Phase II trial of pegylated interferon and thalidomide in malignant metastatic melanoma

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Pegylated interferon and thalidomide demonstrate immunomodulatory and antiangiogenic activity, and efficacy in melanoma. The combination was evaluated in a phase II trial. Eligibility included biopsy-confirmed malignant melanoma with metastases and progression, maximum of two earlier systemic therapies, performance status of 0–2, and adequate hepatic, bone marrow and renal function. Pegylated interferon was administered at a dose of 0.5 μg/kg subcutaneously weekly and thalidomide 200 mg orally daily. Toxicity was evaluated every 2 weeks and response every 8 weeks. Eighteen patients were enrolled in this trial. Median age was 55.5 years (range: 29–80 years). Seventeen patients had visceral metastases and one had lymph node-only metastases. Two patients had brain metastases. Nine patients had received earlier adjuvant therapy and 16 patients had received earlier therapy for metastatic disease. Performance status was 0, 1 and 2 in 11, six and one patients, respectively. Severe (grade 4) toxicities observed were anemia in two patients and thrombocytopenia in one patient. No treatment-related deaths occurred. Dose escalation of thalidomide to 300 mg daily was feasible in four patients. One therapy-related hospitalization for nausea and dehydration occurred. No objective responses were noted; three patients demonstrated disease stabilization. The regimen of pegylated interferon and thalidomide was well tolerated. The combination, however, failed to demonstrate clinical efficacy in pretreated metastatic malignant melanoma.

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Introduction

Malignant metastatic melanoma is a malignancy with dramatically rising incidence. Surgical resection, if feasible, is the mainstay of therapy and affords the best chance of durable remissions. With current available therapy, metastatic melanoma remains a terminal diagnosis in the majority of the patients. The remissions induced by systemic therapy are relatively rare [1]. Chemotherapy with single-agent dacarbazine (DTIC) has demonstrated modest response rates with median progression-free survival of 2.6 months and median survival outcome of 7.8 months [2].

Immunotherapy has resulted in durable remissions and hence is considered the backbone of metastatic melanoma therapy. Interferon therapy is approved as adjuvant therapy in resected malignant melanoma with high risk of relapse, due to the statistically significant benefit in relapse-free survival and overall survival (OS). A randomized trial in high-risk (T4 or node-positive) melanoma revealed an increment in median relapse-free survival from 1 to 1.7 years, median survival increment from 2.8 to 3.8 years with adjuvant interferon-α2b therapy, as compared to observation [3]. The disease-free survival rate increased from 26 to 37%. Interferon-α2b is currently indicated in adjuvant therapy of melanoma with high risk for systemic recurrence.

In metastatic melanoma, chemotherapy with DTIC is commonly used [1]. Interleukin and interferon have also been evaluated. Biochemotherapy demonstrated very promising response rates in phase II trials, which disappointingly did not translate into a survival benefit when compared with DTIC chemotherapy alone in a phase III trial [4]. The survival outcome in metastatic malignant melanoma continues to be poor, highlighting the need for evaluation of novel therapeutic strategies.

Intron A (interferon-α2b) is a highly purified interferon produced by recombinant DNA techniques. It has demonstrated immunomodulating, antiproliferative and antiangiogenic properties [5–7]. It is currently indicated in the treatment of various diseases, including chronic myelocytic leukemia, renal cell carcinoma, and hepatitis B and C [6,7].

Schering-Plough Research Institute developed a polyethylene glycol formulation of interferon-α2b (PEG-Intron, SCH54031; Schering-Plough Corporation, Kenilworth, New Jersey, USA). This formulation has the advantage

of prolonging the half-life of Intron from 4.3 to 34 h [8]. This enables once weekly instead of once daily or three times weekly subcutaneous administration and enhances the compliance and quality of life of patients. Pegylated interferon was shown to be safe and well tolerated at doses of 0.5, 1.0 and 1.5 μg/kg/week in three studies performed in hepatitis C patients. The efficacy observed in hepatitis C was significantly higher than Intron A in the phase III study [9]. A phase I study demonstrated the safety of pegylated interferon at doses up to 7.5 μg/kg/week [10]. The most frequently reported adverse effects were anorexia (77%), nausea (74%), fatigue (63%), headache (60%), injection site reaction (57%), and fever and chills (54%) [10]. Clinically, interferon-α2a has demonstrated activity in metastatic melanoma. Response rates are approximately 10–15% in untreated disease and 5–10% in pretreated patients [1].

In-vitro studies of interferon indicate antiangiogenic effect as a promising avenue of treatment in advanced melanoma [11]. In animal models, it has shown decreased neovascularization in rabbits with herpetic keratitis [11]. The antiangiogenic effects of interferon have led to its successful use in vascular lesions such as cutaneous hemangiomas and Kaposi's sarcomas [12,13]. Melanoma tumor cells have shown induction of epidermal hyperplasia with increased levels of angiogenic promoters such as basic fibroblast growth factor, vascular endothelial growth factor and interleukin-8 [14]. This provides the rationale for interferon administration for angiogenesis inhibition in melanoma.

Thalidomide is administered orally and is well tolerated. Clinically, the agent has been evaluated in multiple malignancies. Thalidomide is approved by the US Food and Drug Administration (FDA) for the acute treatment of the cutaneous manifestations of moderate to severe erythema nodosum leprosum and for the treatment of newly diagnosed multiple myeloma in combination with dexamethasone. It has also demonstrated efficacy in relapsed and refractory myeloma, renal cell carcinoma and prostate cancer [15,16]. Antiangiogenic activity of thalidomide was described by D'Amato *et al.* [17]. Inhibition of basic fibroblast growth factor-induced corneal neovascularization was demonstrated in rabbits [18,19]. A phase II study of thalidomide in patients with metastatic melanoma, renal cell, ovarian and breast cancers by Eisen *et al.* [20] demonstrated declines in serum and urine vascular endothelial growth factor.

On the basis of the immunomodulatory and antiangiogenic mechanisms of actions of interferon and thalidomide, and their clinical efficacy and tolerability, a phase II clinical trial of the combination was conducted in metastatic melanoma. Pegylated interferon was utilized in this trial due to the convenience of weekly administration and data regarding better tolerability.

Patients and methods

The protocol was reviewed and approved by the Wayne State University Institutional Review Board. Eligibility included patients with locally advanced unresectable, locally recurrent or metastatic malignant melanoma. Bidimensionally measurable or evaluable disease was required with prestudy imaging for disease assessment, within 28 days of registration. Earlier surgery or radiation therapy had to be completed at least 28 days before enrollment. Patients with brain metastases were eligible only if the intracranial lesions were stable for at least 6 weeks after therapy. A maximum of two earlier systemic therapy regimens for metastatic melanoma were allowed. Earlier biologic therapy including interferon was permitted. Performance status had to be between 0 and 2 as per the Zubrod criteria. Normal kidney, liver and bone marrow functions were required.

Pregnant or lactating patients were excluded. Patients with reproductive potential had to agree to practice effective contraception while on the therapy and for a minimum of 4 weeks after discontinuing therapy. Patients agreed to abide by the birth control and pregnancy testing requirements of the STEPS program. Male patients were required to agree to practice effective contraception and to use a latex condom during all sexual encounters with women of childbearing potential while on the therapy and for a minimum of 4 weeks after discontinuing therapy. Women of childbearing potential had to agree to start contraception a minimum of 4 weeks before beginning the treatment. Written informed consent was signed by all patients enrolled on the study. Patients had to be willing and able to comply with the Federal Drug Agency mandated STEPS program (STEPS is a registered trademark of Celgene Corporation, Thalidomide, Celgene Corporation, Summit, New Jersey, USA).

Treatment and evaluation plan

Pegylated interferon was administered at a dose of 0.5 μg/kg of body weight and thalidomide was administered orally at a starting dose of 200 mg daily at bedtime. If patients tolerated therapy for 4 weeks without any toxicities higher than grade 1, then the thalidomide dose could be escalated by 100 mg at a time to a maximum dose of 400 mg daily. Dose modifications for toxicity were required per protocol guidelines. The doses planned for each of the agents were low as the intent of the trial was to evaluate synergy between the two agents and due to the concerns regarding toxicities in a pretreated patient population.

Toxicity was evaluated every week and graded per National Cancer Institute Common Toxicity Criteria

version 2.0 (National Cancer Institute, Bethesda, Maryland, USA) and response was assessed every 8 weeks. Serum chemistries and blood counts were determined weekly for the first 4 weeks and then every 2 weeks unless indicated clinically. Imaging was performed every 8 weeks to evaluate response. Assessment of response was carried out by the RECIST criteria. Acetaminophen was recommended for prophylaxis against the influenza-like symptoms induced by interferon. Patients were treated with an appropriate bowel regimen to prevent constipation caused by thalidomide.

Treatment was continued until disease progression, death, intolerable toxicity, treatment delay of 4 weeks or greater, or if the patient wished to withdraw for any reason.

Dose modifications were performed for toxicity as per protocol guidelines. For grade 4 neutropenia or thrombocytopenia, treatment was held and restarted with one dose level reduction for both agents (0.3 μg/kg for pegylated interferon and 150 mg for thalidomide) when recovery to grade 2 or less. For neuropathy grade 2 or higher, dose of thalidomide was reduced after holding therapy until recovery to grade 1 or less. No reescalation of dose was allowed after dose reduction. For serious dermatologic reactions such as Steven Johnsons syndrome or toxic epidermal necrolysis, thalidomide was discontinued permanently.

Statistical methods

This single-institution phase II trial was planned with a Simon two-stage minimax design [21]. The primary endpoint was complete or partial response. We wished to distinguish these regions of the true, unknown response rate: at most 0.05 versus at least 0.20. The two-stage design called for a maximum of 32 response-evaluable patients, 18 in stage 1 and 14 in stage 2. Patients were considered response-evaluable if they completed at least 2 weeks of therapy. The design had a type I error of 0.072 and power of 0.901. At least one response among the first 18 response-evaluable patients was needed to justify beginning stage 2 of the study design. After accruing 18 patients, only 17 were response-evaluable and accrual had slowed considerably so accrual was stopped. Terminating stage 1 of the study with only 17 instead of the intended 18 response-evaluable patients reduced the planned statistical power to 0.899. With no responders, it was concluded that the sample response rate among the response-evaluable patients ($0/17 = 0\%$) better supported the null hypothesis that the true, unknown response rate was at most 0.05.

Exact, minimum-width 90% confidence intervals (CIs) for response and toxicity rates were calculated using the Casella method [22] as implemented in StatXact software [23]. OS was measured from treatment start date to the date of death from any cause. Standard Kaplan–Meier estimates of the censored OS distribution was computed. Owing to the small sample sizes, survival statistics (e.g. median) were estimated more conservatively using linear interpolation [24] among successive event times on the Kaplan–Meier curve.

Results

Eighteen patients, 10 men and eight women, were enrolled in the first stage of the study (Table 1). Study was closed to accrual after the first stage. The median age of the patient population enrolled was 56 years (range: 29–80 years). Seventeen patients had visceral metastases and one had lymph node-only metastases. Two patients had been treated for stable brain metastases. Ten patients had failed both chemotherapy and immunotherapy regimens, two patients had received earlier biochemotherapy, and four patients had received earlier chemotherapy. Performance status was 0, 1 and 2 in 11, six and one patient, respectively. Seven of 18 patients had an elevated lactate dehydrogenase level (range: 121–3553 U/l). The majority of the patients had bulky disease; 14 patients had three or more organ sites involved with metastases and four patients had two organ sites involved.

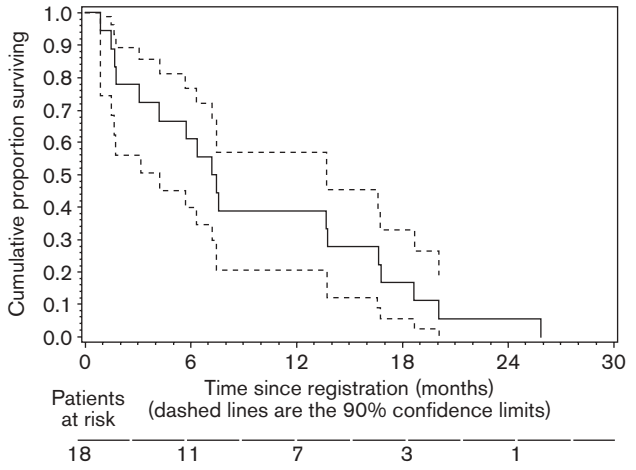
Table 1 Patient characteristics

Characteristic	No. (%), total 18 patients
Median age	55.5 years (range 29–80 years)
Sex	
Male	10 (56)
Female	8 (44)
Zubrod performance status	
0	11 (61)
1	6 (33)
2	1 (6)
Lactate dehydrogenase	
Normal	11(61)
Elevated	7 (39)
Sites of metastases	
Visceral	17 (94)
Lymph node only	1 (6)
Histology	
Melanoma	13 (72)
Nodular melanoma	4 (22)
Ocular	1 (6)
Race	
Caucasian	18 (100)
African-American	0 (0)
Adjuvant therapy	
Yes	10 (56)
No	8 (44)
Earlier therapy	
Biochemotherapy	2 (11)
Chemotherapy	4 (22)
Both	10 (56)
None	2 (11)
No. of organ sites involved with metastases	
≥ 3	14 (78)
2	4 (22)
Stage of disease	
M1a	1 (6)
M1b	4 (22)
M1c	13 (72)
Time from diagnosis to metastases	Median 22.5 months
Time from metastases to protocol enrollment	Median 7.3 months

Table 2 Toxicity among 18 treated patients

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
Neutropenia	2	4	0	0
Anemia	6	3	1	2
Thrombocytopenia	7	0	0	1
Fatigue	5	10	2	0
Constipation	6	0	1	0
Somnolence	1	0	0	0
Bradycardia/heart block	2	1	2	0
Neuropathy	4	3	1	0
Skin rash	1	2	0	0
Myalgias	2	0	0	0
Anorexia	5	3	0	0
Nausea/emesis	2	2	1	0
Dehydration	0	0	1	0
Depression	1	0	0	0
Diarrhea	1	0	0	0
Hypothyroidism	1	1	0	0
Edema	1	1	0	0
Dyspnea	0	2	1	0

Fig. 1



Kaplan–Meier graph of overall survival with 90% confidence interval limits.

A total of 33 cycles of therapy were administered with mean of two cycles (range: 1–5 cycles). Dose escalation of thalidomide to 300 mg daily was feasible in four patients. All the patients who were dose escalated, however, had disease progression at the first assessment. Three patients required dose reduction: two due to constitutional symptoms (myalgias, fevers and flu-like symptoms) and one due to heart block.

The commonly seen toxicities were fatigue, neutropenia, anemia, neuropathy and constipation (Table 2). These were not severe and were managed clinically. Severe (grade 4) toxicities observed were anemia in two patients and thrombocytopenia in one patient. Platelet transfusions were not required. No treatment-related deaths occurred. One therapy related hospitalization occurred for anemia, nausea, emesis and dehydration. No objective responses were noted; three patients demonstrated disease stabilization for a rate of 3/18 = 17% (90% CI, 0.06–0.35). The stable disease durations were 4, 5 and 15 months. The median survival was 7.2 months, with 90% CI, 4.1–13.6 months (Fig. 1). The 6-month and 1-year OS rates were 58% and 35%, respectively.

Discussion

This phase II trial evaluated the efficacy and toxicity of the combination of interferon and thalidomide in pretreated metastatic melanoma. The rationale for the combination was compelling, due to the antiangiogenic and immunomodulating activity of each of the agents individually, as well as demonstrated synergy [25]. Clinically, however, the combination revealed minimal efficacy in our phase II trial. The results are comparable to the response rates and survival outcomes noted in other trials of pegylated interferon in metastatic melanoma [26,27]. A randomized dose escalation study evaluating three different dose levels (180, 360 and 450 μg) subcutaneously weekly was reported [26]. The objective overall response rates were 6, 8 and 12%, respectively, at increasing dose levels, and median survival ranged from 7 to 9 months. A statistically significant survival difference exists favoring the higher dose of pegylated interferon but the arms were not well balanced for known prognostic risk factors within melanoma. Our trial utilized a much lower dose of pegylated interferon (35–50 μg weekly) due to the concerns regarding toxicity with the addition of thalidomide therapy. The combination, however, was well tolerated and easy to administer even in this population of pretreated patients. The toxicity profile of pegylated interferon seemed to be less severe than that observed with recombinant interferon. Pegylated interferon in combination with temozolomide demonstrated a promising response rate of 31% with three of 35 patients showing durable complete remissions [27]. The dose of pegylated interferon was the same as that used in our trial of 0.5 μg/kg and the regimen was well tolerated. Hence, for combination therapy this dose of pegylated interferon at 0.5 μg/kg seems to be appropriate.

Thalidomide has also been evaluated in combination with temozolomide in two trials [28–30] in metastatic melanoma with minimal activity. The objective response rate was 12% in one study in pretreated metastatic melanoma and the observed median survival was 5.2 months [28]. In another phase II trial in patients with brain metastases, 12% had an objective response but rapid progression in extracranial sites was noted [29]. In the Cancer and Leukemia Group B trial in patients with brain metastases, no objective responses were noted and a high proportion of patients had thromboembolic events (four of 16 patients) [30]. Interestingly, the consistent 10–20% incidence of thromboembolic events noted in

other trials of recombinant interferon and thalidomide was not observed in our trial using pegylated interferon.

With only three of 18 patients demonstrating disease stabilization and in the absence of objective responses in our study, it is unlikely that this combination will be further evaluated in metastatic melanoma. Durable disease stabilization, however, is known to impart significant clinical benefit in melanoma as shown by a trial using melacine [31], and in renal cancer as shown by the FDA approval of sorafenib therapy [32]. The phase II trial of melacine in metastatic melanoma yielded a response rate of only 10% but an impressive median time to progression of 8 months in evaluable patients. Sorafenib also elicited a response rate of only 4% in metastatic renal cancer but demonstrated a significant improvement in time to progression (median of 6 months with sorafenib versus 3 months with placebo), leading to its FDA approval in metastatic renal cancer.

The management of metastatic melanoma presents a very difficult challenge for researchers and clinicians. Even a recently published trial of dacarbazine with or without BCL-2 antisense oligonucleotide (oblimersen sodium) revealed disappointing results with overall response rates of 13% in the combination arm and median survival of 9 months [2]. This reflects the dismal prognosis observed in patients with metastatic melanoma. In addition to the quest for efficacious agents, we face the critical decision regarding the level of activity in phase I or II trials that would deem a novel agent worthy of development in melanoma therapy. Increasing knowledge of the host and tumor-related factors required for the agent to be active would help obtain an enriched population of patients on clinical trials. Subsequently, it would enable use of appropriate therapy to address and target the individual tumor and host-related factors in metastatic melanoma.

In conclusion, pegylated interferon and thalidomide combination demonstrated reasonable tolerability, but minimal efficacy in metastatic melanoma. Future investigation of this regimen in advanced melanoma cannot be recommended.

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