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Clinical Activity of Cisplatin and Prolonged Oral Administration of Etoposide in Previously Treated, Anthracycline-Resistant, Metastatic Breast Cancer Patients: A Phase II Study

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Background. This phase II study evaluates the antitumor activity and tolerance of cisplatin and prolonged oral administration of etoposide in metastatic breast cancer previously exposed to anthracyclines. ***Procedure.*** Twenty-seven patients with metastatic breast cancer who developed tumor progression following anthracyclines were entered in the study. The patients were treated with combination chemotherapy of cisplatin 50 mg/m^2 IV day 1 and oral etoposide 50 mg/m^2 days 1–17. Cycles were repeated every 29 days. ***Results.*** Twenty-six patients were evaluated for toxicity and response. Complete remission was observed in 1 of 26 (4%) patients and partial remission in 12 of 26 (46%). Median duration of response was seven months. Pain relief was noted in 9 of 15 (60%) of the symptomatic patients. Myelosuppression was the major toxicity encountered and four (15%) patients required hospitalization for granulocytopenic fever. Nonhematologic toxicity was mild. ***Conclusions.*** The combination of cisplatin with prolonged oral etoposide is active and tolerable in the management of patients with relapsed metastatic breast cancer previously treated with an anthracycline-based regimen. Med. Pediatr. Oncol. 34:10–13, 2000.

Key words: cisplatinum; etoposide; metastatic breast cancer; phase II

INTRODUCTION

Despite intensive investigative efforts, metastatic breast cancer (MBC) remains an incurable disease with a dismal outcome. Patients relapsing following anthracycline-based regimens have a brief survival, measured in months. Etoposide, a topoisomerase-II inhibitor, introduced as a single agent, oral intake and prolonged daily dose, was found to be active in patients with germ cell tumors, small cell lung cancer, ovarian carcinoma, lymphoma, and advanced breast cancer previously exposed to chemotherapy [1–7]. Etoposide exhibited synergistic acitivity with cisplatin, in experimental systems [8,9], first-line treatment in a prospective randomized trial [10] and in a phase II trial in chemotherapy refractory MBC [8].

The randomized trial [10] compared the cisplatin/etoposide (PE) combination to the standard cyclophosphamide/methotrexate/5-fluorouracil (CMF) regimen and demonstrated that the PE combination was effective as front-line chemotherapy. A trend of superiority over CMF was observed, albeit of borderline significance. Because of the high level of activity, other trials of the PE regimen in refractory MBC patients were pursued [6–8,11–13]. The trials showed an overall response rate ranging from 0% to 33%; the total response rate of all these studies was 18% (25/145), and VP-16 was mostly scheduled to be given in 3 days. To evaluate the antitumor activity and tolerance of cisplatin and prolonged oral adminisration of etoposide in MBC, we undertook a phase II study in 27 patients previously exposed to anthracycline-based regimens.

MATERIALS AND METHODS

Patient Eligibility

Patients with measurable or evaluable MBC who developed tumor progression following anthracycline (adriamycin mitoxantrone)-based chemotherapy were entered into the study. A interval of less than 1year from the last treatment was required if anthracyclines were given in an adjuvant setting. Other eligibility criteria included a World Health Organization (WHO) performance status of 0–2, WBC $\geq$4,000/mm^3, platelets $\geq$100,000/mm^3, serum bilirubin $\leq$1.5 mg/dl, serum creatinine $\leq$1.3 mg/dl, and at least 1 month from prior chemotherapy and 1 day off from prior hormonotherapy. Our institutional Ethics Committee approved the protocol, and informed consent was obtained from all patients.

Pretreatment Evaluation

Baseline investigations included a complete history and physical examination, complete blood cell count,

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liver and kidney function tests, and electrolyte levels. Other baseline procedures included chest X-ray in 10 patients (37%), computerized tomography scan in 18 (67%), liver echography in 3 (11%), bone scintigraphy in 11 (41%), and skeletal X-ray in 4 (15%).

Treatment Plan

Cisplatin (P) 50 mg/m^2 was given intravenously on day 1 for 30 min, with adequate hydration and antiemetic therapy. Etoposide (E) was administered orally at a dose of 50 mg/m^2/day for 17 consecutive days. The projected dose per cycle was calculated, and 50 mg and 100 mg etoposide capsules were distributed over the 17 day period. Patients were instructed to take etoposide about 30 min before breakfast. Complete blood counts were performed weekly, and etoposide was discontinued if the WBC was <2,000/mm^3 and/or the platelet count was <75,000/mm^3. Cycles were repeated on day 29 if the WBC was >4,000 mm^3 and the platelet count was >100,000/mm^3. The doses of P and E were reduced by 25% in subsequent cycles if the nadir WBC was <1,000/mm^3 and or the nadir platelet count was <50,000/mm^3 or if discontinuation of etoposide before 17 days was required. Hematopoietic colony-stimulating factors were not used.

Laboratory Monitoring and Evaluation of Response

Clinical evaluation and blood chemistry were evaluated before each cycle. Detailed evaluation for response to therapy was performed every two cycles, and responders received a maximum of six cycles of EP. Response to therapy was evaluated according to World Health Organization criteria [14].

Data Analysis

Time to treatment response, time to tumor progression, survival, and duration of response were calculated from the onset of therapy. Calculation of survival was performed according to the Kaplan-Meier method [15]. Evaluation for toxicity was carried out before each cycle with the Common Toxicity Criteria scale [16].

RESULTS

Twenty-seven patients were entered into the study. Patients characteristics are shown in Table I. Fifty-six percent of the patients had a poor performance status (grade 2), and 70% had more than one site of disease. Prior adjuvant or neoadjuvant chemotherapy was given to 85% of the patients, and nine (33%) had received more than one prior chemotherapy regimen for metastatic disease. Adriamycin- and/or mitoxantrone-containing regimens were given for metastatic disease in 15 patients (56%). The number of EP cycles ranged from one to six (median of four cycles), and the total number of cycles given was 98. Treatment was stopped because of tumor progression in 20 patients, in 6 patients after stabilization of response, and in 1 patient because of drug toxicity 16 days after onset of chemotherapy; this patient was not evaluated for response, time to tumor progression, or survival.

TABLE I. Patient Characteristics

Characteristics	No.	Percentage
1. Patients	27	
2. Age (years): median (range)	49 (29–73)	
3. Menopausal status		
Premenopausal	15	56
Postmenopausal	12	44
4. Prior neoadjuvant chemotherapy, CAF	7	26
Prior adjuvant chemotherapy		
CMF	9	33.5
CAF	7	26
Prior anthracyclines for metastatic disease	13	48
5. Prior hormonal therapy	13	48
6. Prior radiotherapy	10	37
7. Site of disease		
Soft tissue	8	30
Bone	11	41
Lung	12	45
Liver	7	26
Lymph nodes	8	30
Local recurrence	10	37
Brain	2	8
8. No. of sites of disease		
1	8	30
2	12	44
3	4	15
>3	3	11

Complete response (CR) was observed in 1 of 26 evaluable patients, and partial response (PR) in 12 of 26 patients (46%), for a total response rate of 50% (95% confidence interval). Eleven patients (42%) had stable disease. During chemotherapy, symptomatic relief was observed in 9 of the 15 symptomatic patients (60%), using the Pain Relief score [6].

The median time to tumor progression was 3 months for the entire group and 7 months for responders. CR continued for 7 months in 1 patient with lung metastasis, and PR continued in two patients for 11 and 10 months. Response to EP according to various parameters is shown in Table II. Objective response was observed at various sites of disease.

Patients with a longer interval from last chemotherapy (>6 months) had a higher response rate than those with a shorter interval from last chemotherapy. The median survival time was 10 months for the entire group, 17 months for responders, 10 months for those with stable disease, and 4 months for nonresponders ($P = 0.0005$, responders vs. nonresponders).

Myelosuppression was the major toxicity encountered (Table III). Hospitalization for granulocytopenic fever was required by four patients (15%) but in only 4 of 98

TABLE II. Estimation of Response

	No. of evaluable patients	No. of responders/ percentage
Site of disease		
Lung	12	5/42
Bone	11	4/36
Local recurrence	10	6/60
Peripheral lymph nodes	8	5/63
Skin	8	4/50
Liver	7	2/29
Brain	2	1/50
Other	4	2/50
Objective response to last chemotherapy (PR or CR)[a]		
Yes	19	10/53
No	6	2/33
Interval from last chemotherapy		
≤6 months	16	6/38
>6 months	11	7/64
Response to adriamycin/mitoxantrone given as last chemotherapy		
Yes	10	6/60
No	2	0/0

[a]Oral etoposide plus cisplatin was the first regime for metastatic disease in 2 patients.

TABLE III. Hematologic Toxicity

	No. of patients/ percentage
Median nadir counts	
WBC/mm^3	2,500
Platelets/mm^3	138,500
Hemoglobin (g/dl)	9
Grade 3 and 4 toxicity	
WBC	11/41
Platelets	6/22
Hospitalization for granulocytopenic fever[a]	
No. of patients	4/15
No. of courses	4/4
Platelet transfusions	
No. of patients	2/7
No. of courses	3/11
Red blooc cell transfusions	
No. of patients	4/15
No. of courses	4/4

[a]There was one treatment-related death from neutropenic sepsis.

cycles (4%). Platelet transfusions were required in three patients (11%) and red blood cell transfusions in four patients (15%). Drug doses were reduced in 9 of 24 patients (37%) who received more than one cycle, owing to myelosuppression. One patient died 16 days after the beginning of the first course with grade 4 neutropenia and thrombocytopenia.

Nonhematologic toxicity was usually mild. Four patients developed grade II stomatitis and 1 patient had mild peripheral neurotoxicity. These and other nonhematological side effects, such as nausea, vomiting, and/or alopecia, did not require dose modification or treatment delay.

TABLE IV. Etoposide as Second-Line Single-Agent Therapy in Metastatic Breast Cancer

Treatment schedule (50 mg/m^2/day)	No. of patients	Response (CR + PR) (n/%)	Reference
Days 1–21 q 4 weeks	4	1/25	18
Days 1–21 q 4 weeks	18	4/22	19
Days 1–21 q 4 weeks	43	15/35	20
Days 1–21 q 4 weeks	25	5/25	21
Days 1–21 q 4 weeks	21	2/10	22

DISCUSSION

Metastatic breast cancer still remains a challenge for the oncologist in routine practice. Ten percent of newly diagnosed breast cancer patients are seen with stage IV disease, and 25–30% of stage I and 50–75% of stage II patients will develop metastasis within 10 years following the original diagnosis. The most common therapy used for treatment of metastatic breast cancer is CMF, with objective clinical response rates ranging between 50% and 70%. Complete response rate is about 15%, and time to tumor progression ranges from 5 to 13 months [10]. This relatively high response rate to chemotherapy is not associated with a dramatic improvement in overall survival. On the other hand, anthracycline-containing regimens are believed to result in a 10–20% increased response rate, with a modest increase in median survival from 14 to 18 months but a decrease in quality of life [5,8].

Taken together, the data from a great deal of literature showed that chronic oral etoposide treatment resulted in a longer response rate than brief schedules of intravenous etoposide or even high-dose oral etoposide, and toxicity was generally manageable. Experimental data indicated that cisplatin and etoposide have additive and synergistic effects [17]. Because of a lack of survival advantage over conventional CMF and increased toxicity [10], there was no inclination to recommend it as first-line treatment. However, its high level of activity was used in advanced breast cancer refractory to adriamycin-based combination chemotherapy. Response rates in the range of 17–37% have been reported, but no complete remission has been achieved [5–8,11–13]. Table IV summarizes the treatment results of five studies with prolonged oral administration of etoposide [18–22]. Because the cytotoxic effect of etoposide is related more to the duration of tumor cell exposure to the drug than to the area under the curve, prolonged exposure might result in an augmented antitumor effect [2].

Considering the extensive pretreatment of patients, the results and the manageable toxicity seem to indicate the

activity of these regimens in treating chemotherapy refractory advanced breast cancer. The duration of oral etoposide administration deserves further evaluation.

Novel agents, such as taxanes, have proved to be effective in advanced breast cancer. In anthracylcine-resistant patients, paclitaxel (Taxol), introduced as a single agent, achieved an objective response rate of 6–48%, whereas docetaxel (Taxotere) achieved an overall response rate of 41%, and a 37% response rate was observed in anthracycline-refractory patients with febrile neutropenia as the major dose-limiting toxicity [23,24]. Vinorelbine, a semisynthetic vinca alkaloid, demonstrated response rates ranging from 16% to 36% in pretreated patients [23,25]. The water-soluble deoxycytidine analog gemcitabine demonstrated an objective response rate of 25% [26]. Generally, treatment results of second-line chemotherapy are disappointing and of short duration, and newer strategies and chemotherapy regimens with antitumor activity for patients relapsed after anthracycline failure are required. For breast cancer patients with disease refractory to hormonal therapy who still have a good performance status and remain candidates for second or further chemotherapy lines, chronic oral E in combination with P is an effective and tolerable palliative treatment with a 50% objective response. The results obtained in our poor-risk group of patients warrant further investigation of these schedules and/or the combination of oral E with new active and well-tolerated drugs, such as navelbine or gemcitabine.

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REFERENCES

1. Johnson DH, Ruckdeschel JC, Kellen JH, et al. A randomized trial to compare intravenous and oral etoposide in combination with cisplatin for the treatment of small cell lung cancer. Cancer 1991; 67:245–249.
2. Miller JC, Einhorn LH. Phase II study of daily oral etoposide in refractory germ cell tumors. Semin Oncol 1990;17(Suppl 2):36–39.
3. Marzla M, Zucchetti M, Colombo N, et al. Low-dose oral etoposide in epithelial cancer of the ovary. Ann Oncol 1993;4:517–519.
4. Remick SC, McSharry JJ, Wolf BC, et al. Novel oral combination chemotherapy in the treatment of intermediate-grade and high-grade AIDS-related non-Hodgkin's lymphoma. J Clin Oncol 1993;11:1691–1702.
5. Icli F, Gunel N, Dincol D, et al. Cisplatin plus VP-16 combination chemotherapy in advanced refractory breast cancer. J Surg Oncol 1992;50:251–253.
6. Cox FB, Burton BC, Olsen GA, et al. Response of refractory breast cancer to a combination of cisplatin and etoposide. Proc Am Soc Clin Oncol 1986;5:64.
7. Krook JE, Loprinzi CL, Schaid DJ, et al. Evaluation of the continuous infusion of etoposide plus cisplatin in metastatic breast cancer. Cancer 1990;65:418–421.
8. Cocconi G, Tomato M, DiCostanzo 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.
9. Mabel JA, Little AD: Therapeutic synergism in murine tumors for combination of cisdiammine-dichloroplatinum with VP16-213 or BCNU. Proc AACR-ASCO 1981;22:357.
10. Cocconi G, Bisagni G, Bacchi M, et al. Cisplatin and etoposide as first-line chemotherapy for metastatic breast cancer: a prospective randomized trial of the Italian Oncology Group for Clinical Research. J Clin Oncol 1991;9:664–669.
11. Giaccone G, Donadio M, Ferrati P, et al. Cisplatin and VP-16 in the treatment of advanced breast carcinoma. Stockholm: ECCO3; 1985. p 170.
12. Athanassiades P, Bacoyiannes H, Kontoyiannes D: Etoposide (VP-16-213) and cis-dichlorodiammine-platinum (DDP) in advanced breast carcinoma resistant to previous chemotherapy. Chemioterapia 1986;5:125–127.
13. Tinsley R, Fuks J, Korzan A, et al. Cisplatin and etoposide for advanced breast cancer: a Phase II trial. Proc Annu Soc Clin Oncol 1986;5:74.
14. Miller AR, Hoogstraten B, Staquet M, et al. Reporting results of cancer treatment. Cancer 1981;47:207–214.
15. Kaplan EL, Meier P: Non-parametric estimation from incomplete observation. J Am Stat Assoc 1958;53:457–481.
16. Franklin HR, Simonetti GP, Dubbelman AC, et al. Toxicity grading systems: a comparison between the WHO scoring system and the Common Toxicity Criteria when used for nausea and vomiting. Ann Oncol 1994;5:113–117.
17. Durand RF, Goldie JH. Interaction of etoposide and cisplatin in an in vitro tumor model. Cancer Treat Rep 1987;71:673–679.
18. Hainsworth JD, Johnson DH, Frazier SR, et al. Chronic daily administration of oral etoposide: a Phase I trial. J Clin Oncol 1989;7:396–401.
19. Palombo H, Estape J, Vinolas N, et al. Chronic oral etoposide in advanced breast cancer. Cancer Chemother Pharmacol 1994;33: 527–529.
20. Martin M, Lluch A, Casado A, et al. Clinical activity of chronic oral etoposde in previously treated metastatic breast cancer. J Clin Oncol 1994;12:986–991.
21. Atienza DM, Vogel CL, Trock B, et al. Phase II study of oral VP-16-213 (etoposide) in patients with advanced breast cancer (abstract). Breast Cancer Res Treat 1993;27:146.
22. Bontenbal M, Planting AS, Verweij R, et al. Second-line chemotherapy with long-term low-dose etoposide in patients with advanced breast cancer. Breast Cancer Res Treat 1995;34:135–189.
23. Valero V: Future direction of neoadjuvant therapy for breast cancer. Semin Oncol 1990;25(Suppl 3):36–41.
24. Valero V. Docetaxel as single-agent threapy in metastatic breast cancer: clinical efficacy. Semin Oncol 1997;24(Suppl 13):11–18.
25. Johnson SA, Harper P, Hortobagyi GN, et al. Vinorelbine: an overview. Cancer Treat Rev 1996;22:127–142.
26. Carmichael J, Possinger K, Phillip P, et al. Advanced breast cancer: a Phase II trial with gemcitabine. J Clin Oncol 1995;3:2731–2736.