A Phase III Randomized Trial of Dacarbazine and Carboplatin with and without Tamoxifen in the Treatment of Patients with Metastatic Melanoma

Sanjiv S. Agarwala, M.D.
William Ferri, M.D.
William Gooding, Ph.D.
John M. Kirkwood, M.D.

The University of Pittsburgh Cancer Institute, Pittsburgh, Pennsylvania.

BACKGROUND. Metastatic melanoma is a disease associated with a poor prognosis, and dacarbazine is still the reference agent. The authors conducted a randomized trial to test the benefit of adding tamoxifen to dacarbazine and carboplatin chemotherapy for previously untreated patients with metastatic melanoma.

METHODS. Eligible patients with histologically confirmed, measurable metastatic melanoma were randomized to carboplatin 300 mg/m^2 and dacarbazine 1 g/m^2 administered intravenously on Day 1 with or without tamoxifen 20 mg/day administered orally throughout the treatment period (C + D ± T). Chemotherapy was repeated in 28-day treatment cycles for a minimum of 2 cycles or until disease progression. The study was designed to be stopped after accrual of 28 patients per treatment arm based on 80% power to detect an improvement in response from 20% to 40% among patients treated with tamoxifen.

RESULTS. A total of 56 patients were randomized; all were evaluable for response and survival. The 2 treatment groups were well balanced for various prognostic factors; 75% of patients had predominant visceral disease. Complete and partial responses combined were 10.7% in the C + D arm and 14.3% in the C + D + T arm ($P = 1.0$). Median survival was 7 months for C + D and 4.6 months for C + D + T (the difference was not significant). The median time to disease progression was worse for the patients treated with tamoxifen ($P = 0.03$). Toxicity was similar in the two groups, with no episodes of deep venous thrombosis.

CONCLUSIONS. The addition of tamoxifen did not improve the response rate, time to progression, or survival compared with chemotherapy with dacarbazine and carboplatin in unselected patients with metastatic melanoma. ***Cancer* 1999;85: 1979–84.** *© 1999 American Cancer Society.*

KEYWORDS: melanoma, metastasis, chemotherapy, hormonal therapy, tamoxifen.

The overall prognosis for patients with metastatic melanoma has not changed significantly in the past 2 decades and dacarbazine [5-(3,3-Dimethyltriazenyl)-1*H*-imidazole-4-carboxamide, DTIC], with a response rate of 15–20%, remains the reference agent despite the absence of any meaningful impact on survival. Interest in combination chemotherapy regimens incorporating tamoxifen was kindled when Del Prete et al. first reported the improved results of a four-drug regimen of carmustine, cisplatin, dacarbazine, and tamoxifen for patients with metastatic melanoma.[1]

Subsequent work with this regimen with and without tamoxifen[2–4] led to the implication that tamoxifen was of key importance to the regimen, which is somewhat hard to explain given the lack of efficacy of tamoxifen as a single agent against this disease.[5] The results of a randomized trial in Italy of dacarbazine with or without

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Address for reprints: John M. Kirkwood, M.D., University of Pittsburgh Cancer Institute, N755 MUH, 200 Lothrop Street, Pittsburgh, PA 15213.

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tamoxifen seemed to confirm this observation;[6] however, subsequent randomized trials have failed to confirm the benefit of tamoxifen shown in that study.[7] We initiated a prospective, randomized clinical trial to compare the efficacy of two active chemotherapeutic agents, dacarbazine and carboplatin, with and without tamoxifen for patients with previously untreated metastatic melanoma at the University of Pittsburgh Melanoma Center. We chose carboplatin over cisplatin due to its therapeutic equivalence with cisplatin in most diseases, its ease of outpatient administration, and its favorable safety profile.

METHODS

Patients with a histologically confirmed diagnosis of metastatic melanoma were entered into the study at the outpatient services facilities of the University of Pittsburgh Cancer Institute. Eligibility criteria included age >18 years, an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, and the presence of tumor that could be measured and followed by either physical examination or radiographic techniques. In addition, patients were required to have adequate hematologic (white blood cell (WBC) count >3000/mm^3, platelet count >150,000/mm^3), renal (calculated creatinine clearance >30 mL/min), and hepatic function. Female subjects were required to be surgically sterile or using an approved method of birth control. Prior chemotherapy was reason for exclusion, as was a history of a second malignancy (except basal cell carcinoma of the skin) or a concomitant serious medical illness. Patients with central nervous system (CNS) metastases that were clinically stable were permitted into the study.

At entry, all patients gave a complete history and underwent a complete physical examination. Laboratory testing included a complete blood count, urinalysis, and serum chemistry profile. Creatinine clearance was measured at baseline and prior to each subsequent treatment cycle. A chest X-ray and computed tomography scanning of the head, chest, and abdomen were carried out for all participants. Detailed measurements of indicator lesions were recorded. All patients gave full and informed written consent.

A history and physical examination were obtained once again on Day 1 of each cycle (every 28 days). Blood counts and serum chemistries, including liver function tests, were repeated every 2 weeks. Radiographic assessment of indicator lesions was performed at the end of every other treatment cycle to assess for response.

Patients were stratified by disease site (visceral, soft tissue, or CNS) and then randomized to 1 of 2 treatment arms: carboplatin (CBDCA) 300 mg/m^2 administered intravenously (i.v.) on Day 1 plus dacarbazine 1 g/m^2 i.v. on Day 1 with or without tamoxifen 20 mg/day administered orally starting on Day 1 and continuing throughout treatment (C + D ± T). All intravenous therapy was administered at the outpatient services facilities of the University of Pittsburgh Cancer Institute. Treatment was repeated in 28-day cycles.

No dose modification for dacarbazine was planned. If the creatinine clearance was <30 mL/min, the CBDCA dose was withheld for that cycle. For a clearance of 30–60 mL/min, the dose of CBDCA was calculated to a target platelet count of 75,000 according to the following formula: CBDCA dose (mg/m^2) = (0.091)(Ccr)/BSA) × (desired % of change in platelet count) + 86.[8] Patients whose creatinine clearance fell to <30 mL/min and did not recover were continued on dacarbazine with or without tamoxifen as assigned until disease progression. If the Day 14 WBC nadir was <1000/mm^3 and the platelet nadir <50,000/mm^3, the dose of CBDCA in the subsequent cycle was reduced by 50mg/m^2. If, on the day of treatment, the WBC count was <3000/mm^3 or the platelet count was <150,000/mm^3, treatment was delayed by 1 week.

To be evaluable for clinical response, patients were required to have received a minimum of two cycles of treatment. Complete response (CR) was defined as the disappearance of all clinical and radiographic evidence of tumor for a minimum of 30 days. Partial response (PR) constituted a reduction of the sum of the product of the perpendicular greatest dimensions of index lesions by at least 50% for a minimum of 30 days, without the appearance of new lesions or progression at any nonindex site. Progression was defined as a 25% or greater increase in the sum of the product of the perpendicular greatest dimensions of index lesions or the appearance of new lesions. Patients who fell into the category between partial response and progression were considered to have stable disease (SD).

The study was planned to proceed in two stages. The accrual goal for the first stage was 28 patients per treatment arm. At that point, the data was to be evaluated and a decision to be made to either stop or continue with the second stage of accrual. The stopping rule, based on Simon,[9] used the conventional 5% type I error with 80% power to detect a 40% response rate for the tamoxifen group when the control group response rate was 20%, and permitted early stopping for either parity between groups or a decisive advantage for tamoxifen.

TABLE 1
Patient Demographics

	No. of patients (%)	
	C + D	C + D + T
No. of patients	28	28
Median age (yrs)	54	56
Gender		
Male	18 (64)	14 (50)
Female	10 (36)	14 (50)
Performance status		
0	19 (68)	16 (57)
1	9 (32)	12 (43)
Disease site		
Visceral	17 (61)	20 (72)
Soft tissue	5 (18)	4 (14)
CNS	6 (21)	4 (14)
Previous treatment		
None	10 (36)	13 (46)
Chemotherapy	0	0
Radiation	11 (32)	5 (18)
Immunotherapy	13 (46)	11 (39)
Surgery	28 (100)	28 (100)

C: carboplatin; D: dacarbazine; T: tamoxifen; CNS: central nervous system.

TABLE 2
Response (Durable: ≥4 Weeks' Duration)

	No. of patients	
	C + D	C + D + T
No. of evaluable patients	28	28
Complete responses	1	1
Partial responses	2	3
Stable disease	5	3
Progressive disease	20	21
Response rate (%)	10.7	14.3

C: carboplatin; D: dacarbazine; T: tamoxifen.

Statistical Methods

Clinical endpoints were best response, durable response (≥4 weeks), survival time, and time to disease progression. Response rates were compared between prognostic strata and treatment arms using the Fisher exact two-tailed test. Treatment effect was analyzed in populations stratified for the various prognostic factors, and testing for homogeneity of the odds ratios among strata was performed. Survival and time to progression were analyzed by Kaplan–Meier plots and log rank tests. Survival time was from date of study accrual until death or until May 1998.

RESULTS

A total of 56 patients were randomized in the first stage of the trial (28 in each treatment arm). All patients were evaluated for response and survival. The characteristics of the two treatment groups are shown in Table 1. The two arms of the study were well balanced for age, performance status, disease site, and prior therapy. A slightly greater number of women were treated on the C + D + T arm. Of the 24 women treated in this trial, 12 were premenopausal. Less than 25% of patients treated on either arm had soft tissue predominant disease. Sites of visceral disease included the liver in 17 patients, the lung in 17 patients, the peritoneum in 3 patients, and the adrenal gland in 4 patients.

Response evaluation is depicted in Table 2. There were 3 responses (1 complete) in the C + D arm (overall response rate, 10.7%; 95% confidence interval [CI], 2.1–28.3) and 4 (1 complete) in C + D + T arm (overall response rate, 14.3%; 95% CI, 4.0–32.7). This difference was not statistically significant ($P = 1.0$). Duration of responses were 3, 3, 6, and 6 months in C + D + T arm and 2 and 16 months in the C + D arm. One patient in the C + D arm who had a partial response was lost to follow-up at 31 months. The number of clinical cycles administered was associated with response. Responders received a median of 4 cycles, whereas nonresponders received a median of 2 cycles or fewer ($P = 0.0125$). However, there was no statistically significant difference in the number of cycles between the two arms of the study. When clinical response rate was analyzed with respect to the prognostic factors of age, gender, performance status, and disease site, no factor emerged as a significant variable. Menopausal status in women was not a predictor of outcome on either arm of the study.

Of the two patients who experienced a CR, one had liver metastases and the other had soft tissue disease. Of the seven PRs, one was in the liver, four were in other visceral organs, and two were in the soft tissues. Of note, no patient with CNS metastases responded to treatment on either arm of the study.

Toxicity was tolerable in both treatment arms. The Grade 3 and 4 toxicities (hematologic and nonhematologic) are depicted in Tables 3 and 4. Overall, the incidence of Grade 3 and 4 toxicity appeared to be higher in the tamoxifen arm. Of note, no episodes of deep venous thrombosis were observed and no patient developed Grade 3 or 4 renal toxicity on either arm of the study.

Survival and Time to Progression

Time to progression was defined as the first date of CR or PR until disease progression. Survival time was calculated as the time from entry into the study until

TABLE 3
Hematologic Toxicity

	No. of patients			
	C + D		C + D + T	
Grade (NCI)	3	4	3	4
Anemia	3	0	7	2
Leukopenia	8	1	10	4
Thrombocytopenia	8	6	12	5

C: carboplatin; D: dacarbazine; T: tamoxifen; NCI: National Cancer Institute.

TABLE 4
Nonhematologic Toxicity

	No. of patients					
	C + D			C + D + T		
Grade (NCI)		3	4		3	4
Emesis	0	0		0	0	
Renal		0	0		0	0
Hepatic		0	0		1	1
Neurologic		1	0		1	0
Infection		1	0		0	0

C: carboplatin; D: dacarbazine; T: tamoxifen; NCI: National Cancer Institute.

the time of death or May 1998. As of May 1998, all patients had been followed for at least 3 years since the last patient was accrued. Of the 56 patients, 55 have died and 1 was lost to follow-up at 31 months. The median overall survival was 6.0 months with a 95% CI of 4.8–10.2 months. The median survival for the C + D + T arm was 4.6 months and for the C + D arm 7.0 months. Survival was not significantly different ($P = 0.1377$, log rank test; Fig. 1). The median time to progression for 7 patients with a clinical response was 3.7 months (Fig. 2). Although there was no significant difference between treatment arms in time to progression ($P = 0.2212$), 1 patient in the C + D arm did not relapse until 16 months, whereas a second patient in that arm had not relapsed when lost to follow-up at 31 months.

DISCUSSION

Multiple single-institution studies of regimens containing tamoxifen have reported results for patients with metastatic melanoma that are superior to historical responses and survival data with dacarbazine.[1–3] A study by McClay et al. also suggested an adverse complication of the regimens containing tamoxifen, namely, phlebothrombosis.[2] One prior randomized study that addressed the role of tamoxifen as an adjunct to chemotherapy of metastatic melanoma was that of Cocconi et al. for the Italian Oncology Group for Clinical Research.[6] Patients were randomized to receive dacarbazine 250 mg/m^2/day for 5 days once every 3 weeks with or without tamoxifen 20 mg/day. A statistically significant improvement in response rates (28% vs. 12%) and survival (48 weeks vs. 28 weeks; $P = 0.02$) was observed for the group treated with tamoxifen. Our study, though smaller, was not able to confirm these results.

The response rate reported in this trial does not differ significantly for patients treated with or without tamoxifen. This study was designed to detect an improvement of 20% of the arm given tamoxifen over the arm given chemotherapy alone, with a probability (power) of 0.80. The 20% increment was chosen because it was felt that an increment of this magnitude was necessary for the difference to be clinically meaningful, and also because of the existing Phase II data demonstrating response rates in the 40–50% range for regimens containing tamoxifen. Our study incorporated an early stopping rule, and it is possible that a small, clinically unimportant treatment benefit of tamoxifen may have existed but was undetected in this trial. There was no impact of gender on treatment outcome. The median survival was 4.6 months for the patients treated with tamoxifen and 7.0 months for patients receiving chemotherapy alone. This difference was not statistically significant, but an analysis of time to treatment failure suggests that patients receiving tamoxifen did, in fact, fare significantly worse ($P = 0.03$, Fig. 3). The two treatments did not differ significantly in terms of survival or time to treatment failure.

It is unclear to us why the results of this trial differ so significantly from those of the Italian study. One of the factors could be the definitions of response used in the two studies. The Italian trial used standard definitions of partial and complete response but did not specify a minimum duration for definition of response. In the current study, patients were considered to have had a response only if tumor regression was sustained for a minimum of 30 days, a definition that is more widely held by the cooperative groups in North America. It is noteworthy that this trial, when analyzed for "best possible response" during treatment irrespective of duration, produced a response rate of 28.6% for the arm given tamoxifen and 14.3% for the arm given chemotherapy alone, and these results are remarkably similar to those of Cocconi et al. (28% vs. 12%). Most patients in the Italian trial had small-volume, nonvisceral disease, unlike the majority of patients treated in our study. Furthermore, in subgroup analysis, the benefits in response rate and survival were confined largely to female subjects. Females did not have an improved outcome in our study, but

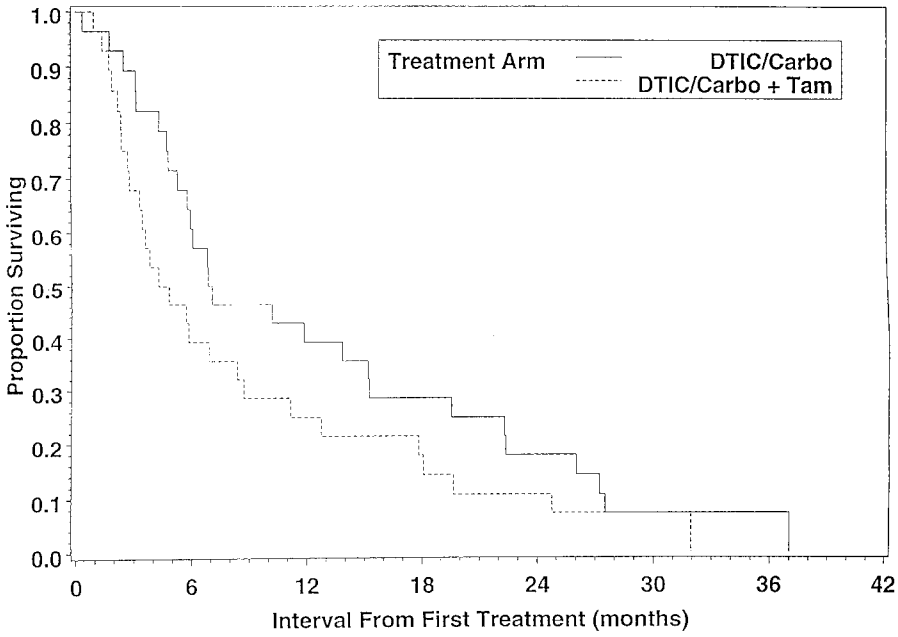

FIGURE 1. Estimated survivorship of the two groups of patients (Kaplan–Meier) is shown ($P = 0.1377$). DTIC: dacarbazine; Carbo: carboplatin; Tam: tamoxifen.

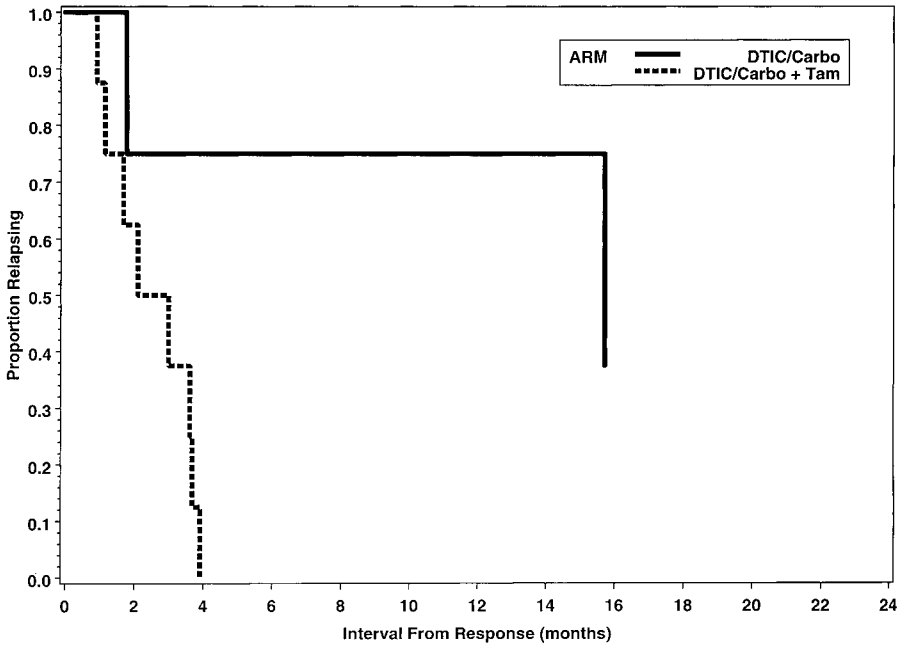

FIGURE 2. Time to relapse by treatment arm is shown for 7 patients with a clinical response. Although the times to relapse were not significantly different ($P = 0.2212$, log rank test), 2 of 4 responding patients in the C + D arm had not relapsed at 16 and 31 months. DTIC: dacarbazine; Carbo: carboplatin; Tam: tamoxifen.

the numbers are too small to draw definite conclusions.

Given the lack of efficacy of tamoxifen as a single agent against melanoma, the results of our study are not surprising. The suggestion that tamoxifen may be of central importance to melanoma chemotherapy has been drawn from a series of small, single-institution trials in which response rates for successive cohorts of patients dropped from 50% to 10% and returned again to 50%, according to whether tamoxifen was introduced or omitted. None of these were randomized trials, however. The authors hypothesized that tamoxifen was synergizing with cisplatin at the cellular level, an observation that has subsequently been evaluated more extensively in studies of melanoma cell lines.[10,11] The current study utilized carboplatin instead of cisplatin, primarily due to our failure to demonstrate antitumor synergism with cisplatin in our earlier Phase II trial[12] and the decreased renal toxicity and ease of CBDCA administration. It was postulated that the use of CBDCA in place of cisplatin would allow evaluation of the potential for tamoxifen synergism

with both the nonclassical alkylator dacarbazine and the platinum coordination compounds. The negative results of this trial have implications relevant to combined chemotherapy regimens in general, beyond the dacarbazine and tamoxifen trial of Cocconi et al.

Our failure to demonstrate a benefit from the combination is not due to a higher rate of response to CBDCA and dacarbazine, as our reference arm achieved a relatively low response rate of 10.7%. This was lower than traditionally reported for single-agent dacarbazine but within the CIs for our sample size. The majority of the patient population studied here had visceral disease (70%), and we did not exclude patients with CNS metastases, although evaluation was based on non-CNS disease for this trial. This could account for the poorer results. It is remarkable that the trial of Cocconi et al. found a response rate of only 12% for patients treated with dacarbazine, despite a predominance of patients with only soft tissue disease in that trial (63%) and the inclusion of patients with surgically resectable disease. This lower-than-expected response rate for dacarbazine alone may have confounded the results of that trial and could account for the difference in outcome observed between the two treatment groups.

Several other recently completed and published studies have also failed to show a benefit for chemohormonal therapy containing tamoxifen over chemotherapy alone. Since this study was completed, the National Cancer Institute of Canada Clinical Trial Group published the results of a randomized, double-blind, placebo-controlled trial of the combination of carmustine, dacarbazine, cisplatin, and tamoxifen versus the same chemotherapy with placebo. For 199 eligible patients, response rates and survival were similar in the 2 treatment arms.[7] In addition, the ECOG recently published the results of a large randomized study (ECOG 3690) comparing combinations of dacarbazine, interferon-α, and tamoxifen in a two-by-two factorial design in the treatment of 258 eligible patients with previously untreated metastatic melanoma. Neither response rate nor survival was superior for the arms of the study given tamoxifen as compared with those given dacarbazine alone.[13]

The history of the treatment of melanoma is replete with reports of promising regimens from single institutions that have not withstood the rigorous evaluation of a randomized Phase III trial. We conclude that for patients with metastatic melanoma, tamoxifen does not add any benefit to chemotherapy with dacarbazine and carboplatin. An intergroup U.S. trial involving the ECOG as well as the Memorial Sloan-Kettering Cancer Center and the Hoosier Oncology Group, in which the tamoxifen-containing Dartmouth regimen was compared with dacarbazine alone, was recently completed and is currently undergoing analysis. The results of this important study, when available, should help resolve once and for all the issue of combination chemotherapy containing tamoxifen for patients with metastatic melanoma, in relation to dacarbazine alone.

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