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Vinorelbine and cisplatin in metastatic breast cancers

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ABSTRACT

Nineteen patients with metastatic breast cancer who had been previously treated with a regimen containing doxorubicin and docetaxel were included in our study. Cisplatin (75 mg/m^2 day 1) and vinorelbine (25 mg/m^2 days 1 and 8) were administered every 3 weeks. The median age was 51 yr (41-69). A total of 98 cycles of chemotherapy was given, with a median of 6 cycles (3-6). Four patients achieved a complete response (21%), and six patients achieved a partial response (32%), with an overall response rate of 53%. Stable disease was observed in five patients (26%), four patients had progressive disease (21%). The median time to progression was 4 months (0-13) and median overall survival was 46 months (39-52). Grade 3-4 toxicities were febrile neutropenia 1%, anemia 3%, neutropenia 11%, nausea-vomiting 1%. This cisplatin/vinorelbine regimen is well tolerated and active in patients who failed anthracyclines and docetaxel treatment. [Turk J Cancer 2006;36(1):23-26].

KEY WORDS:

Metastatic breast cancer, vinorelbine, cisplatin

INTRODUCTION

The agents, commonly used in chemosensitive breast cancer management, are cyclophosphamide, methotrexate, fluorouracil and anthracyclines (1). Combined regimens of anthracyclines and taxanes, which also are effective alone each, are used as the first line treatment of metastatic breast cancer, in many countries (2,3). Active, well-tolerated new treatment regimens, showing no cross-resistance with anthracyclines, are needed when the anthracyclines could not be used because of cardiac dysfunction. It has been shown that cisplatin is active in breast cancer management, either alone or combined with new agents such as docetaxel, gemcitabine (Objective response: 47-54%) (4-7). Vinorelbine (VNR), is a third generation semisynthetic vinca alkaloid and microtubule inhibitor. It destabilizes microtubules which is different from taxanes. The response rate with VNR monotherapy in metastatic breast cancer is around 41-50% (8,9). VNR is commonly used in metastatic breast cancer management, either alone or combined with docetaxel, paclitaxel, doxorubicin (10-12). Vinorelbine's synergetic antitumoral activity with cisplatin is shown in animal models (13). High response rate is reported with this combination in either anthracycline-sensitive or resistance cases (14,15). Cisplatin-VNR combination has been interesting because of different mechanisms of the two drugs and the difference between their myelotoxicities. We have analyzed the effectiveness and safety of cisplatin-

VNR combination retrospectively in our breast cancer patients previously treated with anthracycline and docetaxel.

MATERIALS AND METHODS

The data of nineteen patients were analyzed retrospectively in our study. All patients had the diagnosis of "metastatic breast cancer" and were treated with anthracycline-docetaxel, previously. Bone marrow, renal, hepatic and cardiac functions were reviewed before the treatment. Informed consent form was taken from each patients before the treatment. Cisplatin 75 mg/m^2 following intravenous hydration and antiemetic treatment, in 1000 cc physiologic serum during 4 hours on first day, VNR 25 mg/m^2 in 250 cc physiologic serum during 20 minutes on first and eighth days were administered in every three weeks. The patients were evaluated with physical examination, abdominal computed tomography, chest x-ray after third and sixth cycles. Whole blood count, creatinine, creatinine clearance and serum electrolyte levels were examined before each cycle. ECOG (Eastern Cooperative Oncology Group) criteria were used for performance status. Response rate above 50% was evaluated as partial response, regression between 25-50% as stable disease, new tumor or response rate below 25% as progression, after chemotherapy. Response and toxicity evaluation after chemotherapy were made according to WHO criteria. Progression time means the period from the beginning of treatment until the progression, and overall survival means the time from diagnosis until the last visit or death. Survival curves for time to progression and overall survival were estimated using the Kaplan-Meier method.

RESULTS

The data of 19 patients previously treated with FAC (5-Fluorouracil, doxorubicin, cyclophosphamide) and docetaxel, was evaluated. Median age was 51 (41-69) and all of the patients had ECOG 0-1 performance status. Estrogen receptor positivity was 32% and 47% of the patients were postmenopausal, 53% were premenopausal. Seven cases (37%) had only liver metastasis, two (11%) had lung, three (16%) had bone, one (5%) had extensive skin involvement and the rest had more than one site of metastasis (Table 1). White blood count was >3500/dL, platelet count >100.000/dL, hemoglobin level >11gr/dl, creatinine <1.5 mg/dL, creatinine clearance >60 ml/min, bilirubin <2 mg/dL in all of the patients. A total of 98 cycles and a median of 6 (3-6) cycles were administered to the patients. Complete response was observed in 4 patients (21%), partial response in 6 (32%), (objective response in 10 patients, 53%), stable disease in 5 (26%) patients and 4 patients (21%) progressed after the treatment (Table 2). The median time to progression was 4 months (0-13), median overall survival was 46 months (39-52). As grade 3–4 toxicity, febrile neutropenia in 1 cycle (1%), anemia in 3 cycles (3%), neutropenia in 11 cycles (11%), and nausea/vomiting in 1 cycle (1%) were observed (Table 3). There were no treatment-related deaths.

Table 1
Patient characteristics

	No (%)
Age (years)	
Median	51
Range	41-69
ECOG performance status	
0	10 (53)
1	9 (47)
ER positive	6 (32)
Premenopausal	9 (53)
Postmenopausal	10 (47)
Site of metastases	
Liver	7 (37)
Lung	2 (11)
Bone	3 (16)
Skin	1 (5)
Multiple sites	6 (31)

Table 2
Chemotherapy responses

	No (%)
Complete response	4 (21)
Partial response	6 (32)
Stable disease	5 (26)
Progressive disease	4 (21)

Table 3
Grade 3-4 toxicity observed in patients (WHO criteria)

	Cycles (%)
Neutropenia	11 (11)
Febrile neutropenia	1 (1)
Anemia	3 (3)
Nausea/vomiting	1 (1)

DISCUSSION

The prognosis is generally poor in the breast cancer patients who develop metastasis in spite of previous anthracycline treatment (Objective response: 21%) (16). After the good results of anthracycline plus taxanes in the adjuvant management of the breast cancer, the new combinations are being investigated. VNR is a promising agent which has a response rate of 41-50% in the first and second line treatment of metastatic breast cancer (8,17). Bonneterre et al. (18), showed that docetaxel (100 mg/m^2) and VNR (25 mg/m^2)-5-Fluorouracil (750 mg/m^2 continuous infusion) combination had equal activity (response rates 43% and 39%, respectively). In another study, Ray-Coquard et al. (14), observed a response rate of 41% with CIVIC (cisplatin 20 mg/m^2 and VNR 6 mg/m^2 1-5 days). In the last study, VNR was given as continuous infusion during 5 days while it was given as bolus intravenously for a total of 2 days, in our study. Szatkowska et al. (19) have administered cisplatin (100 mg/m^2) and VNR (30 mg/m^2) and observed a 40% objective response rate. The objective response rate is 53% in our study. The lower objective response rate in Szatkowska's study made the investigators think that higher doses of cisplatin was not more useful and also could increase the toxicity. Heterogeneity of previous treatment (FAC/CMF) and the usage of carboplatin instead of cisplatin could also affect the response rate. All the patients received docetaxel following FAC, in our study. Günel et al. (20) have administered cisplatin and VNR to the patients previously treated with anthracycline and paclitaxel and showed an objective response rate of 25%. The unlikeliness of our results could be because of using docetaxel instead of paclitaxel. Vassi et al. (15,21) observed an objective response rate of 47% and 49% in two different studies using the same combinations of two drugs as in our study. Mustacchi et al. (22), reported nearly the same response rate (52.9%) with ours (53%). The heterogeneity of the response rates in those studies mentioned above could be related to the heterogeneity of the previous treatments and usage of paclitaxel in some of them instead of docetaxel. Most common treatment-related toxicity was neutropenia (11%) in our study as in the others (9-22). There was only one febrile neutropenia in our study and this low toxicity could be because of the small number of the patients. No treatment-related deaths, nephrotoxicity, neurotoxicity were observed in our patients. Cisplatin-VNR combinations seem to have safety for being used in the management of metastatic breast cancer patients who received anthracycline-taxane in the adjuvant setting, with the acceptable myelotoxicity.

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