Phase II Trial of Tamoxifen, Etoposide, Mitoxantrone, and Cisplatin in Patients with Metastatic Breast Carcinoma

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BACKGROUND. Based on previous data demonstrating a potentially synergistic interaction between tamoxifen and cisplatin in metastatic melanoma therapy, a Phase II study was performed to assess the activity of tamoxifen, etoposide, mitoxantrone, and cisplatin (TEMP) in patients with metastatic breast carcinoma.

METHODS. Forty-six patients with metastatic breast carcinoma were treated with tamoxifen, 10 mg orally, twice a day for 28 days; etoposide, 100 mg/m^2, on Days 1–3; mitoxantrone, 10 mg/m^2, on Day 1; and cisplatin, 30 mg/m^2, on Days 1 and 2. Forty-four patients (7 with bone-only disease) were evaluable for response and toxicity after at least 1 cycle of therapy. All patients had previously received doxorubicin-containing regimens in either the adjuvant or metastatic setting.

RESULTS. The overall objective response rate for the 37 patients with visceral and/or soft tissue disease was 41% (95% confidence interval, 25–58%). The objective response rate among women previously treated with doxorubicin in the adjuvant setting was 58% (14 of 24). Only 1 of 13 patients with metastatic carcinoma who had failed doxorubicin responded. Five of seven patients with bone-only disease had subjective improvement of bone pain without worsening of bone scans. Approximately 59% of patients had Grade 3 or 4 neutropenia at some time in their therapy and 1 patient died of neutropenic sepsis. Logistic regression analysis (n = 37) revealed that response was not related to estrogen receptor (ER) status or to the presence of visceral metastases.

CONCLUSIONS. TEMP appears to be an active regimen for patients with either ER positive (tamoxifen-resistant) or ER negative metastatic breast carcinoma that progresses after adjuvant doxorubicin therapy. Moreover, among patients who developed metastatic disease either during or <12 months after adjuvant doxorubicin therapy, TEMP had a higher response rate than would have been predicted from previous studies. Although the mechanism remains to be elucidated, these results suggest a potentially synergistic role for tamoxifen in etoposide/cisplatin-based chemotherapy of breast carcinoma. ***Cancer* 1996; 78:1906–11.**

KEYWORDS: breast carcinoma, treatment, cisplatin, tamoxifen, etoposide, mitoxantrone.

Despite the effectiveness of several chemotherapeutic agents in untreated patients with breast carcinoma, previously treated metastatic breast carcinoma remains a significant therapeutic challenge. The current study was designed to test the effectiveness of combining tamoxifen with a cisplatin-based regimen in patients with metastatic breast carcinoma. Although earlier attempts to combine chemotherapeutic and hormonal agents for the treatment of breast carcinoma

did not show a clear benefit with combined therapy,[1] these studies were not designed to exploit the potentially synergistic effect of tamoxifen with cisplatin. Although the efficacy of tamoxifen in breast carcinoma is generally thought to be mediated through its interaction with the estrogen receptor (ER), tamoxifen has several additional biochemical mechanisms, including inhibition of calmodulin and protein kinase C activity[2,3] and, at high doses, a multidrug resistance modulating effect.[4-6] Moreover, clinical studies from this institution[7,8] and others[9] have shown an important and potentially synergistic role for tamoxifen in cisplatin-based chemotherapy for metastatic melanoma; furthermore, laboratory data using melanoma cell lines suggest that tamoxifen potentiates cisplatin cytotoxicity independent of the tumor cell's level of ER expression.[10,11]

Cisplatin (CDDP)/etoposide combinations are known to have significant activity in untreated patients with breast carcinoma,[12,13] although the response rate is generally <20% in the patients who have received 1 or more previous chemotherapies for advanced disease.[14-16] In view of favorable results with the combination of a CDDP-based multiagent chemotherapy program and tamoxifen in patients with metastatic melanoma, a Phase II study of a CDDP/etoposide/mitoxantrone combination with tamoxifen (TEMP) in patients with advanced breast carcinoma was performed. Because doxorubicin-based therapy is generally considered among the most effective breast carcinoma treatment regimens, it was decided to treat only patients who had either received a full course of doxorubicin-containing therapy or had progressed while receiving a doxorubicin-based regimen. The goal was to determine whether a significant response rate with TEMP could be achieved in a group of patients whose therapeutic alternatives were generally limited.

PATIENTS AND METHODS

From February 1989 to December 1994, 46 patients with metastatic breast carcinoma were enrolled on 1 of 2 institutional protocols designed to evaluate the effectiveness of TEMP chemotherapy in patients with metastatic breast carcinoma. In one study, TEMP alone was administered and patients were followed for progression after a maximum of six cycles; in the companion trial, patients with stable or responsive disease after two to three cycles of TEMP were eligible to proceed to high dose chemotherapy and autologous stem cell transplantation (ASCT). All patients were required to have previously received, either in the adjuvant or metastatic setting, a full course (four to six cycles) of a doxorubicin-based therapy (patients who had clearly progressive disease while on doxorubicin received only one to three cycles). Additional eligibility requirements included histologically documented breast carcinoma, measurable or evaluable disease, no prior radiation or chemotherapy within 4 weeks of treatment on protocol, left ventricular ejection fraction > 60% by multiple gated acquisition, bilirubin and creatinine levels < 1.5 times the upper limit of normal, serum glutamic oxaloacetic transaminase < twice the upper limit of normal, and signed informed consent.

TABLE 1
Patient Characteristics

	No.
No. of patients	
Total enrolled and eligible	44
With bone-only disease	7
Evaluable/measurable/analyzed	37
Median age (yrs) (range)	44 (25-72)
Setting of doxorubicin treatment	
Adjuvant	29
Metastatic	15
Estrogen receptor	
Positive	21
Negative	21
Unknown	2
Sites of metastasis	
Bone	19
Chest wall-subcutaneous	18
Lung/pleura	14
Lymph node	14
Liver	10
Skin	3
Ascites	1
Other	4
Number of metastatic sites	
1	19
2	15
> 2	10

Patients received tamoxifen, 10 mg, orally twice a day throughout the course of chemotherapy; etoposide, 100 mg/m^2, intravenously on Days 1-3; mitoxantrone, 10 mg/m^2 on Day 1; and CDDP, 30 mg/m^2 on Days 1 and 2. Patients were treated in the hospital with pre- and posthydration for the CDDP. CDDP was administered over 2 hours, etoposide over 1 hour, and mitoxantrone over 15 minutes. Antiemetics were comprised of dexamethasone, metaclopromide, lorazepam, and perphenazine as needed; ondansetron was used after it became commercially available. Cycle length was intended to be 21 days. Treatment was delayed by 1 week if, at the scheduled time of retreatment, Grade 2 granulocyte or platelet toxicity persisted. The use of growth factors was not required,

TABLE 2
Descriptive Characteristics of Patients Responding (N = 15)

Patient	Age (yrs)	Doxorubicin setting	Sites (primary, secondary)	ER (status)	Previous tamoxifen	TEMP response
1	46	Adjuvant	CW	+	Yes	CR
2	34	Adjuvant	Lung, CW	+	Yes	PR
3	72	Metastatic	Liver, CW	+	Yes	PR
4	47	Adjuvant	Skin, CW	+	Yes	PR
5	38	Adjuvant	Lung, lymph node, liver	+	Yes	PR
6	33	Adjuvant	CW, bone	+	No	PR
7	44	Adjuvant	CW	–	No	CR
8	44	Adjuvant	CW	–	No	PR
9	44	Adjuvant	Lung, lymph node	–	No	PR
10	46	Adjuvant	Lymph node, liver	–	No	PR
11	41	Adjuvant	CW	–	No	PR
12	42	Adjuvant	Lymph node	–	No	PR
13	28	Adjuvant	Lung, liver	–	Yes	PR
14	42	Adjuvant	Bone, lung, node	–	Yes	PR
15	49	Adjuvant	Lymph node	–	Yes	PR

ER: estrogen receptor; TEMP: tamoxifen, etoposide, mitoxantrone, and cisplatin; CW: chest wall; +: positive; –: negative; CR: complete response; PR: partial response.

but was allowed in the event of clinically significant neutropenia. Drug-related toxicity was recorded according to the World Health Organization criteria.[17]

Patients with measurable disease on physical exam were evaluated after each course of treatment. Patients requiring computed tomography, chest radiograph, or other imaging studies for tumor measurement were evaluated after every second therapy. A complete response (CR) was defined as the complete disappearance of all evidence of disease; a partial response (PR) as a decrease in the greatest dimensions of 1 or more indicator lesions by 50% or more; stable disease (SD) as < a 50% decrease or <25% increase in the size of indicator lesions without the growth or appearance of other lesions; and progressive disease as an increase in the size of metastases by 25% or more.

Exact confidence intervals (CI) for response rates were computed.[18] Logistic regression[19] was used to examine the effect of ER, doxorubicin setting (adjuvant or metastatic), and site of metastases (visceral versus nonvisceral disease as well as individual sites) on response.

RESULTS

Forty-six patients with metastatic breast carcinoma were enrolled on the TEMP protocols. Two patients who were later found to be ineligible because of lack of evaluable disease at enrollment were removed from all analyses, leaving 44 patients evaluated for response. Pretreatment characteristics are shown in Table 1. Seven patients with bone-only disease were considered separately, leaving 37 patients assessable for response rate. Two patients in this latter group were not evaluable because of 1) loss to follow-up and 2) treatment with nonprotocol chemotherapy prior to evaluation. In addition, in this group of patients with advanced disease, three patients received only one cycle of TEMP prior to a Grade 4 infectious complication (one patient) or progression of disease (two patients). All five of these patients were counted as progressive disease in the analysis of response.

Therapeutic Responses

The overall response rate for the 37 patients with visceral, skin, and/or soft tissue disease was 41% (95% exact CI, 25–58%), with 2 CR and 13 PR observed. Among the subgroup of 24 patients who had relapsed during or after adjuvant doxorubicin-containing chemotherapy the response rate was 58% (95% exact CI, 37–78%). Of the 8 women who had received adjuvant chemotherapy with doxorubicin during or <12 months before relapsing, 4 responded. Of the 13 patients who had previous doxorubicin therapy for metastatic disease, only 1 objective PR was observed. Characteristics of the patients with CR and PR are outlined in Table 2. Thirteen of 15 responding patients went on to ASCT within 1 to 4 months after TEMP; therefore, response durations to TEMP were not reported. Long term follow-up analysis of ASCT patients currently is being analyzed and will be reported separately.

To identify variables that might be associated with

TABLE 3
Logistic Regression Analysis Predicting Response to TEMP (N = 35)[a]

Variable	Odds ratio	95% CI	*P* value
Visceral metastasis	0.97	(0.21, 4.52)	0.97
ER positivity	1.53	(0.29, 8.14)	0.62
Doxorubicin, metastatic setting	0.06	(0.01, 0.63)	0.02

TEMP: tamoxifen, etoposide, mitoxantrone, and cisplatin; CI, confidence interval; ER: estrogen receptor.
[a] Two patients were excluded due to unknown estrogen receptor status.

a likelihood to respond, logistic regression (n = 37) was performed using the presence or absence of visceral metastases, ER status, and previous doxorubicin treatment setting as covariables. This analysis revealed that the likelihood of responding to TEMP was not related to ER status or to the presence of visceral metastases (Table 3). The analysis also shows that patients who received doxorubicin in the metastatic setting were significantly less likely to respond than those who were treated with adjuvant doxorubicin ($P = 0.02$). Further logistic regression analysis revealed that the likelihood of response to TEMP was also not related to the presence of a metastasis at a particular site ($P \geq 0.16$ for individual sites) or to the number of metastatic sites ($P = 0.64$).

Because of the technical limitations in objectively assessing the response of osseous metastases, the responses of seven patients with bone-only disease were considered separately. Of these seven patients, five had subjective improvement in symptoms without worsening of bone scans (four of five ER positive patients and one of two ER negative patients). All five responding bone-only patients proceeded to ASCT.

Toxicity

Toxicity for all 44 eligible patients is outlined in Table 4. Although midcycle laboratory studies were not obtained on 10 patients (23%), 59% of patients experienced Grade 3 or 4 neutropenia at some point in their therapy. One patient died of an overwhelming *Escherichia coli* neutropenic sepsis after the third cycle of chemotherapy. In view of previous reports of a high incidence of venous thromboses in patients undergoing chemohormonal therapy compared with those undergoing conventional chemotherapy,[1] there was concern over this complication with TEMP treatment. However, only two circulatory complications were noted: a thrombosis at the site of a permanent indwelling subclavian catheter and a nonhemorrhagic central nervous system stroke. No significant renal, cardiac, or neurologic toxicities were observed.

TABLE 4
Toxicities (N = 44)

	No. (%)
Absolute granulocyte count	
None	13 (30)
Grade 1 or 2	5 (11)
Grade 3 or 4	26 (59)
Hemoglobin	
None	7 (16)
Grade 1 or 2	23 (52)
Grade 3 or 4	14 (32)
Platelets	
None	15 (34)
Grade 1 or 2	17 (39)
Grade 3 or 4	12 (27)
Infection	
None	36 (82)
Grade 1 or 2	4 (9)
Grade 3 or 4	3 (7)
Grade 5	1 (2)
Thrombotic	
None	42 (95)
Grade 1 or 2	0
Grade 3 or 4	2 (5)
Renal	
None	39 (89)
Grade 1 or 2	5 (11)
Grade 3 or 4	0

DISCUSSION

CDDP and etoposide combination regimens have been shown to be active in patients with advanced breast carcinoma, with an overall response rate of approximately 50% in patients previously untreated for metastatic disease.[12,13] In contrast, the CDDP/etoposide response rate for patients previously treated in the metastatic setting has been low, typically less than 20%.[14–16] In this trial, a regimen of CDDP/etoposide/mitoxantrone combination chemotherapy with the addition of tamoxifen has been evaluated in a group of patients previously treated with doxorubicin. The rationale for this regimen is based on in vitro data that suggest a synergistic cytotoxic effect between CDDP and tamoxifen in ER negative melanoma cells[9,10] as well as previous clinical data suggesting a significant increase in response rate with the addition of tamoxifen to a cisplatin-based regimen in patients with metastatic melanoma.[6,8] Although the mechanism of tamoxifen/CDDP synergy is not understood, it does appear to be independent of ER status. A response rate of 58% was found among women previously treated with adjuvant doxorubicin, moreover, 50% of women who had progressed within 12 months of an adjuvant doxorubicin-containing regimen responded to TEMP.

This response rate was higher than would be expected from previously reported cisplatin/etoposide combinations alone, although a study in which women were treated with doxorubicin-containing regimens and then an etoposide-cisplatin-based regimen was not available for direct comparison. Interestingly, the likelihood of response to TEMP was found to be independent of the ER status of the original tumor. This implies that tamoxifen's mechanism of action in TEMP may be ER independent, similar to the findings in laboratory studies of melanoma cell lines.[10,11]

The 50% response rate among patients treated with TEMP who developed metastatic breast carcinoma within 12 months of doxorubicin-based adjuvant therapy compared favorably with the results from recent Phase II trials with either paclitaxel or docetaxel. These trials, including those examining paclitaxel alone,[20-22] or in combination,[23] or docetaxel alone,[24,25] or in combination[26] found comparable response rates in patients with metastatic breast carcinoma. However, the minimal 8% objective response rate to TEMP therapy for patients who had failed doxorubicin in the metastatic setting was inferior to that reported for patients treated with taxane-based therapies. The reason for this difference in response rates in patients with de novo resistance to adjuvant versus metastatic doxorubicin is not clear; it may be related to the greater number of cross-resistant agents the latter group received as treatment prior to TEMP. In comparison with nontaxane based combination chemotherapies, TEMP efficacy appears to be superior to mitoxantrone/CDDP,[27] mitoxantrone/5-fluorouracil/L-leucovorin,[28] and etoposide/carboplatin[29,30] combinations in the treatment of patients with metastatic breast carcinoma who had prior anthracycline exposure. TEMP also appears to be superior to the relatively new agents gemcitabine[31] and vinorelbine.[32]

Toxicity with TEMP was mainly hematologic, including one death from neutropenic sepsis in a patient who had been heavily pretreated. Overall, hematologic toxicity was significant with 59% of all patients experiencing Grade 3 or 4 neutropenia. Growth factor use may diminish this problem in the future. Although there was concern that tamoxifen therapy in conjunction with standard chemotherapeutic agents might lead to an unacceptable incidence of thrombotic complications, thromboses occurred in only two patients. The combination of cisplatin and tamoxifen at these doses did not lead to neurologic toxicity.

In summary, TEMP chemotherapy, which combines tamoxifen with an etoposide/CDDP-based regimen, appears to have significant activity in patients who have failed recent adjuvant doxorubicin chemotherapy. This activity is independent of the tumor's ER status. Perhaps not surprisingly, TEMP was not found to be an effective combination for heavily pretreated patients who had progressed during or after doxorubicin-based chemotherapy in the metastatic setting. However, TEMP is a useful combination for the treatment of patients with metastatic breast carcinoma who have received previous full dose adjuvant doxorubicin therapy and for whom therapeutic options are currently limited. The high response rate among women who progress within 12 months of doxorubicin therapy suggests that tamoxifen may play a role in the regimen's higher than expected efficacy. A direct comparison of etoposide, mitoxantrone, and platinum with and without tamoxifen will be needed to clearly define the role of tamoxifen in this regimen.

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