Cancer Chemother Pharmacol (2009) 64:161–167
DOI 10.1007/s00280-008-0861-0

ORIGINAL ARTICLE

Phase I study of the combination of docetaxel, temozolomide and cisplatin in patients with metastatic melanoma

Kevin B. Kim · Wen-Jen Hwu · Nicholas E. Papadopoulos · Agop Y. Bedikian · Luis H. Camacho · Chaan Ng · Ingrid M. Hernandez · Angela M. Frost · Monica A. Jack · Patrick Hwu

Received: 11 June 2008 / Accepted: 11 October 2008 / Published online: 11 November 2008

Abstract
Purpose In a search for more effective combination chemotherapy for the treatment of metastatic melanoma, we conducted a phase I trial of a novel combination of docetaxel, temozolomide, and cisplatin.
Methods Patients with inoperable or recurrent metastatic melanoma with a Zubrod performance status of 2 or less and adequate organ function were eligible. The dose of docetaxel was escalated between cohorts of patients, and the doses of temozolomide and cisplatin were fixed. A standard 3 + 3 dose escalation design was used to determine the maximum tolerated dose (MTD).
Results Among 23 patients who were enrolled, 21 were evaluable for toxicity. Eighteen patients (78%) had stage IV-M1c disease. The dose-limiting toxicities were myelosuppression and pulmonary embolism. The MTD was 30 mg/m^2 docetaxel on days 1, 8, and 15 when given with 150 mg/m^2 temozolomide on days 1–5, and 20 mg/m^2 cisplatin on days 1–4, repeating every 4 weeks. Among 19 patients evaluated for response, 6 (32%) had partial responses and 5 (26%) had stable disease. Among 14 chemo-naive patients, 6 (43%) had a partial response and 4 (29%) had stable disease. Nine patients developed brain metastases by the time of the last follow-up evaluation, and the median time to brain metastases for all 19 evaluable patients has not been reached.
Conclusions This combination was well tolerated and appears to be a promising treatment for patient with metastatic melanoma.

Keywords Phase I · Melanoma · Chemotherapy · Docetaxel · Temozolomide · Cisplatin

Introduction

Systemic therapy for metastatic melanoma remains disappointing. The median survival is not improved significantly with the currently available chemotherapy regimens [1]. The rates of clinical response to most single agents, such as dacarbazine, temozolomide, vinca alkaloids, platinum analogues, and taxanes, are less than 15% [2–6]. Combinations of cytotoxic drugs have produced response rates of up to 40% [7–9]. For example, dacarbazine-based combinations, such as cisplatin, vinblastine, and dacarbazine and the Dartmouth regimen (cisplatin, carmustine, dacarbazine, and tamoxifen) produce response rates superior to those of dacarbazine alone. However, these regimens are limited by the short duration of responses and low complete response (CR) rates. Although combining cytotoxic chemotherapy with the biologicals interleukin-2 and alpha-interferon (i.e., biochemotherapy) has resulted in overall response rates of 40–60% with about 10–20% CRs, biochemotherapy cannot be offered to a substantial proportion of patients with metastatic melanoma because of their age, concomitant illnesses, or lack of marrow reserve [10–15]. Furthermore, recent phase III trials have not demonstrated a clear

This study was supported by Sanofi-Aventis.

K. B. Kim (✉) · W.-J. Hwu · N. E. Papadopoulos · A. Y. Bedikian · L. H. Camacho · I. M. Hernandez · A. M. Frost · M. A. Jack · P. Hwu
Department of Melanoma Medical Oncology, Unit 430, The University of Texas M. D. Anderson Cancer Center, 1515 Holcombe Blvd., Houston, TX 77030, USA
e-mail: kkim@mdanderson.org

C. Ng
Department of Diagnostic Radiology, The University of Texas M. D. Anderson Cancer Center, Houston, TX, USA

survival benefit from biochemotherapy compared with conventional chemotherapy in patients with metastatic melanoma [2, 16, 17]. As demonstrated in most of the phase III studies of the combination regimens, the incidence of toxicity increases with an increased number of drugs combined compared to a single drug regimen or a combination of lesser number of drugs, without improvement in a median survival. Therefore, new chemotherapy regimens are needed that have less morbidity than biochemotherapy, but more potent antitumor activity than current standard chemotherapies.

In several phase II trials testing the efficacy of paclitaxel or docetaxel as a single agent for advanced melanoma, response rates were 13–16% [4–6]. Recently, we evaluated a taxane-based combination regimen (cisplatin, paclitaxel and dacarbazine) at The University of Texas M. D. Anderson Cancer Center. Among 46 patients with metastatic melanoma evaluated for response, 21 (46%) had a clinical response [18]. The use of a taxane instead of vinblastine in the traditional cisplatin–vinblastine–dacarbazine, a combination regimen thus appeared to produce superior clinical efficacy in our small study.

Temozolomide is an oral alkylating agent, that, like dacarbazine, is metabolized to the active alkylating agent, 5-(3-methyltriazen-1-yl)imidazole-4-carboximide (MTIC). However, temozolomide converts to MTIC spontaneously, unlike dacarbazine, which requires metabolic activation [19]. In a large randomized phase III trial in patients with metastatic melanoma, temozolomide was equivalent to dacarbazine in clinical efficacy, but had a slight advantage in quality of life [2]. Another advantage of temozolomide over dacarbazine is that temozolomide penetrates the blood–brain barrier [20, 21], and thus may have activity against melanoma metastases in the central nervous system. Therefore, brain metastases might be delayed or even inhibited by temozolomide administration.

We conducted a dose-escalating phase I study of the combination of docetaxel, temozolomide and cisplatin in patients with metastatic melanoma. We designed this trial to find the maximum tolerated dose (MTD) of docetaxel, while combined to fixed doses of temozolomide and cisplatin as these two agents are more widely used drugs for the treatment of metastatic melanoma. Docetaxel was chosen in the combination instead of paclitaxel unlike our previous phase I trial, because of the change in the study sponsor.

Patients and methods

Patient selection

To be eligible for the study, patients had to have a histologically confirmed diagnosis of advanced or inoperable melanoma and clinically measurable metastases. Other inclusion criteria were a Zubrod performance status score of 2 or less and adequate hematologic (absolute neutrophil count $\geq$1,500/μL; platelet count $\geq$100,000/μL) and renal functions (serum creatinine level within the normal limit). Patients must have had adequate hepatic function with a normal serum bilirubin level. Patients with increased serum transaminases levels up to 2.5 times the upper limit of normal were allowed to enter the study if their serum alkaline phosphatase level was normal. Those with an increased serum alkaline phosphatase level up to four times the upper limit of normal were also allowed if their serum transaminases levels were normal. Both chemo-naive and previously-treated patients were enrolled. However, patients who had previously received all three study drugs or related drugs (taxanes, temozolomide, and platinums) were excluded. Patients with uncontrolled brain metastases (symptoms due to brain metastases or who required steroidal or anticonvulsant drugs for the management of brain metastases) were ineligible, but those with controlled, asymptomatic brain metastases (no evidence of progression in brain metastases for at least 3 months after complete surgical tumor resection, stereotactic radiosurgery, or whole-brain irradiation) were allowed to participate. Patients with clinically symptomatic cardiac or pulmonary disease were excluded.

The protocol for this study was approved by the Institutional Review Board of The University of Texas M. D. Anderson Cancer Center, and all of the patients gave written informed consent before enrollment, in accordance with institutional and government guidelines.

Treatment plan

For this study, the dose of docetaxel was escalated between patient cohorts, and doses of temozolomide and cisplatin were fixed. The doses of docetaxel, temozolomide, and cisplatin in the first patient cohort were 20, 150, and 20 mg/m^2, respectively. Table 1 lists the dose escalation scheme. Docetaxel was administered intravenously over 1 h on days 1, 8, and 15; temozolomide was administered orally on days 1–5; and cisplatin was administered intravenously on days 1–4. Each treatment cycle was repeated every 4 weeks. The maximum number of treatment cycles planned was six; however, patients who continued to have disease regression were allowed to receive more than six cycles as long as they tolerated treatment well.

Before each treatment cycle began, patients had to have recovered from myelosuppression as indicated by an absolute neutrophil count of >1,500/μL and a platelet count of >100,000/μL. In addition, the hepatic function must have recovered [total bilirubin $\leq$1.0 mg/dl (ULN), alkaline phosphatase level $\leq$300 IU/l (2.5 times the ULN), and serum aspartate transaminase level $\leq$75 IU/l (1.5 times the

Table 1 Dose escalation scheme

Dose level[a]	Daily dose (mg/m^2)		
	Docetaxel (days 1, 8, 15)	Temozolomide (days 1–5)	Cisplatin (days 1–4)
−1	15	150	20
0[a]	20	150	20
1	25	150	20
2[b]	30	150	20
3	35	150	20

[a] Starting dose level

[b] Maximum tolerated dose: this dose level is recommended for a phase II study

ULN)]. Patients were premedicated with dexamethasone and with antiemetics consisting of a $5HT_3$ antagonist with or without lorazepam. Prophylactic administration of growth factors to prevent neutropenia was allowed except during the first treatment cycle; however, therapeutic administration of growth factors for treatment-related neutropenia was permitted at any time.

Intrapatient escalation of dose levels was not permitted. For a given patient, dose reduction was permitted on the basis of toxicities experienced during the previous cycle. Only the dose of docetaxel was reduced. The dose(s) was reduced to 1 level lower if the patient did not recover within 1 week after day 1 of the next scheduled treatment for cycles 2 and beyond. The dose level was not returned to the original level in subsequent cycles given to that patient.

Patients were removed from the study for any of the following reasons: (1) withdrawal of consent, (2) disease progression, (3) unacceptable toxicity, (4) requirement of dose reductions of more than two levels due to toxicity, (5) treatment delay of more than 21 days due to toxicity, and (6) violation of the study protocol or patient noncompliance.

Toxicity evaluation

Toxicity was assessed according to the US National Cancer Institute Common Terminology Criteria for Adverse Events v3.0 (available at: https://webapps.ctep.nci.nih.gov/webobjs/ctc/webhelp/welcome_to_ctcae.htm). Patients were evaluated every 4 weeks with vital sign measurements, physical examination, and a review of toxicity. Complete blood counts with differential counts were done for all patients once a week, and serum electrolyte levels, creatinine levels, liver function, and phosphorus and magnesium levels were measured at least once every 4 weeks while they were in the study.

Dose-limiting toxicity (DLT) was defined as the toxicity observed during the first cycle as follows: (1) grade 4 neutropenia with infection or fever (temperature $\geq$38.3°C); (2) grade 4 neutropenia lasting >7 days; (3) platelet counts <20,000/μl; (4) grade 3 or 4 nonhematologic toxicity, except manageable nausea, vomiting, diarrhea, or fatigue; (5) delay of chemotherapy for >7 days owing to toxicity; or (6) administration of less than 75% of the planned dose of docetaxel owing to toxicity.

Response evaluation

Responses were evaluated after every 2 cycles of the treatment using computed tomography (CT) and/or magnetic resonance imaging and, in the case of clearly visible cutaneous lesions, by direct visual measurement using a ruler. For patients with skin lesions, photographs of the skin lesions were done at baseline and after every 2 cycles. Patients who achieved a clinical response underwent repeat imaging studies at least 4 weeks later for confirmation of response.

In our study, the WHO response evaluation criteria were used to compare with the clinical efficacy of our previous phase II study of the combination of cisplatin, paclitaxel and dacarbazine, which also used the same response evaluation criteria [18]. A CR was defined as the disappearance of all clinical and imaging evidence of all tumors for a minimum of 4 weeks. A partial response (PR) was defined as a reduction of more than 50% in the sum of the products of the largest perpendicular diameters of all measurable lesions for at least 4 weeks. Progressive disease (PD) was defined as 25% or greater increase in the sum of the products of the largest perpendicular diameters of all measurable lesions or the appearance of any new lesion within the first 2 cycles (8 weeks) after the registration. All other responses were categorized as stable disease (SD). Overall clinical response included both CRs and PRs.

Statistical analysis

The primary objective of this phase I study was to determine the MTD of docetaxel in combination with temozolomide and cisplatin in patients with metastatic melanoma. The MTD was defined as the highest dose at which the incidence of DLT was less than 33%. A standard 3 + 3 dose escalation design with five predefined dose levels was used to determine the MTD. We planned to have at least six patients enrolled at the MTD.

The duration of clinical responses was measured from the time a clinical response was first achieved until the time of disease progression. The durations of time to progression and overall survival were measured from the start of treatment.

Results

Patient characteristics

From December 2004 to August 2006, 23 patients were enrolled and treated in the study. The pretreatment characteristics of the patients are listed in Table 2. The median age of the patients was 58 years, and the median Zubrod performance status score was 1. One patient had metastatic melanoma of choroidal origin. Six patients (26%) had received prior systemic therapy for metastatic disease. One patient had brain metastases that had been treated and controlled with gamma-knife surgery prior to that patient's entering the study.

Twenty-one patients were evaluable for toxicity, and 19 were evaluable for response. Three patients at dose level 3 did not complete the first cycle of treatment because of an inability to take temozolomide as prescribed (noncompliance), the decision to receive alternative/naturopathic medicine, or the decision to discontinue treatment owing to financial concerns. One patient at dose level 2 decided not to continue treatment during the second cycle, because she could not travel to the study center as required by the protocol.

Table 2 Patient characteristics

Characteristic	No. of patients (%)
Total patients enrolled in the study	23
Sex	
Male	13 (57)
Female	10 (43)
Age	
Median	58 years
Range	37–74 years
Zubrod performance status	
0	8 (35)
1	14 (61)
2	1 (4)
Disease stage	
IIIC	1 (4)
IV	
M1a	1 (4)
M1b	3 (13)
M1c	18 (78)
Serum lactate dehydrogenase level	
Normal	10 (44)
Higher than upper limit of normal	12 (52)
Unknown	1 (4)
Prior treatment	
None	13 (57)
Interferon therapy (adjuvant)	5 (22)
Biologic therapy	2 (9)
Chemotherapy	5 (22)
Radiation	6 (26)
Site of metastases	
Dermis/subcutaneous/soft tissue	11 (48)
Lymph nodes	14 (61)
Lung	14 (61)
Liver	6 (26)
Bone	4 (17)
Brain	1 (4)
Other visceral organs	14 (61)
Number of organs with metastases	
Median	3
Range	1–5

Treatment

The 23 patients received a total of 84 cycles of treatment, with a median of 2 cycles per patient (range, <1–8). Three, six, six and eight patients were treated at dose levels 0, 1, 2 and 3, respectively. A reduction of docetaxel was required at least once during the course of treatment in 2, 3, and 4 patients at dose levels 1, 2, and 3, respectively.

The dose intensity of docetaxel, defined as the proportion of a dose administered over the total planned dose, was as follows: 100, 92, 96, and 79% at dose levels 0, 1, 2, and 3, respectively. The dose intensity of docetaxel at dose level 3 would have been 86% if the three patients who did not complete the first treatment cycle owing to reasons other than disease progression or intolerable toxicity were excluded from the analysis.

Toxicity

The most common toxic effects were fatigue (100%), lymphopenia (90%), anemia (90%), alteration in taste and/or smell (81%), nausea (71%), thrombocytopenia (71%), vomiting (62%), skin rash (62%), headache (62%), neutropenia (62%), arthralgia/myalgia (52%), peripheral neuropathy (52%), edema (43%), cough (43%), watery eyes (43%), and diarrhea (38%). Table 3 summarizes the grade 3 and 4 toxic effects by dose level. Three patients had DLT during the first cycle: one at dose level 2 and two at dose level 3. At dose level 3, one patient had a pulmonary embolism, and another patient received less than 75% of the planned docetaxel dose owing to grade 4 neutropenic infection during the first cycle. The patient with DLT at dose level 2 had a grade 3 non-neutropenic infection (*Staphylococcus capitis* in blood) with lymphopenia, which required intravenous antibiotics. Because of the infection, the second cycle of chemotherapy had to be delayed for more than 7 days.

Table 3 Grade 3/4 toxicities

Toxicity	No. of evaluable patients, by dose and grade of effect							
	Level 0 ($n = 3$)		Level 1 ($n = 6$)		Level 2 ($n = 6$)		Level 3 ($n = 6$)	
	Gr 3	Gr 4	Gr 3	Gr 4	Gr 3	Gr 4	Gr 3	Gr 4
Neutropenia	0	0	2	1	1	1	2	1
Infection with neutropenia	0	0	0	0	0	0	0	1[a]
Lymphopenia	3	0	4	1	1	0	1	1
Anemia	0	0	1	0	1	0	0	0
Thrombocytopenia	0	0	1	1	1	0	1	0
Infection with normal neutrophil counts	0	0	0	0	1[a]	0	0	0
Vomiting	0	0	1	0	0	0	1	0
Diarrhea	0	0	1	0	0	0	0	0
Pulmonary embolism	0	0	0	1	0	1	0	1[a]
Fatigue	0	0	0	0	1	0	0	0

[a] Denotes the dose-limiting toxicity, as defined in the protocol, observed during the first cycle

Because two of the six DLTs occurred at dose level 3, dose level 2 was selected as the MTD.

Responses

Among 23 treated patients, 4 could not be evaluated for response because of early treatment discontinuation for reasons other than toxicity or disease progression, as described above. Among the 19 patients evaluated for response, 6 (32%) had a PR, and 5 (26%) patients had SD. The median duration of follow-up was 10.4 months among all 19 patients (range, 1.8–34.1+ months), the median time to progression was 5.2 months (range, 1.7–22.7 months), and the median overall survival duration was 10.4 months (range, 1.8–34.1+ months).

Among the six patients with a PR, the median duration of response was 5.7 months (range, 5.0–21.5 months). One of the responders had an ongoing PR that continued for at least 18.7 months (the time of last follow-up). The sites of disease that responded among the six patients with PR were subcutaneous tissue/skin (1 patient), lymph nodes (6 patients), lungs (4 patients), adrenal gland (2 patients), and liver (1 patient). The median duration of disease control among five patients with stable disease was 7.2 months (range, 4.3–9.1 months).

None of the five patients who had previously received systemic chemotherapy had a disease response, and there was only one who had SD. Among the 14 chemotherapy-naive patients evaluable for response, six had PRs (43%), four had SD (29%), and four had PD (29%).

Table 4 lists the responses by dose level. At dose level 2, four of five patients evaluable for response had disease control for at least 8 weeks (3 PRs and 1 SD).

Five patients had disease progression in the brain while receiving the study treatment, and four additional patients ultimately had disease progression in the brain after they were taken off the study. The median time to disease progression in the brain among the 19 evaluable patients has not been reached.

Table 4 Response to treatment

Dose level	No. of patients				
	Total number	Partial response	Stable disease	Progressive disease	Not evaluable
0	3	1	0	2	0
1	6	1	2	3	0
2	6	3	1	1	1
3	8	1	2	2	3

Seven patients remained alive at the time of last patient contact, conducted between October 2007 and December 2007. The duration of overall survival for these patients ranged from 14.3 to 34.1 months.

Discussion

Although great strides have been made in the investigation of novel therapies for melanoma, cytotoxic therapy and immunotherapy remain the mainstays of treatment in patients with advanced melanoma. Our study was designed to determine the MTD of docetaxel in combination with temozolomide and cisplatin, to test the safety and, to a limited degree, clinical efficacy of this novel combination for metastatic melanoma. In this study, a weekly dosing schedule of docetaxel was used, because this schedule is considered to be better tolerated and with a similar clinical efficacy, compared to a dosing schedule of once in 3- or 4-week cycle [22]. We found that the MTD of docetaxel was 30 mg/m^2 (days 1, 8, and 15) when given with temozolomide

(150 mg/m^2 on days 1–5) and cisplatin (20 mg/m^2 on days 1–4) every 4 weeks. The DLTs were infection with or without neutropenia, and pulmonary embolism. Neutropenia was anticipated on the basis of the toxicity profile of each drug. Although myelosuppression occurred commonly, most affected patients were able to continue treatment with the support of growth factors. One patient had an asymptomatic pulmonary embolism that was discovered during the first cycle of treatment. Given that the risk of developing venous thrombosis is significantly increased in patients with active metastatic malignancy, this pulmonary embolism might not have resulted from the treatment. For instance, Gladish and colleagues reported that the incidence of pulmonary embolism was 10% in 41 patients with metastatic melanoma. The rate of pulmonary embolism in our study was 15% (3 of 21 patients), and the pulmonary embolism occurred in the other 2 patients (one during the 4th cycle on dose level 1 and the other during the 5th on dose level 2) was more likely related to the disease progression, although we cannot rule out its relationship to the study drugs [23]. Regardless, it would be reasonable to include the occurrence of embolism as a DLT, because it occurred within 4 weeks of the start of treatment. Occurrences of peripheral neuropathy were not as severe as anticipated from a combination regimen that included docetaxel and cisplatin: there was no grade 3 or 4 peripheral neuropathy, and, among six patients treated at the MTD, including four who received six cycles of treatment, only one patient experienced a grade 2 neuropathy. The weekly dosing schedule of docetaxel and the lower daily dosing schedule, rather than a higher 1-day dosing schedule, of cisplatin might explain the mild degree of peripheral neuropathy.

Although clinical efficacy was not a primary end point of this study, this combination regimen appeared to be active in our patient population. It is interesting to note that 6 of 14 evaluable chemotherapy-naive patients had a clinical response (PR), and four more had SD. In addition, at the MTD, which is the recommended dose for a phase II study, four of five patients evaluable for response had disease control for at least 8 weeks; three of them had a PR.

The combination of temozolomide and cisplatin in patients with metastatic melanoma has been tested in a number of phase I and phase II trials. The overall objective response rates ranged from 29 to 49% in those studies [24–26]. Our study, which added docetaxel to the combination, was a phase I trial, and only five patients treated at the MTD were evaluable for response. Therefore, we cannot draw any conclusions about whether docetaxel provided a benefit over what would have been achievable with temozolomide and cisplatin alone, although such a benefit is suggested by our results. A randomized comparative trial would be needed to determine the relative benefit of the 3-drug combination versus the 2-drug combination.

In our study, nearly a half of the 19 evaluable patients ultimately had disease progression in the brain, and five of these had disease progression in the brain while receiving the combination therapy. Although the number of patients in our study was too small for us to draw a firm conclusion, the dose of temozolomide that we used in combination with docetaxel and cisplatin did not appear to benefit patients in terms of preventing brain metastases.

The clinical activity and safety of the combination regimen in our study justify further investigation with a randomized phase III trial, which compares the clinical efficacy of this combination with that of standard therapy. It would also be interesting to combine temozolomide and cisplatin with albumin-conjugated paclitaxel (Abraxane) to test whether that combination would result in superior clinical efficacy but less severe myelosuppression, since a phase II study of Abraxane as a single agent showed a great promise in patients with metastatic melanoma [27]. In addition, targeted drugs, such as Bcl-2 antisense or other targeted small molecules, might be incorporated to improve the regimen's clinical activity.

Acknowledgments The authors thank Ms. Virginia M. Mohlere for her editorial assistance.

References

1. Anderson CM, Buzaid AC, Legha SS (1995) Systemic treatments for advanced cutaneous melanoma. Oncology (Huntingt) 9:1149–1158 discussion 1163–1144, 1167–1148
2. Middleton MR, Grob JJ, Aaronson N et al (2000) Randomized phase III study of temozolomide versus dacarbazine in the treatment of patients with advanced metastatic malignant melanoma. J Clin Oncol 18:158–166
3. Atkins MB (1997) The role of cytotoxic chemotherapeutic agents either alone or in combination with biological response modifiers. In: Kirkwood JK (ed) Molecular diagnosis, prevention and therapy of melanoma. Marcel Dekker, New York, p 219
4. Einzig AI, Hochster H, Wiernik PH et al (1991) A phase II study of taxol in patients with malignant melanoma. Invest New Drugs 9:59–64
5. Legha SS, Ring S, Papadopoulos N, Raber M, Benjamin RS (1990) A phase II trial of taxol in metastatic melanoma. Cancer 65:2478–2481
6. Bedikian AY, Weiss GR, Legha SS et al (1995) Phase II trial of docetaxel in patients with advanced cutaneous malignant melanoma previously untreated with chemotherapy. J Clin Oncol 13:2895–2899
7. Buzaid AC, Legha SS, Winn R (1993) Cisplatin, vinblastine, and dacarbazine versus dacarbazine alone in metastatic melanoma: preliminary results of a phase III Cancer Community Oncology Program (CCOP) trial. In Proc Am Soc Clin Oncol 389
8. Chapman PB, Einhorn LH, Meyers ML et al (1999) Phase III multicenter randomized trial of the Dartmouth regimen versus dacarbazine in patients with metastatic melanoma. J Clin Oncol 17:2745–2751
9. Luikart SD, Kennealey GT, Kirkwood JM (1984) Randomized phase III trial of vinblastine, bleomycin, and cis-dichlorodiam-

mine-platinum versus dacarbazine in malignant melanoma. J Clin Oncol 2:164–168
10. Atkins MB, O'Boyle KR, Sosman JA et al (1994) Multiinstitutional phase II trial of intensive combination chemoimmunotherapy for metastatic melanoma. J Clin Oncol 12:1553–1560
11. Atzpodien J, Lopez Hanninen E, Kirchner H et al (1995) Chemoimmunotherapy of advanced malignant melanoma: sequential administration of subcutaneous interleukin-2 and interferon-alpha after intravenous dacarbazine and carboplatin or intravenous dacarbazine, cisplatin, carmustine and tamoxifen. Eur J Cancer 31A:876–881
12. Flaherty LE, Robinson W, Redman BG et al (1993) A phase II study of dacarbazine and cisplatin in combination with outpatient administered interleukin-2 in metastatic malignant melanoma. Cancer 71:3520–3525
13. Gibbs P, Iannucci A, Becker M et al (2000) A phase II study of biochemotherapy for the treatment of metastatic malignant melanoma. Melanoma Res 10:171–179
14. Legha SS, Buzaid AC (1993) Role of recombinant interleukin-2 in combination with interferon-alfa and chemotherapy in the treatment of advanced melanoma. Semin Oncol 20:27–32
15. Legha SS, Ring S, Bedikian A et al (1996) Treatment of metastatic melanoma with combined chemotherapy containing cisplatin, vinblastine and dacarbazine (CVD) and biotherapy using interleukin-2 and interferon-alpha. Ann Oncol 7:827–835
16. Rosenberg SA, Yang JC, Schwartzentruber DJ et al (1999) Prospective randomized trial of the treatment of patients with metastatic melanoma using chemotherapy with cisplatin, dacarbazine, and tamoxifen alone or in combination with interleukin-2 and interferon alfa-2b. J Clin Oncol 17:968–975
17. Ives NJ, Stowe RL, Lorigan P, Wheatley K (2007) Chemotherapy compared with biochemotherapy for the treatment of metastatic melanoma: a meta-analysis of 18 trials involving 2, 621 patients. J Clin Oncol 25:5426–5434
18. Papadopoulos NE, Bedikian AY, Ring S, Kim KB, Camacho L, Eton O (2003) Phase II study of CTD (cisplatin, paclitaxel, DTIC) in metastatic melanoma (MM). In Proc Am Soc Clin Oncol, Chicago, IL 718 (abstr 2889)
19. Stevens MF, Hickman JA, Langdon SP et al (1987) Antitumor activity and pharmacokinetics in mice of 8-carbamoyl-3-methyl-imidazo[5,1-d]-1,2,3,5-tetrazin-4(3H)-one (CCRG 81045; M & B 39831), a novel drug with potential as an alternative to dacarbazine. Cancer Res 47:5846–5852
20. Patel M, McCully C, Godwin K, Balis FM (2003) Plasma and cerebrospinal fluid pharmacokinetics of intravenous temozolomide in non-human primates. J Neurooncol 61:203–207
21. Ostermann S, Csajka C, Buclin T et al (2004) Plasma and cerebrospinal fluid population pharmacokinetics of temozolomide in malignant glioma patients. Clin Cancer Res 10:3728–3736
22. Hainsworth JD, Burris HA 3rd, Greco FA (1999) Weekly administration of docetaxel (Taxotere): summary of clinical data. Semin Oncol 26:19–24
23. Gladish GW, Choe DH, Marom EM, Sabloff BS, Broemeling LD, Munden RF (2006) Incidental pulmonary emboli in oncology patients: prevalence, CT evaluation, and natural history. Radiology 240:246–255
24. Tas F, Argon A, Camlica H, Topuz E (2005) Temozolomide in combination with cisplatin in patients with metastatic melanoma: a phase II trial. Melanoma Res 15:543–548
25. Daponte A, Ascierto PA, Gravina A et al (2005) Temozolomide and cisplatin in advanced malignant melanoma. Anticancer Res 25:1441–1447
26. Bafaloukos D, Tsoutsos D, Kalofonos H et al (2005) Temozolomide and cisplatin versus temozolomide in patients with advanced melanoma: a randomized phase II study of the Hellenic Cooperative Oncology Group. Ann Oncol 16:950–957
27. Hersh EM, O'Day S, Gonzalez R, Samlowski WE, Gordon MS, Hawkins MJ (2005) Open-label, multicenter, phase II trial of ABI-007 in previously treated and previously untreated patients with metastatic malignant melanoma. In American Society of Clinical Oncology, Orlando, FL Part I of II (1 June Supplement):7558