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ORIGINAL ARTICLE

Long-Term Survival in Metastatic Melanoma Patients Treated with Sequential Biochemotherapy: Report of a Phase II Study

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ABSTRACT

The overall survival for patients with metastatic melanoma is very poor, with a median survival of 8.5 months. In this Phase II trial, we assessed the efficacy, safety, and tolerability of a sequential biochemotherapy schedule, using dacarbazine as antiblastic agent and immunomodulant doses of interleukin-2 and interferon-alfa. Thirty-one eligible patients with metastatic melanoma received dacarbazine IV as antiblastic therapy and interluekin-2, plus interferon-alfa SC as sequential immunotherapy, for 6 months. Responding and nonprogressing patients were subsequently maintained on immunotherapy treatment for further 6 months. Twenty-nine patients had an adequate trial, and were assessable for both response and toxicities, with a median follow-up of 49 months. The overall response rate was 52 percent (3 CR and 12 PR), SD was 8 (27 percent) and PD were achieved in 6 patients (21 percent). The median survival duration of responders was 28 months, significantly longer ($p < 0.001$) than the 16 months of nonresponders. Therapy was well tolerated and produced a significant improvement in progressive-free survival. Further studies, thus, are recommended for larger groups of patients not only to confirm these results, but also to apply this biochemotherapy regimen as adjuvant postsurgical treatment in early stages of malignant melanoma.

INTRODUCTION

Once an uncommon cancer, the incidence of malignant melanoma is now rapidly increasing through the world, accounting for approximately 3 percent of all cancers diagnoses in the United States and Europe (1). During the past decade the incidence of melanoma has increased at a rate that exceeds all other neoplasms except lung cancer in women. A present, the incidence increases by 5–7 percent yearly (2, 3 and the death rate from melanoma has doubled over the last decades.

The prognosis of malignant melanoma is strongly related t the stage of detection (4). The overall prognosis is excellent fo early diagnosed primary melanoma treated by adequate surger (5), while the overall survival rate in patients with tumor-positiv nodes is 46 percent at 5 years (6). Once melanoma has meta tasized to distant sites, the prognosis is grave, with a media survival of only 4–9 months in most series (7, 8).

The treatment of patients with metastatic melanoma de pends on multiple factors including overall condition and ag of patients, site and number of metastases and disease pac The appropriate systemic medical treatment for disseminate melanoma is still controversial. There are numerous chemothe apeutic agents that have proved to be active in the treatmer of metastatic melanoma. However, no agent has consistentl shown a response rate greater than 25 percent and most response are of short duration (9, 10). Considered the modest activity o single-agent chemotherapy, a number of different combination

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of dacarbazine, nitrosureas, vinblastine, cisplatin, and taxanes with or without tamoxifen, have been evaluated in the treatment of disseminated melanoma with a response rate ranging from 20 to 45 percent (11–13).

Hence, the widespread interest in developing biologic therapies against melanoma, with a particular focus on IFN-α and interleukin-2 (IL-2) which in a multitude of studies has produced single agent response with a range of 11 to 20 percent. However, the continued interest in these agents is not so much the result of their overall response rate, but comes from the consideration that some of the complete responses are durable, with up to 5 to 10 percent of patients who may achieve long-term survival (14). In the early 1990s, several investigators began to study intensive regimens that included combination chemotherapy and the biologic agents IFN and/or IL-2 (15). The rationale for combining cytotoxic chemotherapy with immunotherapy is based on evidence that combination therapy has become a mainstay for many solid tumors (16). Because immune surveillance and tumor destruction is a complex, multistep process that involves many aspects of the immune system, the notion of combination chemotherapy with biological response modifiers seems valid (14). Moreover, the modest clinical effectiveness of chemotherapy and cytokine therapy given separately prompet evaluation of the two modalities given in sequential way.

The primary objective of this study was to evaluate the therapeutic potential, in terms of tumor response rate, in the overall survival and to investigate the possibility of prolonging the median time to progression (TTP) of patients with metastatic melanoma. The secondary objective was to assess the quality and grade of toxicities associated with this biochemotherapeutic sequential regimen, combining administration of dacarbazine with low doses of IL-2 and IFN-α, in metastatic melanoma outpatients.

PATIENTS AND METHODS

Patients selection

Thirty-one consecutive patients with metastatic melanoma were enrolled onto this study. All patients presented histologically confirmed, progressive metastatic melanoma. Eligibility criteria were measurable lesions, a Karnofsky score of 40 or more, life expectancy of at least 6 months; absolute granulocyte count $\geq 1{,}500/\mu l$; platelet count $\geq 150{,}000\ \mu l$; serum bilirubin and serum creatinine ≤ 1.5 times the upper limit of laboratory normal; and AST, ALT, and alkaline phosphatase ≤ 3 times the upper limit of laboratory normal; no brain metastases, no prior chemotherapy, radiotherapy or hormonal therapy after diagnosis, and no concomitant therapy with drugs influencing immunity as corticosteroids. All patients were followed at the Oncological Day Hospital, Department of Internal Medicine of the Florence University. Patients must be 18 years of age and had to sign a written informed consent, according with institutional regulations. Patient characteristics are listed in Table 1.

Table 1. Patient demographics and disease characteristics

Patients assessable ($n = 29$)	
Males	18
Females	11
Mean patients age (range) 57 (34–72)	
Karnofsky's performance status (%)	
≥40	2
>60	11
>80	16
Predominant metastatic site (%)	
Liver	4
Lung	6
Lymph nodes	10
Soft tissues	9
Metastatic sites (%)	
1	16
2 or more	13

Clinical assessments

All patients, before the start of treatment, underwent clin examination, complete blood count and biochemical analy chest computed tomography scan or x-ray, liver computed mography scan or ultrasonography, brain computed tomo phy or magnetic resonance imaging scan, radionuclide b scan, and cardiologic evaluation. Monthly, before each treatm course, patients underwent clinical examination, determina of complete blood count, and biochemical analysis. After 2 cles and, thereafter, every 2 months until progression, they w required to have a chest computed tomography scan or x-ray liver computed tomography scan or ultrasonography.

Treatment plan

This was an open-label Phase II study whose primary was tumor response. Safety, overall survival, and TTP were sessed as secondary end points.

The biochemotherapy regimen was administered entirely an outpatient basis. Each treatment course consisted of six day cycles of chemotherapy given over a 6-month period. tients received also 6 cycles of IL-2 and IFN-α. Respon and non progressing patients were subsequently maintai on the immunotherapy treatment for an additional 6-m period.

Chemotherapy consisted of dacarbazine (DTIC) at the 200 mg/m^2 of body-surface area given on Days 1–5 of chemotherapy cycle (28 days). DTIC was administered I 250 mL of dextrose 5 percent in water over 30 minutes. ing this 28-day course, patients also received IL-2 (Proleu Chiron-Italia), 4.5 MU administered SC on Days 7–13 of cycle and IFN-α, 6.0 MU IFN-α SC, 2 times a week on D 15–28 every 4 weeks, for 6 months as immunotherapy. Resp ing and nonprogressing patients were subsequently mainta on an immunotherapy treatment for an additional 6 mo consisting of 4.5 MU IL-2 SC daily on Days 1–7 (first w and subsequently IFN-α, 6MU SC, 2 times a week on second, third, and fourth of each month. Altogether pat received biochemotherapy for 6 months and responding

nonprogressing patients received immunomodulant doses of cytokines for the following 6 months.

Response and toxicity

Response evaluations and treatment related toxicities were assessed according to World Health Organization (WHO) criteria (18). Tumors were evaluated by radiography, and computed tomography al baseline and at 4-week intervals thereafter. Tumor measurements were based on the sum of the products of the bidimensional diameter of the lesions. To be classified as a complete responder (CR), a patient had to have complete regression of the disease and be free of symptoms related to the carcinoma for a minimum of 4 weeks. Patients with a reduction greater than 50 percent in lesion size and no new lesions were classified as partial responders (PR), while those presenting a reduction in lesion size <50 percent were classified as minor responders. Patients were rated as having progressive disease (PD) if any new lesion appeared, if tumor size increased by 25 percent over pretreatment measurements, or for deterioration in clinical status consistent with disease progression. Patients who failed to meet the criteria of CR, PR, or PD and who remained on-study for at least 2 months, were classified as having stable disease (SD). Responses had to persist for at least 4 weeks; given the scanning intervals in this study, this requirement effectively became 6 weeks. All tumor measurements in responding patients were reviewed and confirmed by a reference radiologist and response was evaluated by patient's physician and another investigator in a blind review of response data.

Statisical methods

An optimal 2-stage design was employed in the protocol (19) using standard statistical methods. If no CR or PR were noted in the first cohort of 14 patients, a response rate of more of than 15 percent could be excluded with a 95% CI, causing the accrual stop. If at least one CR or PR was observed, more of 30 patients were entered in the study to determine the response rate more accurately. So, the primary goal of this Phase II study was tumor response. Safety, overall survival, and TTP were assessed as secondary endpoints

RESULTS

Between April 1996 and May 1999, 31 patients entered this study. Two patients were considered ineligible because they refused treatment after inclusion. Hence, 29 patients had an adequate trial, and were assessable for both response and toxicities, with a median follow-up of 49 months among long-term survivors (range 35+ to 60+ months).During the study we measured dose-intensity (percentage of administered doses) of biochemotherapy (6 months) for all patients and immunotherapy (12 months) for responding and nonprogressing patients.

Dose-intensity for chemotherapy (DTCI) was 92 percent and 88 percent for immunotherapy. In total, patients received 161 cycles of chemotherapy and 227 cycles of immunotherapy.

Table 2. Tumor response by predominant metastatic sites

Localization	No.	CR(%)	PR(%)	SD(%)	PD(
Liver	4	—	1 (25)	2 (40)	1 (2
Lung	6	1 (17)	2 (33)	1 (17)	2 (3
Lymph nodes	10	1 (10)	5 (50)	3 (30)	1(1
Soft tissue	9	1 (11)	4 (44)	2 (22)	2(2

The overall objective response rate was 52 percent (95 % C 34–57 percent), CR were 3 with a median duration of more th 36 months (37+ and 60+). PR were 12 with a median of months (19+ to 60+). SD were achieved in 8 patients (27 pe cent; 95% CI, 12–42 percent) with, a very long survival durati in 3 patients, 27+, 60+, and 60+) months. The last 6 patien had PD (21 percent; 95% CI, 6–36 percent). The median surviv duration of responders was 27+ months, which was significant longer ($p < 0.001$) than the 15+ months of nonresponders. M dian survival duration for all patients was 20.1 months. Seven p tients (24 percent) are still alive at last follow-up (60+ month The median TTP was of 7.9 months. The high incidence of lon term progression-free disease in this study probably reflects t high overall-response rate (52 percent). Patients whose disea did not respond had median TTP of 4.1 months. No statistical si nificant evidence was found as to a preferential site of respons Tumor responses by dominant measurable sites are reported Table 2.

Toxicity

All 29 patients were valuable for toxicity. The most co mon side effects were myelosuppression, flu-like symptor and fatigue, mainly during the initial 3 months of treatme Even these symptoms tended to be mild and limited to WH Grade 1 or 2. No WHO Grade 4 toxicity was achieved duri the study. Overall, the treatment was well tolerated, in 2 cas the dose was reduced due to Grade 3 hematological toxici (neutropenia), while for 2 patients it was sufficient to postpo the next treatment by 7 days. Grade 3 anemia was observ in 2 patients and leukopenia without fever and thrombocitop nia was also reported in 2 patients. Table 3 shows a list of t adverse events observed during the study, reported by sever

Table 3. Toxicities according to World Health Organization scale

	No. patients at toxicity grade (%)		
Side effect	1	2	3
Anemia	14(49)	13(44)	2(7)
Thrombocitopenia	12(42)	15(51)	2(7)
Leukopenia	16(55)	11(38)	2(7)
Alopecia	24(83)	5(17)	—
Nausea/vomiting	14(48)	14(48)	1(3)
Anorexia/weight loss	17(59)	12(41)	—
Fatigue	13(45)	14(48)	2(7)
Flu-like symptoms	13(45)	15(52)	1(3)
Cardiac toxicity	25(86)	4(14)	—
Liver toxicity	22(76)	7(24)	—
Renal toxicity	24(83)	5(17)	—
Neurological toxicity	26(90)	3(10)	—

grade. No deaths associated with treatment occurred in the study.

DISCUSSION

In the last 2 decades the treatment strategy of advanced melanoma has evolved from single agent chemotherapy to combination chemotherapy, immunotherapy and now biochemotherapy. The median survival of patients with advanced melanoma varies between 6 and 9 months, and only 1–2 percent have long-term complete response after treatment (20). However, significantly higher response percentages ranging between 40 percent and 55 percent have been observed when the combination of cytokines (IFN, IL-2) has been added to chemotherapy (21, 22). These encouraging results led to a large randomized Intergroup study conducted by ECOG (23) that compared chemotherapy with combined bio-chemotherapy by Legha's regimen with several modifications (24) but with several modifications. The results of this large trials were very disappointing, perhaps due to reduction of vinblastine dose, the limited number of chemotherapy cycles (a maximum of 4) and the complexity of the biochemotherapy regimen, that may have contributed to the low response rate in the cooperative group setting.

Our study was performed to assess the antitumor efficacy and toxicity of a new sequential biochemotherapy schedule for metastatic melanoma. The rationale for combining immunotherapy with cytotoxic chemotherapy rests on several factors. Synergic or addictive effects have been reported with the addition of cytokines to chemotherapy producing encouraging results in advanced melanoma (25). In particular, Eton et al. (26) confirmed that cytokines substantially augment the clinical activity of chemotherapy in the treatment of this disease. In addition, these 2 modalities have different mechanisms of action, have largely nonoverlapping toxicities and do not produce cross resistance. Many of these biochemotherapy regimens require inpatient treatment because they have substantial toxicity. A number of investigators have endeavoured to develop regimens with less toxicity and that could be administered in the outpatient setting, replacing IL-2 administered intravenously with the subcutaneous route at low dose. Unfortunately, up to now, biochemotherapy regimens involving IL-2 at low doses appear to produce lower response rates (27). Moreover, in line with present European practice, we used low-dose immunotherapy for immune modulation, in order to achieve less toxicity and the possibility to extend immunotherapy up to 12 months in responding and/or nonprogressing patients. Although the present study was performed in patients with poor prognosis, this sequential biochemotherapy schedule has proved highly effective with a very low toxicity. Moreover, we achieved an overall objective response of 52 percent and a particular very long survival duration, 28 months in responding patients and 15 months in non-responders: this much longer survival rate compared to the standard 6–9 months, could be related to the fact that most patients entered in the study had a single metastatic localization in the soft tissues or lymphonodes. Even, in patients who showed no objective response, disease stabilization was relatively high (27 percent). In conclusion, despite the limited n ber of patients in our study, chemotherapy (DTIC) and prolon low-dose cytokines immunotherapy (IL-2 and IFN-α) may a promising approach to the treatment of advanced melano that strengthens the already widespread opinion that advan melanoma is best treated with combined chemoimmunoth peutic drugs. Moreover, this outpatient biochemotherapy imen can be administered with modest toxicity and little of neutropenic fever, hypotension, or renal and cardiac to ity. Further studies, thus, are recommended for larger gro of patients not only to confirm these results but also to e uate the efficacy of treatment also in terms of clinical be fit response and the possibility to apply this biochemother schedule as adjuvant postsurgical treatment in early stage malignant melanoma.

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