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Vincristine with high-dose etoposide in advanced breast cancer: a phase II trial of the Piedmont Oncology Association

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Abstract Vincristine (VCR) and etoposide (VP-16) have been shown to be synergistic in a murine model, and this combination was studied in a phase II trial. Eligibility required measurable disease, a performance status of 0–2, a life expectancy of ≥2 months, an interval of at least 3 weeks since the receipt of previous radiation therapy or chemotherapy and recovery from related toxicity, no prior treatment with VCR or VP-16, and no more than two prior chemotherapy regimens (only one for treatment of metastatic disease). Treatment consisted of 0.5 mg i.v. (bolus) VCR followed by 200 mg/m^2 VP-16 given over 2 h. Both drugs were given daily for 3 consecutive days every 3 weeks (total dose: VCR, 1.5 mg; VP-16, 600 mg/m^2). A total of 18 patients with metastatic breast cancer were accured; 14 had adjuvant chemotherapy and 8 had chemotherapy for advanced disease. As judged by International Union Against Cancer (UICC) criteria, one complete response (CR) and three partial responses (PR) were obtained, for a CR+PR rate of 22% (95% confidence interval, 6%–48%). All responders had soft-tissue involvement only. Six patients had stable disease and 8 showed progression. The median time to treatment failure was 3.5 months, and the median survival from study entry was 8.3 months. The major toxicity was myelosuppression, with 9 patients (50%) experiencing a total WBC of $<1{,}000/mm^3$. Grade 2–3 neurologic toxicity was noted in 6 patients (33%) and grade 3 nausea and vomiting was noted in 5 (28%). The combination of VCR and VP-16 is active in advanced breast cancer but is not convincingly superior to either of these agents used alone.

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Introduction

Metastatic breast cancer continues to be a major treatment dilemma for the medical oncologist. Although standard chemotherapy regimens can result in response rates of 50%–80%, patients are rarely, if ever, cured and the reduction in tumor burden is of a partial and brief nature. Clearly, the inability to achieve a complete eradication of the residual tumor demands that new therapies be developed.

Vincristine as a single agent has modest activity in breast cancer, with a 20% cumulative response rate being reported in 164 patients [11]. Most single-agent vincristine trials were conducted in the 1960s and used weekly doses of about 2 mg, with the highest response rates being seen in patients treated with weekly doses of 35–75 μg/kg. Only modest activity has been observed for vincristine given as a 5-day infusion [6, 7].

Etoposide (VP-16) has been reported to have only minimal activity in advanced breast cancer. Conventional doses of 45–75 mg/m^2 given three to five times per week were associated with a complete and partial response rate of 7% in more than 300 patients with metastatic breast cancer who had failed prior chemotherapy for metastatic disease [13, 14]. In one of the largest trials, an objective response rate of only 7% was noted in 119 patients treated with doses ranging from 45 to 75 mg/m^2 given for 5 consecutive days every 3 weeks [1]. Only one phase II trial evaluated etoposide in patients with breast cancer who had not received prior chemotherapy for metastatic disease; 3 of 20 (15%) patients responded to a dose of 230 mg/m^2 given daily for 3 consecutive days [15]. The effectiveness of high-dose etoposide in previously treated patients with metastatic breast cancer is unclear. Fraschini and colleagues [4] treated 15 patients with doses of 300–450 mg/m^2 daily for 3 days every 3 weeks and noted only 1 response (7%).

Bezwoda and co-workers [2] gave etoposide at doses of 1,500–2,500 mg/m^2 to 23 patients and noted 6 responses (26%).

Synergism between vincristine and etoposide has been demonstrated in a murine leukemia model [8, 9], with cures (≥60-day survivors) being noted in 33% of 135 treated animals. In these experiments, vincristine and etoposide used as single agents displayed cure rates of 2% and 7%, respectively. The sequence of drug administration did not alter the efficacy of the combination [9]. Although single-agent trials of etoposide in metastatic breast cancer have been associated with only a modest response, there is good rationale for combining vincristine and etoposide for clinical trial; vincristine and etoposide have different mechanisms of action and different toxicity profiles, and both agents are associated with meaningful response rates in a wide variety of human cancers.

A phase I trial showed that conventional-dose vincristine (1.5 mg given by bolus injection every 3 weeks) in combination with progressively increasing doses of etoposide given by 2-h infusion was well tolerated, with the dose-limiting toxicity consisting of myelosuppression at doses of etoposide exceeding 500 mg/m^2 [10]. Etoposide doses of 500 mg/m^2 were well tolerated, with rapidly reversible grade 4 myelosuppression being noted in only 3 of 18 treated patients. It was also noted that vincristine-induced neuropathy was not intensified by the addition of etoposide. Six of the patients with heavily pretreated breast cancer in this phase I trial showed no response, but one remained stable over a 10-month period while receiving 15 courses of therapy. A 3-consecutive-day schedule of etoposide was selected for this trial because this schedule was commonly used in other clinical trials. The total dose was based on our phase I data. The current trial was designed to assess the efficacy and toxicity of vincristine and high-dose etoposide in patients with metastatic breast cancer.

Patients and methods

Eligibility for patient entry required histologically documented breast cancer with disease progression, measurable or evaluable disease, a performance status of 0–2, a life expectancy of ≥2 months, an interval of 2 weeks from prior surgery and recovering from acute effects, an interval of >3 weeks since the receipt of previous radiation therapy or chemotherapy and recovery from related toxicity, no prior chemotherapy with vincristine or etoposide, and no more than two prior chemotherapy regimens (only one for treatment of metastatic disease). Laboratory data for patient entry required a granulocyte count of >1,800/μl, a platelet count of >100,000/μl, a hemoglobin value of >10 g/dl, a bilirubin level of ≤1.5 times normal, SGOT/SGPT values of ≤2 times normal, an albumin value of >3.0 g/dl, a creatinine level of <1.8 mg%, a blood urea nitrogen (BUN) value of <1.5 times normal, and written informed consent meeting all federal, state, and institutional guidelines. Patients were ineligible if they had serious medical or psychiatric illness that would prevent their giving informed consent or limit their survival, any primary neurologic disease (e.g., multiple sclerosis or amyotrophic lateral sclerosis), or any secondary neurological defect [e.g., cerebrovascular accident (CVA) with residual defects or demonstrable peripheral neuropathy secondary to cancer, diabetes, or prior chemotherapy].

Table 1 Patients' characteristics, response, and toxicity

	Number (%)
Number of patients evaluable	18 (100)
Median age (years)	50
Age range (years)	34–84
Performance status (0–1)	14 (78)
Disease-free interval ≤2 years	11 (61)
Estrogen receptor status:	
Positive	5 (28)
Negative	10 (56)
Unknown	3 (17)
Prior treatment:	
Radiation	13 (72)
Endocrine	11 (61)
Chemotherapy – adjuvant	14 (78)
Chemotherapy – metastases	8 (44)
Sites of metastasis:	
Soft tissue (chest wall, nodes)	10 (56)
Lung + pleura	8 (44)
Liver	6 (33)
Bone	5 (28)
Number of sites:	
1	9 (50)
2	6 (33)
3+	3 (17)
Response:	
Complete	1 (6)
Partial	3 (17)
Stable	6 (33)
Progression	8 (44)
Toxicity – maximum per patient	
WBC (per mm^3):	
>4,000	1 (6)
2,000–4,000	5 (28)
1,000–2,000	3 (17)
<1,000	9 (50)
Fever and neutropenia	2 (11)
Platelets (per mm^3):	
>100,000	10 (56)
50,000–100,000	2 (11)
25,000– 50,000	4 (22)
<25,000	2 (11)
Hemoglobin (g/dl):	
>11	5 (28)
9.5–10.9	2 (11)
8 – 9.4	6 (33)
6.5– 7.9	5 (28)
Nausea/vomiting (grade):	
0–1	12 (67)
2	1 (6)
3	5 (28)
4	0 (0)
Constipation (grade):	
0	12 (67)
1	4 (22)
2	1 (6)
3	1 (6)
Peripheral neuropathy (grade)	
0	7 (39)
1	5 (28)
2	5 (28)
3	1 (6)
4	0 (0)

At protocol entry all patients received a complete history and physical examination including weight and height measurement; performance status assessment; determinations of hemoglobin, hematocrit, white count with differential, and platelets; a chemistry profile; and a chest X-ray. Patients with symptoms or signs of bone, liver, or CNS involvement were investigated with appropriate radiographic procedures. Hematologic parameters were checked weekly, and neurologic examination, weight measurement, and performance status assessment were repeated before each course. Soft-tissue lesions were evaluated every 3 weeks. The chest X-ray was repeated twice at 3-week intervals and then every 6 weeks if it was abnormal due to metastatic disease. Metastatic lesions on bone and liver scans were reassessed at 6 weeks and then every 3 months. Treatment consisted of 0.5 mg i. v. (total dose by bolus) vincristine followed by 200 mg/m^2 etoposide given over 2 h. Both drugs were given daily for 3 consecutive days every 3 weeks (total dose: vincristine, 1.5 mg/course; etoposide, 600 mg/m^2 per course).

For patients who developed grade 2 neurotoxicity as judged by WHO criteria [12], the subsequent dose of vincristine was decreased by 50%. If the toxicity persisted, the previous dose was decreased by 50% and then continued in this manner until the neurotoxicity reached grade 1 or less. Subsequent dose escalation in 10%–25% increments was undertaken at the physician's discretion. Toxicity that included loss of reflexes, mild paresthesias, moderate constipation, myalgias, or jaw pain were not used to modify the vincristine dose. For patients with grade 3 or 4 neurologic toxicity or grade 4 nonhematologic toxicity (except for nausea and vomiting), treatment was discontinued and the patient was removed from the protocol. No dose modification was made on the basis of nadir blood counts if there was recovery (granulocytes, $>1{,}000/mm^3$; platelets, $>100{,}000/mm^3$) by day 21. If hematologic recovery was not complete by day 21, treatment was delayed for 1 week. If granulocyte and platelet counts recovered by day 28, the previous dose of etoposide was decreased by 25%. Further courses were given at this dose unless further toxicity necessitated dose reduction. If myelosuppression did not resolve by day 28, counts were checked weekly until recovery and treatment was continued with a 50% reduction of the etoposide dose; the etoposide dose was escalated 10%–25% for subsequent courses. For $\geq$ grade 2 elevation of bilirubin, SGOT, or SGPT values or other nonhematologic toxicity, the vincristine and etoposide doses were reduced by 25%, and for $\geq$ grade 2 nonneurologic, nonhematologic toxicity (except for nausea/vomiting and alopecia), the etoposide dose was reduced by 25%.

Results

The pretreatment characteristics of the 18 patients entered on trial are presented in Table 1. In all, 14 (78%) of the patients had received adjuvant chemotherapy and 8 (44%) had received chemotherapy for metastatic disease. All patients had received at least 1 prior chemotherapy regimen and 11 (61%) had received prior hormonal therapy.

The response to treatment is presented in Table 1. Of 18 patients, 1 achieved a complete response and 3 showed a partial response, for a response rate of 22% (95% confidence interval, 6%–48%). The complete responder was a 84-year-old woman who had received adjuvant chemotherapy with cyclophosphamide, methotrexate and fluorouracil (CMF) prior to a chest-wall and axillary recurrence. After further local recurrence and failure of irradiation and further chemotherapy, the patient received six cycles of vincristine and etoposide with complete resolution of chest-wall and axillary disease. Therapy was stopped due to neurotoxicity and the lesions recurred 2 months later. All of the 3 partial responders had received adjuvant chemotherapy but none had undergone chemotherapy for metastatic disease. All 3 of the partial responders had soft-tissue disease only. Of these patients, 2 had tumor progression after receiving 5 and 9 cycles of therapy, respectively; the 3rd patient declined further treatment after completing 6 cycles and died 6 weeks later of progressive disease.

Six patients (33%) on study had stable disease and 8 (44%) progressed while on therapy. The median time to treatment failure (from the date of first treatment until the date taken off study for any reason) was 3.5 months (range, 0.8–8.8 months). All patients entered on trial ultimately progressed; the median survival from study entry was 8.3 months.

The toxicity data are detailed in Table 1. The major toxicity was myelosuppression, with 9 patients (50%) experiencing a total WBC nadir of $1{,}000/mm^3$. In all, 2 patients required hospitalization for fever and neutropenia and both recovered. Another patient developed angioedema after receiving her first dose of etoposide and was removed from the study. Altogether, 5 patients (28%) had hemoglobin levels of <8 g/dl and 2 patients (11%) experienced platelet counts of $<25{,}000/mm^3$. Grade 3 nausea and vomiting were noted in 5 patients (28%) and grade 2–3 peripheral neurotoxicity was noted in 6 patients (33%). One patient was hospitalized for severe nausea, vomiting, and dehydration as well as *Escherichia coli* sepsis and subsequently recovered.

Discussion

Previous studies with single-agent vincristine have yielded response rates of 20%; etoposide therapy in patients who have received prior therapy for metastatic breast cancer has been associated with response rates of 7%. The complete and partial response rate of 22% obtained in the current trial suggests that the combination of vincristine and etoposide is not likely to be substantially superior to single-agent therapy with either of these agents, but the wide 95% confidence interval of 6%–48% for complete and partial response makes this uncertain. We elected to stop accrual after 18 patients because we felt that the response rate was not substantial enough to justify the major myelosuppression associated with this treatment. All responders in our trial had soft-tissue metastases and only 1 of 8 who had received prior chemotherapy for metastatic disease responded.

The myelosuppression associated with our regimen was substantial; 50% of our patients developed nadir WBC counts of $<1{,}000/mm^3$ and 2 patients required hospitalization for fever and neutropenia. The 33% incidence of peripheral neurotoxicity was similar to that seen with vincristine alone [1]. It appears that etoposide did not compound the expected neurotoxicity seen with vincristine alone. High-dose etoposide is currently being used in high-dose combination chemotherapy/autologous bone-marrow rescue regimens for advanced breast cancer, although its therapeutic role in these intensive treatment regimens is unclear [3]. Recent data suggest that prolonged oral

administration of low-dose etoposide for 2–3 weeks may be associated with a higher therapeutic index and that this schedule should be tested in patients with metastatic breast cancer [5]. Standard i.v. doses of etoposide given on a 3-day schedule have no current role in the management of patients with advanced breast cancer.

Note added in proof: Recently Martin et al. reported a 35% response rate (15 or 43 patients) to oral etoposide (50 mg/m^2 day for 21 days every 4 weeks) in women with metastatic breast cancer who had prior chemotherapy [Martin M, Lluch A, Casada A, et al. (1994) J Clin Oncol 12: 986]

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