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ORIGINAL ARTICLE

Vinorelbine/VP-16 (etoposide) in metastatic breast cancer: a phase II study

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Summary

Purpose: *This phase II study was conducted to evaluate the efficacy and tolerability of vinorelbine (navelbine) and oral VP-16 (etoposide) in pretreated metastatic breast cancer (MBC) patients.*

Patients and methods: *Twenty-two female patients with therapy-resistant metastatic breast cancer were treated with vinorelbine 25 mg/m^2 i.v. on days 1 and 8 and oral VP-16 50 mg/m^2/day for 14 days. Cycles were repeated every 28 days. Treatment was given until clear evidence of disease progression.*

Results: *Complete remission was observed in 3 (14%) patients, and partial remission or stable disease in 10 (45%) patients. Median duration of response was 4 months (range 2-8). Symptomatic improvement, irrespective of imaging methods results, as evaluated through improved performance status (PS), the lack of requirement for urgent palliative radiotherapy, and a decrease in steroids and analgesics doses was demonstrated in 10 (45%) patients through a special questionnaire completed by all patients. Side effects were manageable. Dose modification due to leucopenic fever were necessary in only 3 patients. Previous radiation therapy did not mitigate the application of full doses of chemotherapy.*

Conclusion: *Vinorelbine/VP-16 combination is active and tolerable in relapsed and heavily pretreated MBC patients.*

Key words: chemotherapy, etoposide, metastatic breast cancer, phase II study, vinorelbine

Introduction

Despite intensive investigative efforts, MBC remains an incurable disease with a dismal outcome. Patients relapsing following anthracycline and/or taxane-based regimens have a brief survival without improved quality of life or marked relief of symptoms. Vinorelbine, a semisynthetic vinca alkaloid introduced as single agent, was found to be active in advanced non-small cell lung cancer, and effective orally or intravenously in first or second line treatment for MBC [1,2]. Activity was also demonstrated in phase II studies combining vinorelbine with pegylated liposomal doxorubicin [3], cisplatin [4,5] and paclitaxel/cisplatin regimens [5]. Etoposide also exhibited synergistic activity with cisplatin in phase II studies [6,7]. To the best of our knowledge, and following a thorough search of the literature, no study combining vinorelbine and VP-16 has been done. To evaluate the antitumor activity and tolerance of vinorelbine and VP-16, we undertook a phase II study in 22 previously treated MBC patients.

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Patients and methods

Patient selection

From 2000 until 2002, 22 female patients refractory to previous chemotherapy for MBC were treated with vinorelbine/VP-16 as part of a phase II study. Eligible patients were those with histologically confirmed measurable or assessable MBC regardless of prior chemotherapy, with a PS 0-2, adequate bone marrow, hepatic and renal function, age <75 and a life expectancy >3 months. Prior to commencement of vinorelbine/VP-16 chemotherapy, a thorough physical examination was performed, along with bone scan and whole body computerized tomographic (CT) scan. Serum tumor markers, such as CEA and CA 15.3, were not included in our patient selection criteria. The protocol was approved by our institutional ethics committee and written informed consent was obtained from all patients.

Treatment plan

Patients received vinorelbine (25 mg/m^2 i.v. rapid infusion, days 1 and 8) and etoposide (50 mg/m^2/day p.o., days 1-14), every 4 weeks. Treatment was repeated for up to 3 cycles in the absence of progression, severe toxicity or patient refusal to continue. Prophylactic granulocyte colony-stimulating factor was used after the first delay due to neutropenia. Appropriate antiemetics were given. No biphosphonate, steroids or palliative radiotherapy was allowed until disease progression.

Criteria for response and toxicity evaluation

Physical examination, chest x-ray, bone scans or whole body CT scans for assessment were repeated according to the pretreatment disease sites every third cycle, at the end of treatment or at disease progression. After progression, patients were treated solely with palliative intent. The Eastern Cooperative Oncology Group (ECOG) criteria were used to define response and PS [8]. PS was evaluated objectively. Symptomatic improvement was defined as decreased or unchanged doses of analgesics and/or no additional radiotherapy or steroids. Toxicity was evaluated according to the National Cancer Institute (NCI) criteria.

Results

Patient characteristics are demonstrated in Table 1. The majority of patients had stage II (IIa or IIb) disease on first presentation and were mainly treated with adriamycin-based chemotherapy. Taxanes alone or combined with adriamycin were commonly administered amongst patients with metastatic disease. In 12 patients, palliative radiation therapy was given to less than 25% of the bone marrow-containing bones prior to commencement of the vinorelbine/VP-16 regimen.

Table 1. Patient clinical and prior therapy characteristics

	n	*%*
No. of patients	22	
Age (years)		
Median	43	
Range	32-65	
Stage at diagnosis		
I	2	9
II	12	55
III	4	18
IV	4	18
Prior adjuvant/neoadjuvant chemotherapy		
HDCT+PSC[1]	1	4
CMF[2]	3	14
CAF[3]	11	50
Taxanes[4]	7	32
Prior adjuvant-neoadjuvant hormonotherapy		
Yes	16	73
No	6	27
Prior treatment for metastatic disease		
Taxanes	10	46
Taxanes/adriamycin	7	32
CAF	1	4
Cisplatin/herceptin	4	18
Prior bone palliative RT		
Yes	15	68
No	7	32
Symptom-free interval, months (range)[5]	8 (1-108)	

[1]high-dose chemotherapy and peripheral stem cell transplantation; [2]cyclophosphamide, methotrexate, 5-fluorouracil; [3]cyclophosphamide, adriamycin, 5-fluorouracil; [4]alone or with adriamycin; [5]interval between end of prior treatment and onset of vinorelbine/VP-16 therapy

Most common sites of disease were the bones, liver and lungs (Table 2). One patient presented solely with an unexplained increase in her CA15-3 level; widespread metastatic disease appeared later.

Median symptom-free interval between the end of first-line treatment and the introduction of the vinorelbine/VP-16 regimen was 8 months (range 1-108).

With a median duration of 4 months (range 2-6), objective response rate was generally poor (Table 2). Three patients entered complete remission following treatment. One patient with lung metastases demonstrated complete regression as seen on CT scan

Table 2. Sites of metastases, response rate, latest status

	n	%
Sites of metastatic disease[1]		
Bone	15	68
Liver	4	18
Lung/pleural effusion	10	46
Lymph nodes	2	9
Local/regional recurrence	2	9
Markers only[2]	1	4
Response to treatment[3]		
Complete remission	3	13
Partial remission	5	23
No change	5	23
Progressive disease[4]	8	41
Symptomatic improvement[5]		
Yes	10	45
No	12	55
Latest status		
No evidence of disease	1	4
Alive with disease	6	27
Dead with disease	14	65
Lost to follow-up	1	4

[1]some patients had more than one metastatic site; [2]shortly after diagnosis, widespread metastatic disease was diagnosed; [3]as assessed through study of markers, bone scans and computerized tomographic scans; [4]no response to treatment; [5]defined as marked improvement in pain and general condition, without increasing analgesics and steroids and no need for more palliative radiotherapy

following 3 cycles of treatment; this patient died of brain metastases. Two other patients with lung metastases and lymph node involvement entered complete remission following 3 and 4 cycles of chemotherapy, respectively, for a mean duration of 5 months (range 4-6). Five patients achieved partial remission and 4 remained with stable disease for a median of 3 months (range 2-5) and 4 months (range 3-6), respectively. However, 10 (45%) patients demonstrated marked symptomatic improvement for a median of 8 months (range 1-108).

Toxicity

Generally, side effects were tolerable and manageable. Only 3 patients were hospitalized due to neutropenic fever and all recovered uneventfully. Mild to moderate stomatitis, nausea, vomiting and diarrhea were noted. Two patients developed mild peripheral neuropathy and moderate-to-severe constipation. One patient suffered from abdominal pain which resolved spontaneously with no signs of paralytic ileus.

Discussion

Phase II studies of vinorelbine have been performed on MBC patients in defined populations with anthracycline-refractory and taxane-resistant disease. Studies conducted on anthracycline-taxane refractory patients or single-agent anthracycline-refractory patients indicate modest overall response rates, ranging from 16-25%, with median response durations ranging from 21-32 weeks [9-11]. On the other hand, summarizing 10 phase II studies of second-line vinorelbine, including 370 patients in a study population not defined by anthracycline/taxane resistance, Seidman found that vinorelbine treatment was associated with complete response rates ranging from 3-10%, overall response rates of 24-57%, and median survival times of 6-19 months [9]. Our 3 patients who entered complete remission following vinorelbine/VP-16 second-line treatment were previously treated with non-anthracycline or taxane-containing chemotherapy. Apart from grade 3-4 neutropenia, the toxicity profile was not severe. However, there is concern over the potential for neurotoxicity with the use of vinca alkaloids after taxanes or the serial use of any antimicrotubular agents. In one report, the use of vinorelbine 30 mg/m^2 every 2-3 weeks in patients with prior paclitaxel treatment resulted in discontinuation of treatment in about 30% of patients because of limiting peripheral neuropathy and severe constipation [12]. In our study, 2 patients demonstrated a mild form of neuropathy and moderate-to-severe constipation, respectively, which did not necessitate cessation of treatment.

Other phase II studies which combined vinorelbine with cisplatin also showed activity in MBC. Mustacci et al. [4] demonstrated a response rate of 52.9% (CR 9.8%), similar in both pretreated and untreated patients. The main toxicity was asymptomatic neutropenia, and 13.4% of patients demonstrated grade 1-2 neurotoxicity. This combination exhibited an improvement of at least one ECOG PS score. Shamseddine et al. [13] proved the efficacy of cisplatin-vinorelbine combination for relapsed and chemotherapy-pretreated MBC. Their study exhibited a general response rate of 61% (CR 26%) with a response duration ranging from 3-9 months. There was no treatment-related mortality. Some authors [4,14,15] have demonstrated good time to progression (8.5 months), a particularly good median overall survival in pretreated patients (16 months), and particular activity in lung and bone metastases. Also, the combination of paclitaxel/cisplatin/vinorelbine proved to be effective in MBC in a phase II study, with acceptable toxicity [5].

Etoposide exhibited synergistic activity with cisplatin in experimental systems [7,10]. The study of Fried et al. [6] demonstrated clinical activity and marked symptomatic relief in 27 patients treated with cisplatin and prolonged oral administration of etoposide in MBC. Overall response rate was 45% (CR 4%) and median duration of response was 7 months. Pain relief was noted in 9/15 (60%) of the symptomatic patients. Myelosuppression was the major toxicity encountered.

Our conclusion is that vinorelbine/VP-16 is active in terms of symptomatic improvement in heavily pretreated MBC patients. Toxicity is mild, even in taxane-refractory patients.

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References

1. Freyer G, Delozier T, Lichinister M et al. Phase II study of oral vinorelbine in first-line advanced breast cancer chemotherapy. J Clin Oncol 2003; 21: 35-40.
2. Ibrahim NK, Rahman Z, Valero V et al. Phase II study of vinorelbine administered by 96-hour infusion in patients with advanced breast cancer. Cancer 1999; 86: 1251-1257.
3. Gebbia V, Mauceri G, Fallica G et al. Pegylated liposomal doxorubicin with vinorelbine in metastatic breast carcinoma: A phase I-II clinical investigation. Oncology 2002; 63: 23-30.
4. Mustacchi G, Muggia M, Milani S, Ceccherini R, Leita ML, Dellach C. A phase II study of cisplatin and vinorelbine in patients with metastatic breast cancer. Ann Oncol 2002; 13: 1730-1736.
5. Lokich JJ, Anderson N, Bern M, Coco F, Dow E. The multifractionated, twice-weekly dose schedule for a three-drug chemotherapy regimen: A phase I-II study of paclitaxel, cisplatin and vinorelbine. Cancer 1999; 85: 499-503.
6. Fried G, Stein ME, Haim N. Clinical activity of cisplatin and prolonged oral administration of etoposide in previously treated, anthracycline-resistant, metastatic breast cancer patients: A phase II study. Med Ped Oncol 2000; 34: 10-13.
7. Cocconi G, Tonato M, Di Costanzo F et al. Platinum and etoposide in chemotherapy for refractory metastatic breast cancer: A phase II trial of the Italian Oncology Group for Clinical Research. Eur J Cancer 1986; 22: 761-764.
8. Oken MM, Creech RH, Tormey DC et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982; 5: 649-655.
9. Seidman AD. Monotherapy options in the management of metastatic breast cancer. Semin Oncol 2003; 30 (Suppl 3): 6-10.
10. Livingston RB, Ellis GK, Gralow JR et al. Dose-intensive vinorelbine with concurrent granulocyte colony-stimulating factor support in paclitaxel-refratory metastatic breast cancer. J Clin Oncol 1997; 15: 1395-1400.
11. Degardin M, Bonneterre J, Hecquet B et al. Vinorelbine as a salvage treatment for advanced breast cancer. Ann Oncol 1994; 5: 424-426.
12. Fazeny B, Zifko U, Meryn S, Huber H, Grisold W, Dittrich C. Vinorelbine-induced neurotoxicity in patients with advanced breast cancer pretreated with paclitaxel: A phase II study. Cancer Chemother Pharmacol 1996; 39: 150-156.
13. Shamseddine AI, Taher A, Dabaja B, Dandashi A, Salem Z, El Saghir NS. Combination cisplatin-vinorelbine for relapsed and chemotherapy-pretreated metastatic breast cancer. Am J Clin Oncol 1999; 22: 298-302.
14. Gurel N, Akali Z, Yanna D. Cisplatin plus vinorelbine as a salvage regimen in refractory breast cancer. Tumori 2000; 86: 283-285.
15. Ray-Coquard I, Biron P, Bachelot T et al. Vinorelbine and cisplatin [CIVIC regimen] for the treatment of metastatic breast carcinoma after failure of anthracycline- and/or paclitaxel-containing regimens. Cancer 1998; 8: 134-140.