Combination of Paclitaxel and Carboplatin as Second-Line Therapy for Patients with Metastatic Melanoma

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Institutional review board (IRB) permission was obtained for this analysis. The medical records of patients who refused research authorization were excluded from our study.

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BACKGROUND. Patients with metastatic melanoma (MM) have very few therapy options. Based on reports of responses to paclitaxel and carboplatin (PC), 31 patients with MM were treated with PC.

METHODS. Data regarding patients treated with PC were abstracted from medical records. Clinical outcomes as determined by the treating oncologist were used for this analysis. Response determination was retrospectively confirmed using Response Evaluation Criteria in Solid Tumors (RECIST).

RESULTS. Thirty-one patients with MM were treated with PC. Patients had a median of 2 previous therapies, with the majority (29; 94%) having failed prior temozolomide (TMZ) or dacarbazine (DTIC) therapy. The most commonly used regimen was weekly paclitaxel (at a dose of 100 mg/m^2) and carboplatin (area under the curve 2) administered on Days 1, 8, and 15 of a 28-day cycle. An objective partial response was noted in 8 patients (26%) with an additional 6 patients (19%) having stable disease; therefore, a clinical benefit was noted in 45% of those patients treated. The median time to disease progression for the entire group was 3 months (range, 0–7 mos), with a median overall survival of 7.8 months (range, 1–14 mos). The clinical benefit derived by the 14 patients, which lasted for a median of 5.7 months (range, 2.5–7.3 mos), was considered to be clinically significant. At the time of last follow-up, eight patients continued to receive PC therapy.

CONCLUSIONS. The PC combination appears to have definite and clinically meaningful activity when used as second-line therapy after TMZ or DTIC. Further evaluation of this regimen, alone or as a 'backbone' for other agents, needs to be considered. ***Cancer* 2006;106:375–82.** © *2005 American Cancer Society.*

KEYWORDS: metastatic melanoma, paclitaxel, carboplatin, second-line therapy.

The incidence of malignant melanoma (MM) has been steadily increasing over the past few decades.[1] Currently, melanoma is the fifth most common cancer diagnosed in men and the seventh most common cancer diagnosed in women.[1] Surgery is curative in a large proportion of patients with early-stage melanoma. However, 10–40% of patients with AJCC Stages I and II disease and 40–80% of Stage III patients die of metastatic disease within 5 years after the original diagnosis.[2] MM has a very poor prognosis, with a median survival of less than 1 year.[2] For a vast majority of patients with MM, there are no effective therapies. Most therapies provide a short-lived palliative benefit.[3,4] Therefore, the development of effective therapies for this patient population remains a priority in oncology.

Over the past several decades, significant clinical research effort has been expended in trying to identify active chemotherapeutic agents in melanoma.[5–12] These studies have demonstrated that very few of the drugs in our chemotherapeutic armamentarium have any efficacy in melanoma. Only five agents, cisplatin, dacarbazine (DTIC),

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carmustine, temozolomide (TMZ), and interleukin-2 (IL-2), have been found to have enough activity in melanoma to be used routinely for the treatment of patients with advanced stage disease.[4,13–16] Among these, only two drugs, DTIC and IL-2, have been approved by the U.S. Food and Drug Administration (FDA) for use in these patients.[9,17,18] Interest in the use of paclitaxel and carboplatin in the treatment of MM patients has been renewed in view of the recent presentation of results from a Phase I/II study of this combination with BAY 43-9006 (sorafenib, an inhibitor of signaling through the Raf/MEK/ERK pathway; Bayer Pharmaceuticals, West Haven, CT).[19] The results of this study (currently available in abstract form only), suggest that this 3-drug combination is very active in MM, with a clinical benefit rate (objective response plus stable disease rate) of 85% and a median time to disease progression of $>$ 5 months. Because the relative benefit of using sorafenib in addition to the combination of paclitaxel and carboplatin (PC) is not known, this study is being followed with a planned Eastern Cooperative Oncology Group (ECOG) Phase III trial in which patients will be randomized to either PC or to the three-drug combination of PC and sorafenib.

Based on previous reports that suggested that the combination of PC had some efficacy in MM, we offered the PC combination to patients with MM who progressed on first-line chemotherapy. Herein, we present our clinical experience of using PC in this patient population.

MATERIALS AND METHODS

This was a retrospective review of our institutional experience with the combination of PC in patients with MM. Institutional review board (IRB) permission was obtained for this analysis. All patients who were treated with combination PC for the treatment of MM were identified from the medical records of the Mayo Clinic (Rochester, MN). Data regarding patient characteristics and outcomes were abstracted for analysis. For each patient, response determination (e.g., complete response, partial response, stable disease, mixed response, or disease progression) by the treating physician was recorded and used for this analysis. Patients who achieved a complete response, partial response, or stable disease were designated as having a clinical benefit for the purposes of this analysis. Each documented response was then confirmed by review of clinical data and imaging studies using the Response Evaluation Criteria in Solid Tumors (RECIST).[20] Imaging studies performed subsequent to the initial response determination were also evaluated to confirm the response. To be classified as having clinical benefit (i.e., response or stable disease), patients were required to demonstrate a response satisfying the RECIST criteria and have a persistent response that could be verified subsequently by a confirmatory imaging study. Patients who were declared in their medical records as having stable disease or a response, but who did not have adequate imaging studies available for confirmation, were considered to be nonresponders. Imaging studies were also reviewed independently by a reviewer who was not involved in the design of the study, data collection, analysis of the data, or preparation of the current study. Comparisons between variables in different groups were made using JMP statistical software (Release 5.1.2; SAS Institute Inc., Cary, NC).

RESULTS

Combination PC chemotherapy was used to treat 31 patients with MM at our institution between March 2003 and January 2005. The majority of patients had advanced metastatic disease with visceral metastases (M1c [84%] and M1b [6%]) with only 3 patients (10%) classified as having M1a disease. The median number of organ sites involved was three (range, one to six organ sites). Sixteen patients (52%) had liver metastases and 18 (58%) had lung metastases. The three patients with M1a disease required therapy because they had symptomatic rapidly progressing skin and lymph node disease.

Overall, the 31 patients were heavily pretreated and had previously received (and failed) a median of 2 systemic therapies for metastatic disease, including 1 prior chemotherapeutic regimen. Eleven patients (35%) had previously been treated with vaccine/immune therapy for metastatic disease. Five patients (16%) had previously received adjuvant therapy with either interferon[21] or granulocyte-macrophage–colony-stimulating factor.[22] All of the patients except 2 patients (i.e., 29 patients [94%]) had previously been treated with TMZ or DTIC. Patient baseline data are presented in Table 1.

Because these patients were not treated according to a prospectively specified protocol, the selection of the schedule and doses was performed according to the choice of the treating physician. The most commonly used regimen was weekly PC (paclitaxel at a dose of 100 mg/m^2 and carboplatin at an area under the curve [AUC] of 2) with therapy administered on Days 1, 8, and 15 of a 28-day cycle. Although the majority of patients (22 patients [71%]) were treated using this weekly regimen, 9 patients were treated using a once-every-3-weeks regimen (paclitaxel at a dose of 175–200 mg/m^2 and carboplatin at an AUC of 5). The latter regimen was used primarily for patient convenience (to eliminate the need to travel a long

TABLE 1
Baseline Characteristics

Total number	31
Median age in yrs	59.6
Male gender	18 (56%)
Disease classification	
M1a	3 (9.6%)
M1b	2 (6.4%)
M1c	26 (84%)
Prior therapy (for metastatic disease)	
All	2 (median)
Chemotherapy	1 (median)
TMZ or DTIC	29 (94%)
Immunomodulatory therapy	11 (35%)
Prior adjuvant immunotherapy (interferon or GM-CSF)	5 (16%)

TMZ: temozolomide; DTIC: dacarbazine; GM-CSF: granulocyte-macrophage–colony-stimulating factor.

distance to the treatment facility). Toxicity was tolerable in the majority of patients, and only four patients required dose reductions or cessation of therapy in response to toxic events. One patient was lost to follow-up after receiving the first dose of chemotherapy, and we were unable to ascertain any information regarding responses to therapy (this patient was included in the subsequent analyses as a nonresponder). Eight patients remained on therapy at the time of last follow-up.

The median duration of therapy for the entire cohort was 3 months. Because therapy was discontinued in view of disease progression, this figure also represents the median time to disease progression. The median duration of follow-up for the entire cohort of 31 patients was 5.7 months. The overall median survival for entire group, measured from the first day of therapy, was 7.8 months (Fig. 1). These data are summarized in Table 2. The first evaluation after the initiation of therapy usually was performed after 1 cycle (3 or 4 weeks), but was performed only after 2 cycles in some patients. Follow-up imaging studies to confirm responses were not obtained in a prespecified manner, but were usually obtained as clinically indicated, usually after an additional two cycles. Response data were not available in the single patient who did not return after her first dose of chemotherapy. One other patient was noted to have stable disease in her medical records. However, as we were unable to adequately document the status of her disease for this review, she was counted among the nonresponders. No patient had a complete response to therapy. Fourteen patients (45%) demonstrated a clinical benefit with PC chemotherapy, with 8 patients (26%) achieving a partial response and 6 patients (19%) having stable disease. The clinical benefit in these patients lasted 2.5–7.3 months. Responses were noted in a variety of metastatic sites including peritoneal deposits, pulmonary parenchymal lesions, and malignant ascites.

Twelve patients (39%) were found to have progressive disease at the first evaluation and therapy was withdrawn. Apart from these 12 patients who developed disease progression early on, 3 additional patients (10%) were clinically noted to have a 'mixed response.' All three of these patients in actuality had disease progression by standard clinical criterion because they had progressive disease at one site, with concurrent stable disease at the other sites of involvement. They were treated with local therapies targeting the sites that progressed with the goal of symptom palliation. The local therapies used were stereotactic radiation for brain metastases, hepatic artery embolization for a progressive liver lesion, and axillary radiation for symptomatic lymph node growth. After the completion of these therapies, and with consideration of the overall clinical situation, PC therapy was reinstituted in all three patients. However, all 3 patients developed progressive disease at multiple tumor locations within 6 weeks after the reinitiation of PC, and treatment was discontinued.

Toxicity leading to significant dose reduction or cessation of therapy occurred in only four patients. All these toxic events occurred in patients who received weekly therapy. Toxicities included peripheral neuropathy, myelosuppression, and diarrhea. Three of these patients were able to continue on therapy with appropriate dose reductions and delays. One patient who had a partial response to PC had to discontinue therapy because of severe neuropathy. This was attributed to paclitaxel, and this agent was discontinued. Subsequently, he was switched to a regimen of docetaxel and carboplatin, and continued to maintain tumor response. After 7 weeks of therapy with this new regimen, he developed an allergic reaction to carboplatin, requiring discontinuation of carboplatin.

The 14 patients who derived a clinical benefit (partial response or stable disease) were able to receive PC for a median of 5.6 months (median time to disease progression) (range, 2.5–7.3 mos), with 8 patients continuing to receive therapy at the time of last follow-up. Thirteen (93%) of the 14 patients had been previously treated with TMZ or DTIC. The majority of the patients (11 of the 14 patients) who had achieved a clinical benefit were treated with the weekly regimen. Viewed differently, half of those treated with the weekly regimen had a clinical benefit (i.e., 11 of 22 patients), whereas only approximately one-third of the patients treated with the every-3-weeks regimen (3 of 9 patients) had a clinical benefit. The overall median

TABLE 2
Results of Therapy

	All patients	Responders	Stable disease	Nonresponders[a]
Total no. of patients	31	8	6	17
Median no. of individual organ sites involved (range)	3 (1–6)	3.5 (1–5)	3.5 (1–6)	3 (1–6)
Median no. of prior systemic therapies (range)	2 (1–4)	2 (1–3)	1.5 (1–2)	1 (1–4)
Prior TMZ or DTIC chemotherapy	29 (94%)[b]	7 (88%)[b]	6 (100%)[b]	16 (94%)[b]
Prior immunotherapy (for systemic disease)	11 (35%)[b]	5 (63%)[b]	2 (33%)[b]	4 (24%)[b]
Weekly regimen used	22 (77%)[b]	7 (88%)[b]	4 (66%)[b]	11 (65%)[b]
Median duration of therapy in mos	3	5	7	1
Median overall survival in mos	7.8	Not reached	14	3
Total median follow-up in mos	5.7	Not reached	12.5	2.6

TMZ: temozolomide; DTIC: dacarbazine.

[a] Includes data regarding patients noted to have disease progression or a mixed response, or who were lost to follow-up or an unverifiable response.

[b] Percentages refer to the correlation with the column total.

survival of this group was 13.8 months, which was longer than the median survival (3 mos) reported for the rest of the group (i.e., those who developed disease progression, had a mixed response, or were lost to follow-up).

The characteristics of the 14 patients who had a clinical benefit were analyzed to determine whether prognostically important disease- and patient-related variables were disproportionately represented in this group. The majority of the patients in this group (13 patients [93%]) had failed prior TMZ or DTIC therapy. When compared with the patients who did not derive a clinical benefit, these patients had similar age and stage distributions. Likewise, patients in each group were similar with regard to the number of previous therapies received (median of 2, and a mean of 1.6 in both groups). The proportion of patients who had previously failed TMZ therapy was similar in this group when compared with the entire cohort. The median number of individual organ sites involved with metastases in the group with clinical benefit was 4 (mean 3.5 organ sites; range, 1–6 organ sites), whereas the corresponding value in the patients who developed progressive disease was 3 (mean 3 organ sites; range, 1–6 organ sites). None of these differences between the two groups were statistically significant. In summary, we could not identify any statistically significant differences in patient/tumor characteristics that could account for the observed partial responses and/or cases of stable disease noted in the 14 patients who gained a clinical benefit from PC therapy.

An independent observer evaluated responses using RECIST criteria[20] in all patients for whom adequate imaging studies were available. This reviewer was unaware of the response determination by the treating physicians. We were able to adequately confirm responses using RECIST criteria in all of the patients except five. These included three patients who were noted to have disease progression, one patient who was lost to follow-up, and another patient who was noted in her medical records to have stable disease. In the latter patient, we were unable to review the imaging studies and therefore included her among the nonresponders in the current analysis.

At the time of last follow-up, 16 patients had died of progressive disease. Fifteen patients were alive, 8 of whom continued to receive the PC combination; 4 patients were receiving other therapies (as part of clinical trials) after developing disease progression while receiving PC, and the status of 3 patients was unknown.

DISCUSSION

The current study data suggest that the PC combination is an active regimen in patients with melanoma who have progressed while receiving TMZ or DTIC. Previous prospective studies testing PC have suggested a small degree of activity in melanoma.[23–26] We believe the current study adds to this body of knowledge.

The PC combination for the treatment of MM patients has been investigated in two recently reported prospective trials (Table 3).[25,26] The rationale for combining these agents has been: 1) platinum-alkylating agents have been demonstrated to have a definite (though minor) degree of activity in melanoma[16,27–29]; 2) taxanes were demonstrated in early clinical trials to have a minor activity in melanoma[30–33]; 3) in vitro and clinical data suggest synergy between these drugs when used in combination in a wide variety of tumors, including melanoma[23,24,34–40]; and 4) the toxicity profiles of these agents do not overlap. Early clinical trials testing the combination of

TABLE 3
Comparison between the Reports of Using Paclitaxel and Carboplatin in Patients with Metastatic Melanoma

	Current study	Hodi et al.[26]	Zimpfer-Rechner et al.[25]
No. of patients	31	15	19
Median age in yrs	59.6	54.0	57.6
Median no. of prior systemic therapies for metastatic disease	2	0	1[a]
Median no. of previous chemotherapy regimens	1	0	See above
Previous immunotherapy (no. of patients)	11 (35%)	5 (33.3%)	See above
Clinical response			
SD	6 (19%)	7 (47%)	3 (19%)
PR	8 (26%)	3 (20%)	0
Median duration of clinical benefit in wks	12	11	8
Median overall survival in wks	31	36	30

SD: stable disease; PR: partial response.
[a] This was a second-line therapy trial in which patients had failed one previous systemic therapy of any kind (chemotherapy, immunotherapy, or chemoimmunotherapy) for metastatic disease.
Note: In each of these studies, the doses and schedules of the paclitaxel and carboplatin combination used were different.

paclitaxel with platinum agents in patients with a variety of diseases noted some responses among melanoma patients.[23,24,27] In a U.S. Phase II study of PC in patients with MM, 17 therapy-naive patients were treated with a 3-weekly regimen of paclitaxel (at a dose of 175 mg/m^2) and carboplatin (AUC of 7.5). Fifteen patients were evaluable in this group; partial responses were noted in 3 patients (20%) and 7 patients (47%) had stable disease, whereas the remaining patients developed disease progression. The average number of cycles administered was 3.5 and the median survival was 9 months. The regimen was relatively toxic, with a majority of patients (73%) experiencing common toxicity criteria (v3) Grade III–IV hematologic toxicity. The authors concluded that further exploration of this regimen was justified based on the responses noted.[26] The German Dermatologic Cooperative Oncology Group (DeCOG) subsequently reported on the results of another Phase II study of weekly PC used as second-line therapy in patients with metastatic melanoma. The regimen utilized paclitaxel (at a dose of 80 mg/m^2) and carboplatin (at a dose of 200 mg/m^2) administered weekly for 6 weeks using an 8-week treatment cycle. Of the 16 patients who received this combination, 3 patients (19%) had stable disease that lasted for 16 weeks. The trial was discontinued because the response rate was deemed to be too low to justify continuing with the trial.[25]

The toxicity of the PC combination may be dependent on the schedule utilized.[41–45] The most commonly used regimen of PC involves therapy delivered every 3 weeks, which is associated with a high rate of hematologic toxicity (as noted by Hodi et al.[26]). The administration of lower-dose, weekly therapy with these agents appears to be better tolerated, with no loss of efficacy noted in patients with other tumor types.[41,42,46] The weekly dosing schedule allows the administration of these agents in the elderly and in heavily pretreated patients, characteristics typical of our target population.[42] Based on these data, it has been our preference to use the weekly regimen. Because the majority of patients in the current study were treated with the weekly regimen, the serious toxic events paradoxically appear to be overrepresented in this group. Weekly therapy also allows for the administration of higher cumulative doses (i.e., higher dose intensity) of paclitaxel, which has been suggested to result in increased efficacy.[47,48] However, currently there is insufficient data on the use of paclitaxel in melanoma patients to conclude that paclitaxel dose intensity corresponds to response rates to therapy.

The obvious limitation of the current study is the retrospective nature of the collected data. Our study is potentially subject to the following biases: selection bias, attrition bias, and response-ascertainment bias. We have meticulously attempted to correct for these biases to minimize their impact on our conclusions. Because patients were selected based on physician preference, selection bias could not be eliminated. However, physician preference was based on the fact that these patients were previously treated (the majority had failed TMZ or DTIC therapy), did not have any other therapy options, and were considered to be terminally ill. These factors generally identify a poor prognostic group (with an expected outcome that is usually worse than average), and therefore would be expected to, if at all, negatively influence our results. Moreover, the group that appeared to derive a clinical benefit did not appear to differ significantly from the remainder of the patients with regard to several important baseline variables. To reduce bias that may be

introduced due to patient attrition, we attempted to obtain all documentation regarding responses from patients who were lost to follow-up. However, adequate confirmation of response was not available in five patients, three of whom were noted to have developed disease progression, one of whom was lost to follow-up, and one of whom had achieved stable disease per her medical records. The latter patient was grouped with the nonresponders for this analysis. Finally, to minimize the impact of response ascertainment bias, we used an unbiased/blinded observer to adjudicate clinical responses based on RECIST criteria. Considering these limitations, the results of the current study clearly suggest that the PC combination has a beneficial role when used for salvage therapy in patients with MM. These findings are especially interesting from a clinical standpoint, because the clinical benefits occurred in patients who progressed while receiving TMZ or DTIC therapy, a group of patients with no standard therapy option.

The current study results compare favorably with the data from the Phase III study comparing TMZ and DTIC.[4] In this Phase III study, the progression-free and overall survival in chemotherapy-naive patients treated with TMZ were 1.9 months and 7.9 months, compared with 3.0 months and 7.8 months, respectively, in the current study.

It is also pertinent here to review the results of the previously mentioned Phase I/II trial which tested the three-drug combination of the Raf-kinase inhibitor sorafenib with PC in melanoma patients. These results were promising, with high rates of disease response and stabilization noted.[19] The paclitaxel dose used in this study was 225 mg/m^2, whereas carboplatin was dosed to achieve an AUC of 6. PC was delivered using an every-3-weeks cycle in this study. The therapy was noted to be well tolerated, with no unexpected adverse events reported (although to our knowledge no details had been published at the time of last follow-up). Comparisons between the results of this Phase I/II study and our experience, as presented herein, are worth making, but need to be interpreted with caution due to differences in schedules and therapy used, as well in the methodology of the studies. The results of both studies suggest that the combination of PC has definite activity in melanoma. The clinical benefit rates appear to be at least as good as (if not better than) most other therapies that may be considered standard for metastatic melanoma. These data clearly provide the justification for further testing this drug combination in the first-line setting. However, the question regarding which regimen (PC delivered weekly or once every 3 weeks) is more effective remains unanswered, although it would appear from previous experience with PC that that the weekly regimen is better tolerated. We speculate that because the clinical benefit rates noted in the Phase I/II study are higher than observed in our report, sorafenib may indeed offer an additional therapeutic benefit when added to the PC component of the regimen. We eagerly await the answer to this question in the upcoming Phase III study comparing the three-drug regimen with PC alone for the first-line therapy of patients with MM.

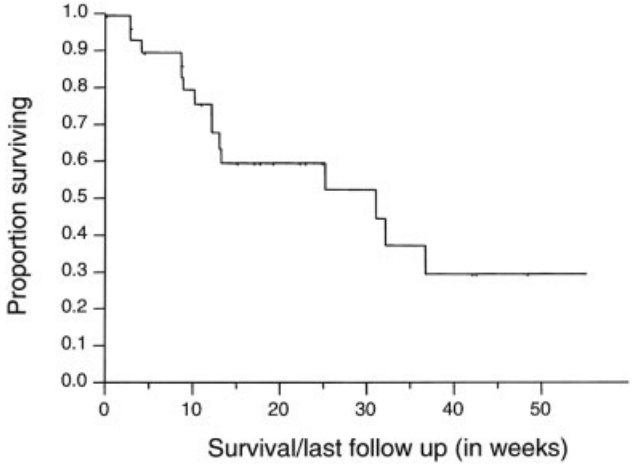

FIGURE 1. Kaplan–Meier curve demonstrating the overall survival of patients treated with the combination of paclitaxel and carboplatin.

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