DOI:10.31557/rro.2381.20240311

Vinorelbine and Docetaxel Combination as the First Line Treatment in Patients with Metastatic Breast Cancer: Results of a Multi-centric Phase II Trial in Iran

Ameri A[1], Shahrad B[1], Fazlalizadeh A[1], Madani H[2], Mousavizadeh A[2], Moghadam S*[1]

1. Department of Radiation Oncology, Imam Hossein Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran.
2. Department of Radiation Oncology, Shohada Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran.

***Corresponding Author:** Moghadam S
Email: rro@isro.org.ir

Abstract

Introduction: We conducted a multi-centric phase II study to evaluate the tumor response and safety of the combination of vinorelbin and docetaxel in treatment of metastatic breast cancer patients.

Patients and methods: Forty one metastatic breast cancer patients, who had at least one measurable lesion and had not been treated for metastasis before, were enrolled from March 2006 to June 2009. Treatment contained vinorelbine 25mg/m^2 IV and docetaxel 30mg/m^2 at day 1 and 8. Cycles were repeated every 21 days for 6 cycles. We evaluated response to chemotherapy every three weeks and toxicity every week.

Results: The mean age of patients was 50.4 years (range 30-81). Twenty eight patients (68.2%) had received prior neoadjuvant anthracycline based chemotherapy. No patient had received adjuvant chemotherapy within the last 3 months. Twenty four patients (58.3%) had two or more metastatic sites. Thirty six patients were evaluable for their response. An objective tumor response (either complete response or partial response) was achieved in 32 (88.8%) and complete response was seen in 9 (25%) patients. Thirteen patients (31.6%) developed grade 3-4 neutropenia and neutropenic fever was reported in 11 (26.8%). Grade 3 anemia was observed in 1 patient (2.4%). No grade 4 non-hematological toxicity was noted and the most frequent grade 3 non-hematological toxicities were hair loss (39%), stomatitis (7.3%) and diarrhea (4.8%). Median time to progression was 7 months and median overall survival was 11 months.

Conclusion: Vinorelbine-docetaxel combination shows a considerable tumor response and manageable toxicity as the first line treatment for metastatic breast cancer. It seems logical to conduct phase III trials to further evaluate this regimen.

Key words: Metastatic breast cancer, chemotherapy, vinorelbine, docetaxel.

Introduction

Breast cancer is the most common malignancy among women and is the second cause of cancer deaths in female population [(1)]. The incidence of this disease is rising rapidly in many developing countries. According to the latest report by the Institute of Cancer in Iran, breast cancer constitutes 25% of all cancers among Iranian women [(2)]. Despite considerable improvements in the detection, early diagnosis and treatment of breast cancer and increased 5-year survival rate in Iranian patients, a significant number of women will relapse and ultimately die of metastatic disease [(3)].

Metastatic breast cancer (MBC) is sensitive to chemotherapy but remains incurable with current therapeutic approaches [(4)]. Combination chemotherapy has increased response rate in comparison with single agent chemotherapy, but few combinations such as docetaxel-capecitabine or paclitaxel-gemcitabine can increase the survival rate [(5,6)].

Combinations of alkylating agents with anthracyclines are widely used in MBC and yield

overall response rates ranging from 40 to 60%, with complete response rates less than 20%, and median response duration less than 15 months [4].

Single agents such as doxorubicin or epirubicin, cyclophosphamide, 5-fluorouracil (5-FU) and methotrexate achieve overall response rates ranging from 20 to 50% in this setting [7]. There are several types of combination therapies with each of docetaxel and vinorelbine combined with other drugs in the literature.The best overall response rate have been obtained in three studies of docetaxel combinations. In TAX 306 study by Nabholtz et al., the combination of docetaxel plus doxorubicin resulted in 59% overall response rate [8]. In a study by Bontenbal et al., docetaxel+doxorubicin regimen was compared to 5-FU + doxorubicine + cyclophosphamide and resulted in 58% and 57% overall response rates respectively [9]. In Bonneterre et al. study, docetaxel+epirubicine were compared to 5-FU+epirubicine+cyclophosphamide and resulted in 59% and 32% overall response rates respectively [10].

A combination of vinorelbine plus 5-FU has also been administered to patients who have failed anthracycline therapy. In a phase II study by Froudarakis et al., vinorelbine plus 5-FU in pretreated MBC patients exhibited substantial activity (overall response rate 43%) and acceptable tolerability [11]. In another phase II study by Dieras et al., first-line administration of vinorelbine plus 5-FU resulted in 62% overall response rate [12].

Although the combination of vinorelbine and docetaxel which is among the most active agents with reasonable tumor response in the treatment of metastatic breast cancer have been experienced in phase I combination clinical trials in advanced breast cancer, most of these studies concluded that more trials are required to clarify different aspects of docetaxel and vinorelbine combination in MBC patients [13,14]. The objective of this study was to evaluate the response rate of metastatic breast cancer to the combination of vinorelbine and docetaxel. We also evaluated the time to progression, overall survival rate and safety profile of vinorelbine and docetaxel combination as the first line treatment for metastatic breast cancer in this group of Iranian patients.

Patients and Methods

Eligibility criteria

In this phase II open label clinical trial we enrolled untreated women with metastatic breast cancer, into the study from March 2006 to June 2009. Patient ≥18 years of age with performance status ≤ 2 according to WHO classification and a life expectancy > 3 months were recruited. All patients had histologically proven breast carcinoma as their first diagnosis and had at least one bi-dimensional measurable lesion.

Patients with a medical history of bone metastasis or malignant pleural effusion (as only site of metastases), known brain or leptomeningieal infiltration, peripheral neuropathy, getting any chemotherapy other than adjuvant treatment and those who had other serious illnesses or medical conditions were excluded. Also pregnant or lactating women were not eligible to participate in this study.

Eligible patients had adequate bone marrow, hepatic and renal function and also had no history of previous chemotherapy except for adjuvant chemotherapy with anthracyclines. The least interval between the last course of adjuvant chemotherapy and the treatment protocol was determined to be > 6 months. This study was done according to Helsinki declaration and ethical procedures involved in Iran. A written informed consent was obtained from each patient before participating in the study.

Treatment plan

Vinorelbine was administered as a short intravenous infusion of 25mg/m^2 in 50 ml normal saline over 6-10 minutes, followed by a rapid infusion of 250ml of normal saline on days 1 and 8. Docetaxel was administered as an intravenous infusion of 30mg/m^2 in 200 ml normal saline over one hour on days 1 and 8. Cycles were repeated every 21 days for a total of 6 cycles.

For all patients dexamethasone 8mg bid (intravenous), one day prior to and one day after the administration of docetaxel (total of 3 days), were prescribed. In the absence of any progression or unexpected adverse events, treatment was continued for a total of six cycles. The use of G-CSF as prophylactic or curative therapy was optional and the use of erythropoietin alpha and antiemetics were allowed at physician's discretion. Blood transfusion was allowed if hemoglobin dropped to less than 10g/dl.

Study assessment

The baseline evaluation was performed by taking medical history, physical examination, pregnancy test, measuring WHO performance status, CBC, SGOT, SGPT, total bilirubin, creatinine, chest X-ray, abdominal ultrasound or computerized tomography (CT) scan and whole body bone scan. All evaluations except chest X-ray, abdominal ultrasound or CT scan and bone scan were repeated at the day 1 of each cycle subsequently. The response to chemotherapy was assessed at the end of the 3rd cycle and at the end of the 6th cycle.

Time to progression was calculated from the date of the first chemotherapy prescription up to the date of the first progression (Kaplan Meier estimation). Overall survival was calculated from the date of the first chemotherapy prescription up to the date of death (Kaplan Meier estimation). The objective response rate was determined by tumor measurement using the Response Evaluation Criteria in Solid Tumors (RECIST) Committee guidelines [15].

All patients who received at least one dose of the medication and for whom the follow-up data was available were considered to be evaluated for safety profile. Toxicities were graded according to the WHO criteria. Renal and liver toxicities were recorded at day 1 of each cycle. Non-hematological toxicities were recorded at each cycle. The maximum grade or severity was reported by cycle and by patient.

Statistical methods

The primary end point was overall tumor response, which was composed of both complete and partial responses. The 95% confidence intervals were determined for response rates and time to progression. Time to progression and overall survival were estimated using the Kaplan-Meier method.

Results

Patient characteristics

A total of 41 women with metastatic breast cancer started vinorelbine with docetaxel as the first-line of treatment. Main patient characteristics are summarized in table 1.

The mean age of patients was 50.4 years (range 30-81 years). The WHO performance status was zero in 17 (41.4%); one in 22 (53.6%) and two in 2 (4.8%) patients. Twenty eight patients (68.2%) had received prior neo/adjuvant anthracyclin based chemotherapy. No patients had received adjuvant chemotherapy within the last 3 months. The most

Table1: Mean OMAS scores in Calendula and placebo groups

characteristics	Patients, n (%)
Total No. of patients	41
Age, mean years	50.4
Range	30-81
Performance at enrollment	
0	17 (41.4%)
1	22 (53.6%)
2	2 (4.9%)
Prior neo/adjuvant therapy	
Anthracycline-based	25 (60.9%)
Taxane-based	3 (7.3%)
Hormone therapy	31 (75.6%)
Main metastatic site	
Lung	18 (43.9%)
Bone	16 (39%)
Liver	10 (24.3%)
Soft tissue	0 (0%)
Number of metastatic sites	
1	17 (41.4%)
2	15 (36.5%)
3	5 (12.1%)
> 3	4 (9.7%)

frequent metastatic sites were lung (43.9%), bone (39%), and liver (24.3%) respectively. Twenty four (58.3%) patients had two or more metastatic sites.

A total of 186 courses of vinorelbine and docetaxel were administered (range 1 to 6) and the median number of chemotherapy cycles was 5.

Tumor response

Thirty six (87.8%) of 41 patients were evaluable for response. An objective tumor response was achieved in 32 (88.8%) of 36 patients (Objective Response = Complete Response + Partial Response), and complete response was noted in 9 (25%) patients. Table 2 demonstrates the tumor response summary.

Toxicity

All patients were evaluable for toxicity. Thirteen patients (31.6%) developed grade 3-4 neutropenia, while neutropenic fever was reported in 11 patients (26.8%). Grade 3 anemia was observed in one patient (2.4%). No grade 4 non-hematological toxicity was noted and the most frequent grade 3 non-hematological toxicities were hair loss (39%), stomatitis (7.3%) and diarrhea (4.8%). Median time to progression was 7 months and median overall survival was 11 months. In general, prophylactic G-CSF was administered in 119 (63.9%) cycles.

Discussion

As in metastatic breast cancer patients, the effective anthracycline based regimens are often contraindicated due to cumulative dose limitation; it seems there is a need for new regimens in this group of patients [13].

Docetaxel is regarded as the single most effective cytotoxic agent for advanced breast cancer with substantial objective response rates in previously untreated patients (up to 68% in phase II trials) and anthracycline-pretreated patients (30% to 43% in phase III trials) [16,17]. Vinorelbine has also shown significant single-agent activity as the first-line or second line treatment in advanced breast cancer therapy, typically inducing objective responses in at least one third of patients [18]. Docetaxel and vinorelbine target microtubules with different mechanisms. The mechanisms of action of docetaxel is promoting tubulin assembly into microtubules, stabilizing microtubules, and inhibiting depolymerization to free tubulin. On the other hand, vinorelbine makes microtubules disrupted by binding them to tubulins irreversibly. These two drugs have demonstrated sequence-dependent synergy in preclinical studies, providing the rationale for combination use in phase I/II trials [19, 20].

There are several studies in the literature in which the synergistic effect of docetaxel and vinorelbine has been investigated in MBC patients [13,14,21,22].

In the latest study by Palmieri et al. in 2012, comparing docetaxel versus vinorelbine in 35 metastatic breast cancers progressing after

Table2: The tumor response among women with metastatic breast cancer treated with the combination of vinorelbine plus docetaxel.

Response	Patients, n (%)
Total patients	41
Evaluable patients	36 (87.8%)
Objective Response (CR + PR)	32 (88.8%)
Complete Response (CR)	9 (25%)
Partial Response (PR)	23 (63.8%)
Stable Disease (SD)	2 (5.5%)
Disease Control (OR + SD)	34 (94.4%)
Progressive Disease (PD)	7 (20.5%)

• A total of 186 cycles of vinorelbine - docetaxel was administered.
• Median number of cycles per patient: 5 (range 1-6).

previous anthracycline therapy; the disease control rate was reported 44% and 12% for docetaxel and vinorelbine groups respectively which is lower than the overall response rates of combination studies, although vinorelbine was much better tolerated [22].

Vici et al. conducted a study using docetaxel 100mg/m^2 (4 cycles) followed by 4 cycles of epirubicin 90mg/m^2 (day 1) combined with vinorelbine 25mg/m^2 (days 1 and 5), with cycles repeated every 3 weeks, on 27 metastatic breast cancer patients in 2005. The reported overall response rate was 55.6% (Partial response:51.9%, Complete Response:3.7%) and the median time to progression was 9 months [23]. In another study by Andres et al. the combination of 60mg/m^2 docetaxel and 24mg/m^2 vinorelbine every two weeks was administered in 30 MBC patients. The overall response rate was 60% (Partial Response: 46.6%, Complete Response: 13.3%). The median time to progression was 7 months the same as our study. Stable disease and progressive disease were reported in 16.6% and 23.3% of patients respectively [24]. Marti et al. reported 46% overall response rate and 28% stable disease with docetaxel plus vinorelbine combination in 50 MBC patients previously treated with anthracyclines. In their study time to progression was 29 weeks [25]. There are other studies which have reported similar results, using a combination of these two drugs [13, 14, 20, 21].

As it is seen, in our phase II clinical trial, we achieved 88.8% overall response rate (Partial response: 63.8%, complete response: 25%) which seems very promising. The disease control rate which is defined as (stable disease+overall response rate) was 94.4%. These results indicated a high tumor response for docetaxel and vinorelbine combination among patients with metastatic breast cancer. Better results in this study might be due to our different protocol as docetaxel (30 mg/m^2 day 1 and 8) and vinorelbine (25 mg/m^2 day 1 and 8) combination were repeated every 3 weeks and also the fact that we used this combination only as the first line treatment for metastatic breast cancer patients. The time to progression was 7 months in our study which is similar to others. However this short time of responses seemed to be a challenging issue in the present study.

Regarding the safety profile, the most common grade 3-4 toxicities in previous studies have been reported to be neutropenia, febrile neutropenia, and stomatitis [13,14,20-22,24,25].

Table3: Summary of hematologic versus non-hematologic toxicities associated with the combination of vinorelbine plus docetaxel in treating women with metastatic breast cancer.

N= 41	Grade 3 (n, %)	Grade 4 (n, %)
Hematological toxicities		
Anemia	1 (2.4%)	0 (0.0%)
Thrombocytopenia	1 (2.4%)	0 (0.0%)
Neutropenia	12 (29.2%)	1 (2.4%)
Febrile neutropenia	11 (26.8%)	0 (0.0%)
Non-Hematological toxicities		
Nausea-Vomiting	0 (0.0%)	0 (0.0%)
Oral Stomatitis	3 (7.3%)	0 (0.0%)
Diarrhea	2 (4.8%)	0 (0.0%)
Hair loss	16 (39%)	0 (0.0%)
Peripheral Neuropathy	0 (0.0%)	0 (0.0%)
Constipation	0 (0.0%)	0 (0.0%)
Local Phlebitis	0 (0.0%)	0 (0.0%)
Hepatic Enzyme Elevation	1 (2.4%)	0 (0.0%)
Bilirubin Elevation	1 (2.4%)	0 (0.0%)
Creatinine Elevation	0 (0.0%)	0 (0.0%)

In our study, the most common grade 3-4 hematological toxicities were neutropenia (29.2%) and febrile neutropenia (26.8%). The most frequent grade 3 non-hematological toxicities were hair loss (39%), oral stomatitis (7.3%) and diarrhea (4.8%). That is almost consistent with the previous studies [3,13,14,20-22,24,25].

Studies of docetaxel and vinorelbine to treat metastatic breast cancer (MBC) have reported dose limiting febrile neutropenia, however routine use of prophylactic granulocyte colony stimulating factor have reduced the number of hematological toxicities [20,23,26].

Conclusions

Vinorelbine-docetaxel combination shows a considerable tumor response and manageable toxicity as the first line treatment for metastatic breast cancer. It seems logical to conduct phase III trials to further evaluate this regimen.

Acknowledgements

This trial was supported by Sanofi-Aventis Iranian affiliate.

References

1. Devita, Vincent T, Lawrence, Theodore S, Rosenberg, Steven A (2008). Cancer: principles and practice of oncology, 8th Edition Lippincott Williams and Wilkins, 1606-9.
2. Goya M. Iranian Annual Cancer Registration Report 2003. Ministry of Health and Medical Education, Health Deputy, Center for Disease Control and Prevention. March 2005 [Persian].
3. Harirchi I, Karbakhsh M, Kashefi A, Momtahen AJ. Breast cancer in Iran: results of a multi-center study. Asian Pac J Cancer Prev. 2004;5(1):24-7.
4. Bonneterre J, Roché H, Monnier A, Guastalla JP, Namer M, Fargeot P, et al. Docetaxel vs 5-fluorouracil plus vinorelbine in metastatic breast cancer after anthracycline therapy failure. Br J Cancer. 2002;87(11):1210-5.
5. O'Shaughnessy J, Miles D, Vukelja S, Moiseyenko V, Ayoub JP, Cervantes G, et al. Superior survival with capecitabine plus docetaxel combination therapy in anthracycline-pretreated patients with advanced breast cancer: phase III trial results. J Clin Oncol. 2002;20(12):2812-23.
6. Demiray M, Kurt E, Evrensel T, Kanat O, Arslan M, Saraydaroglu O, et al. Phase II study of gemcitabine plus paclitaxel in metastatic breast cancer patients with prior anthracycline exposure. Cancer Invest. 2005;23(5):386-91.
7. Clavel M, Catimel G. Breast cancer: chemotherapy in the treatment of advanced disease. Eur J Cancer. 1993;29A(4): 598-604.
8. Nabholtz JM, Falkson C, Campos D, Szanto J, Martin M, Chan S, et al. Docetaxel and doxorubicin compared with doxorubicin and cyclophosphamide as first-line chemotherapy for metastatic breast cancer: results of a randomized multicenter phase III trial. J ClinOnco. 2003;21(6):968-75.
9. Bontenbal M, Creemers GJ, Braun HJ, de Boer AC, Janssen JT, Leys RB, et al. Phase II to III study comparing doxorubicin and docetaxel with fluorouracil, doxorubicin, and cyclophosphamide as first line chemotherapy in patients with metastatic breast cancer: results of a Dutch Community Setting Trial for the Clinical Trial Group of the Comprehensive Cancer Centre. J Clin Onco. 2005; 23(28):7081-8.
10. 10. Bonneterre J, Dieras V, Tubiana-Hulin M, Bougnoux P, Bonneterre ME, Delozier T, et al. Phase II multicentre randomized study of docetaxel plus epirubicin vs 5-fluorouracil plus epirubicin and cyclophosphamide in metastatic breast cancer. Br J Cancer. 2004;91(8):1466-11.
11. 11. Froudarakis ME, Catimel G, Guastalla JP, Rebattu P, Clavel M. Phase II trial of navelbine and fluorouracil as second-line chemotherapy in metastatic breast carcinoma. Oncology. 1998;55(1):87-8.
12. Dieras V, Extra JM, Bellissant E, Espie M, Morvan F, Pierga JY, et al. Efficacy and tolerance of vinorelbine and fluorouracil combination as first-line chemotherapy of advanced breast cancer: results of a phase II study using a sequential group method. J Clin Oncol. 1996;14(12):3097-104.
13. Campone M, Fumoleau P, Delecroix V, Deporte-Fety R, Perrocheau G,Vernillet L, et al. Phase I dose-finding and pharmacokinetic study of docetaxel and vinorelbine as first-line chemotherapy for metastatic breast cancer. Ann Oncol. 2001;12(7):909-18.
14. Delord JP, Dalenc F, Pinguet F, Nguyen L, Lochon I, Poublanc M, et al. A phase I dose-escalating and pharmacokinetic study of docetaxel and vinorelbine as first-line chemotherapy for metastatic breast cancer. Oncology. 2007;72(5-6):322-5.
15. Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, et al. New guidelines to evaluate the response to treatment in solid tumors.

J Natl Cancer Inst. 2000;92 (3):205-16.
16. Trudeau ME. Phase I-II studies of docetaxel as a single agent in the treatment of metastatic breast cancer. Semin Oncol. 1999;26(3 Suppl 8):21-6.
17. Burris HA 3rd. Single-agent docetaxel (Taxotere) in randomized phase III trials.Semin Oncol. 1999;26(3 Suppl 9):1-6
18. Domenech GH, Vogel CL. A review of vinorelbine in the treatment of breast cancer. Clin Breast Cancer. 2001;2(2):113-28.
19. Lavelle F, Bissery MC, Combeau C, Riou JF, Vrignaud P, André S. Preclinical evaluation of docetaxel. Semin Oncol. 1995;22(2 suppl 4):3-16.
20. Kornek GV, Ulrich-Pur H, Penz M, Haider K, Kwasny W, Depisch D,et al. Treatment of Advanced Breast Cancer with Vinorelbine and Docetaxel With or Without Human Granulocyte Colony-Stimulating Factor. Journal of Clinical Oncology. 2001;19(3): 621-27.
21. Cals L, Nouyrigat P, Valenza B, Pedinelli FJ, Juin P. Weekly combination of docetaxel and vinorelbine in metastatic breast cancer: a phase I/II study. Oncology. 2004;67(3-4):257-61.
22. Palmieri C, Alifrangis C, Shipway D, Tat T, Watson V, Mackie D, et al. A Randomized Feasibility Study of Docetaxel Versus Vinorelbine in Advanced Breast cancer. Oncologist. 2012;17(11):1429-e47.
23. Vici P, Foggi P, Colucci G, Capomolla E, Brandi M, Giotta F, et al. Sequential Docetaxel Followed by Epirubicin-Vinorelbine as First-line Chemotherapy in Advanced Breast Cancer. Anticancer Res. 2005;25(2B):1309-14.
24. Andres R, Mayordomo JI, Isla D, Marti JL, Escudero P, Fillipovich E, et al. Responses to docetaxel plus vinorelbine in metastatic breast cancer patients failing high-dose chemotherapy. Br J Cancer. 2002;86(6):1017-8.
25. Marti JL, Bueso P, Mayordomo JI, Isla D, Saenz A, Escudero P, et al. Combination chemotherapy with docetaxel plus vinorelbine in metastatic breast cancer patients with prior exposure to anthracyclines. Ann Oncol. 2001;12(8):1061-5.
26. Limentani SA, Brufsky AM, Erban JK, Jahanzeb M, Lewis D. Phase II study of neoadjuvant docetaxel, vinorelbine, and trastuzumab followed by surgery and adjuvant doxorubicin plus cyclophosphamide in women with human epidermal growth factor receptor 2-overexpressing locally advanced breast cancer. J Clin Oncol. 2007;25(10):1232-8.