy and 14 (46.6%) who had received hormone therapy before PVn salvage treatment.

Table 1. Patient characteristics and response

Total patient's numbers	30 (average age: 47.3)
Premenopausal	14 (46.6%)
ER+/PR+	12 (40%)
Her-2/neu Over-expression	9 (30%)
Previous chemotherapy	30 (100%)
Previous radiotherapy	23 (76.6)
Previous hormonal treatment	14 (46.6%)
Sites of metastasis	
One site	7 (23.3%)
Two sites	7 (23.3%)
≧ Three sites	16 (53.3%)
Bone	17 (56.7%)
Liver	14 (46.7%)
Lung	16 (53.3%)
Skin / chest wall	6 (20%)
Lymph node	13 (43.3%)
Brain	4 (13.3%)
Response	
Complete response	4 (13.3%)
Partial response	17 (56.7%)
Overall response rate	21 (70%)
Stable disease	7 (23.3%)
Progressive disease	2 (6.67%)

* No. of patients (%).

The sites of metastasis were described in Table 1 also. Among 30 patients, 7 (23.3%) had one site, seven (23.3%) had two sites, and sixteen (53.3%) had three or more than three sites. The metastatic sites included bone (17 patients, 56.7%), liver (14, 46.7%), lung (16, 53.3%), skin or chest wall (6, 20%), supraclavicular lymph node (13, 43.3%), and brain (4, 13.3%).

About the eight patients were excluded, the reason were due to only one cycle of treatment and cannot be evaluated about the response to this chemotherapy. In the eight excluded patients, there were three patients who were lost of following up after one course of PVn treatment. In four patients, due to poor performance or condition or family's asking, who were changed to oral-form chemotherapy. About the other one patient, she was transferred to hospice ward after only PVn one time.

Response and survival data

The median cycles with PVn regimen were 6 (range, 2-6). All the patients were assessable for response. Among the 30 patients, 21 had objective responses (70%), including 4 complete responses (13.3%) and 17 partial responses (56.7%) (Table 1). By subgroup analysis, in second-line treatment group, the objective response was 71.4% (15 in 21 patients), and in third-line treatment group, the objective response was 77.8% (7 in 9 patients). No significant difference was found between the two groups.

The clinical benefit was up to 97.3%. The average of time to progression was 7.79 months (95% CI: 1.5~24.2 months). The average of overall survival was 13.2 months (95% CI: 4~32.9 months). The curve of time to progression and overall survival are presented in Figure 1.

Toxicity

The main toxicities are listed in Table 2 and most of them were hematologic complications. Grade 3 or 4 neutropenia was observed in 15 patients (63.3%), and neutropenic fever developed in 11 patients (36.7%). Two patients (6.7%) had grade 1 or 2 nephrotoxicity, and 4 (13.3%) had grade 1 or 2 neurotoxicity. There were 9 cases (30%) developed grade 3 or 4 nausea and vomiting. No treatment-related death occurred in this study.

Discussion

In this study we evaluated efficacy and safety of combination chemotherapy of cisplatin and vinorelbine (PVn) in patients with advanced breast cancer. The combining cisplatin and vinorelbine was based on their different mechanisms without overlapping toxicity, especially myelotoxicity[11]. Subsequent investigations with the same combinations have been reported[5-7,13-14]. These average response rate was during 25~73%, and time to progression was around 3~12.5 months. In our study, the overall response rate was 70%, including 4 complete remissions (13.3%). The time to progression was 7.79 months and the overall survival was 13.2 months. The results are comparable with previous studies (Table 3).

Table 2. Toxicity of cisplatin plus vinorelbine

No. of patients (%) (per-patient)	Grade 1	Grade 2	Grade 3	Grade 4
Neutropenia	1 (3.3%)	3 (10%)	4 (13.3%)	11 (36.7%)
Nausea/Vomiting	1 (3.3%)	3 (10%)	8 (26.7%)	1 (3.3%)
Nephrotoxicity	1 (3.3%)	1 (3.3%)	0 (0%)	0 (0%)
Neurotoxicity	3 (10%)	1 (3.3%)	0 (0%)	0 (0%)
Neutropenic fever	11 (36.7%, No Grade)			
Alopecia	0 (0%)			

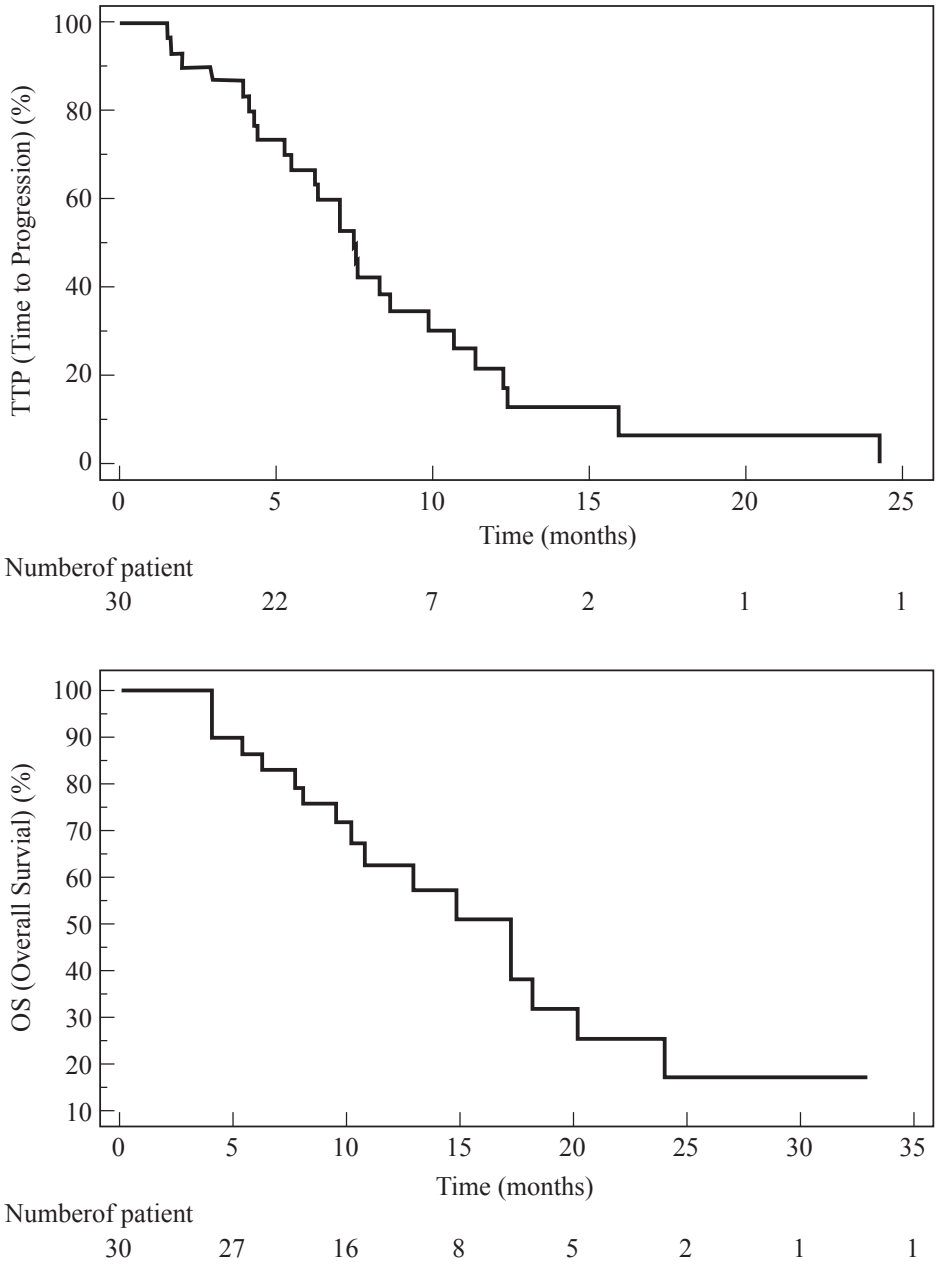

Fig 1. The curve of time to progression and overall survival.

Table 3. Comparison of previous reports and our study

Reference	Line of chemotherapy	Patient's numbers	RR	TTP	MS
Hochster et al[18]	1st	22	73	N/A	N/A
Ray-Coquard et al[5]	2nd	58	41	3	N/A
Vassilomanolakis et al[13]	2nd	53	49	5	12
Shamseddine et al[6]	2nd ~ 3rd	23	61	4	12
Mustacchi et al[1]	1st	32	52.9	8.5	16.6
Gunel et al[7]	2nd	24	25	12.5	N/A
Our study	2nd ~ 3rd	30	70	7.79	13.2

However if we consider a treatment beyond second line, the present study is superior to other studies in all the 3 indicators[5,6,13]. In above three previous study, the response rate was around 41% to 61%, time to progression was around 3~5 months, and median survival was about 12 months. The reason of the superior result in our study may be due to the fact that almost all patients were able to complete six courses of this regimen (median cycles: 6, and average cycles: 4.7), and there was no treatment-related death. Another factor to contribute the superior data is the exclusion of patients who took only one cycle of the regimen.

But we observed higher rate of neutropenia and neutropenic fever in our study. In previous studies grade 3 or 4 neutropenia developed around 50% of the patients with dose-limiting side effects[5-7,13]. In Shamseddine's study[11], the neutropenia (included Gr 3 or 4) showed only 3%, but the rate of neutropenia was 63.3% in our study. Especially, only 3% neutropenic fever was reported during the treatment course by Shamseddine's study. In our study, eleven patients (36.7%) developed at least one episode of neutropenic fever during the treatment course. According to previous report, myelosuppression by cisplatin occurs in 11~30%, and vinorelbine in 15~36%. Risk of myelosuppression increases when vinorelbine is used in combination with cisplatin. The more rates of myelosuppression from Cisplatin and Vinorelbine may be caused by patients' characteristics.

During this study, the use of granulocyte colony-stimulating factor (G-CSF filgrastim) was permitted, after the first course of treatment for patients who experienced Grade 3 or 4 granulocytopenia ($\leq$1,000 cells/mm^3) or in those who developed neutropenic fever between cycles of chemotherapy. The prophylasix with G-CSF was given after every course of chemotherapy thereafter. Because of prophylaxis of G-CSF, there was no treatment-related mortality resulting from neutropenia. And the median survival was still better then previous study. The prophylasix of G-CSF may be necessary for this regimen.

Conclusion

The combination chemotherapy of cisplatin and vinorelbine (PVn) is effective and with modest toxicity as a palliative regimen in advanced breast cancer as a second line salvage treatment. The toxicity profile is manageable, making this regimen as a good choice for patients with late stage breast cancer. But because this study was retrospective, and the patient's number was small, the result may have the overestimation of response rate. A prospective phase II study is worthy to conduct in the future.

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合併順鉑 (Cisplatin) 及溫諾平 (Vinorelbine) 在治療晚期乳癌病人：單一醫學中心之經驗

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摘 要

引言：順鉑 (Cisplatin) 及溫諾平 (Vinorelbine) 的組合已被證明在治療晚期乳癌病人是有效且安全的。在這篇文章中，我們花蓮慈濟醫學中心使用順鉑及溫諾平 (PVn) 的組合作爲第二線於晚期乳癌病人之緩和治療。 方法：利用病例回顧方式，我們分析了接受 PVn 療法在 2002 年 10 月至 2008 年 9 月之間的三十名患者，患者每三個星期接受了順鉑 (75mg/m2) 第一天，以及溫諾平 (25mg/m2) 第一及第八天治療，治療以六個週期爲目標。我們分析此計畫之效率、存活時間、及副作用。結果：在 30 名患者之中，總反應爲 70% (21 名病人)，包括 4 個完全反應 (13.3%) 和 17 個部份反應 (56.7%)。疾病進展時間爲 7.79 月，整體存活時間爲 13.2 月。副作用方面，等級 3 或 4 嗜中性白細胞減少症爲 15 名患者 (63.3%) 和在 11 名患者發生嗜中性白細胞減少發燒 (36.7%)。結果與之前的研究相較，發現我們有較高的反應率、較長的疾病進展時間及爲整體存活時間，但也有較高的嗜中性白細胞減少症的比率，但沒有治療造成之死亡被發現。結論：合併順鉑及溫諾平治療在晚期乳癌病人是有效且安全的。