Journal of BUON **15:** 470-474, 2010

ORIGINAL ARTICLE

Concurrent chemoimmunotherapy: is it still the best option for the treatment of metastatic melanoma in patients with good performance status?

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Summary

Purpose: *To determine the efficacy, toxicity and survival of metastatic melanoma patients with Eastern Cooperative Oncology group good performance status (ECOG PS 0–1) receiving concurrent chemotherapy and immunotherapy.*

Methods: *From March 2003 to August 2008, 25 patients with metastatic melanoma were enrolled in the study. No patient had previously received chemotherapy or immunotherapy. Patients with ECOG PS 0-1 were treated with cisplatin+vinblastine + DTIC (CVD) and interferon-A2a (IFN-a).*

Results: *Response rate was 11/25 (44%): complete response (CR) 2, partial response (PR) 9, stable disease (SD) 11, progressive disease (PD) 3. Adverse effects were mild. The most common toxicities were nausea, vomiting and fever. Grade 3 and 4 toxicity was more common in hematologic parameters. No treatment-related deaths occurred. The median overall survival (OS) was 14 months and time to progression 8.0 months.*

Conclusion: *Concomitant chemoimmunotherapy appeared to be a beneficial option for metastatic melanoma patients with good PS. Therapeutic approaches with less toxicity and regimens that could improve OS are still highly desired in the treatment of advanced malignant melanoma.*

Key words: chemotherapy, immunotherapy, metastatic melanoma, performance status, survival, toxicity

Introduction

It is rather disappointing to see how little, if any, progress has been made over the last three decades in the systemic treatment of metastatic melanoma [1].

Metastatic melanoma has shown only limited responsiveness to systemic antitumor therapy, with median OS of 6-9 months and complete responses in a modest number of cases.

It is currently unclear whether any combination therapy for the treatment of metastatic melanoma is superior to standard single-agent chemotherapy in terms of response rates and OS. However, no cancer is curable or meaningfully controlled with single-agent treatment. Melanoma is no exception in that regard [2]. The alkylating agent dacarbazine (DTIC) is considered to be the most active drug for the treatment of metastatic melanoma, with an objective response rate of approximately 15%. However, in some recent multicenter trials objective tumor response was only 7-8% [3]. Nevertheless, DTIC remains the mainstay of chemotherapy for metastatic disease [4]. The majority of DTIC-induced responses are partial and transient [2]. Several cytotoxic agents have been combined with no considerable benefit [5]. IFN-α has been extensively studied as a single agent in advanced melanoma. When used as a monotherapy, IFN-α produced response rates comparable with those achieved with single-agent DTIC. When IFN-α and chemotherapy were used in combination the improvement was negligible or very moderate in randomized phase III trials [6]. However, IFN-α combined with cytotoxic drugs yielded response rates of up to 50% [7].

The rationale for combining cytotoxic drugs with IFN in melanoma lies in the assumed different antitumor mechanisms. The wide spectrum of IFN-induced immunomodulatory and antiproliferative effects together with the antitumor activity of cytotoxic agents may be additive or synergistic [8].

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Received 01-09-2009; Accepted 23-10-2009

Methods

From March 2003 to August 2008, 25 patients with metastatic melanoma and good PS were treated with combination biochemotherapy (Table 1). The treatment required 10-day hospital stay. No patient had previously received chemo- or biotherapy.

Inclusion criteria

Histologically confirmed malignant melanoma; metastatic disease with metastatic lesions not amenable to radical surgery; measurable or assessable lesions; ECOG PS 0-1; expected survival beyond 2 months; age 16-70 years; no concomitant diseases; no history of other malignant neoplasm except *in situ* cervical carcinoma; and oral consent of the patient.

Exclusion criteria

Patients who did not fulfill the inclusion criteria; choroidal primary disease site; presence of unresectable central nervous system metastases; voluminous liver metastases associated with hyperbilirubinemia or liver insufficiency; and any other contraindications for any of the planned drugs.

Treatment schedule

Treatment consisted of dacarbazine 850 mg/m^2 i.v., day 1; vinblastine 1.6 mg/m^2 i.v., days 1-5; and cisplatin 20 mg/m^2 i.v., days 1-4 (CVD), plus IFN-α (Roferon A, Roche) 3×10^6 IU s.c., days 1-10. The treatment cycle was repeated on day 22. Dacarbazine was administered in 500 ml 5% dextrose water over 1-2 h. Vinblastine was given as a short infusion over 15-30 min.

Table 1. Patient characteristics (n=25)

Characteristics	*No. of patients*	*%*
Age (years), median (range)	57 (30-70)	
ECOG PS		
0	6	24
1	19	76
Metastatic sites		
Skin	6	24
Lymph nodes	9	36
Lungs	9	36
Liver	6	24
Other	2	8
Number of metastatic sites		
1	8	32
2	8	32
3	9	36

Cisplatin was administered in 250 ml normal saline and infused over 30 min. All patients received adequate prehydration for prevention of cisplatin nephrotoxicity and were premedicated with ondansetron 20-32 mg i.v. once daily and dexamethasone 20 mg as a short 15-30 min infusion in 250 ml normal saline, and lorazepam 1 mg i.v. every 8 h. Paracetamol 500 mg p.o. was given for prevention of IFN-associated fever. Patients with progressive disease (PD) were excluded from therapy after 2 cycles, while the remaining (complete response/CR, partial response/PR, stable disease/SD) received 6 cycles of chemoimmunotherapy at most.

Dose modification criteria

No dose modifications were anticipated. In general, in patients with grade 3 or 4 toxicity according to National Cancer Institute (NCI) common toxicity criteria the treatment was interrupted and withheld until the toxicity grade was restored to 1 or 2.

Evaluation of response and toxicity

Pretreatment evaluation included physical examination, complete blood count and organ function tests. Staging was based on clinical and imaging examinations. Physical status and adverse effects were recorded and laboratory tests including full blood count, serum biochemistry and liver function tests were done every 3 weeks. Response was evaluated every 6 weeks. Responses and adverse effects were evaluated according to the World Health Organization (WHO) and NCI criteria, respectively.

Response criteria

CR required complete disappearance of all clinically and radiographically detectable disease for at least 4 weeks. PR required at least a 50% reduction in the size of all measurable lesions as measured by the product of the greatest perpendicular diameters without appearance of new lesion(s). SD was defined as a reduction of <50% or increase of <25% of the measurable disease without appearance of new lesion(s). PD was defined as an increase of >25% in the size of any existing measurable lesion or the appearance of a new lesion(s). Response duration was defined as the period when an objective response was first documented until the appearance of PD.

Statistical analysis

The results obtained were evaluated according to

the methodology of descriptive and analytic statistics. Survival was calculated from treatment initiation until death from any cause. Mean and median survival were calculated. Survival curves were constructed according to Kaplan-Meier method [9]. 95% confidence intervals for response rate were calculated using the normal approximation.

Results

Patients characteristics are shown in Table 1. Therapeutic response is shown in Figure 1. Two patients achieved CR (a 62-year-old female and a 54-year-old male) with bilateral multiple metastatic lesions in the lungs that lasted 14 and 18^{+} months, respectively. The objective response rate (CR+PR) was 11/25 (44%; Table 2).

Toxicities are shown in Table 3. All patients experienced mild adverse effects. Grade 3 and 4 toxicity was more common in hematologic parameters. The occurrence of nausea could be ascribed to cisplatin and DTIC. Fever and arthralgias were characteristic for IFN. No treatment-related deaths occurred.

Overall survival is shown in Figure 2 and time to progression in Figure 3.

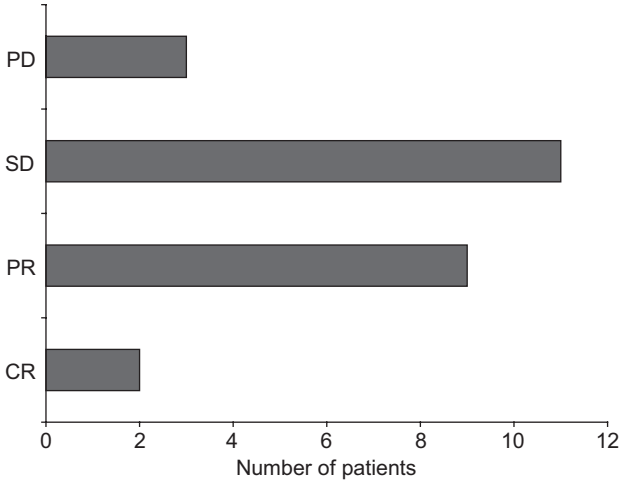


Figure 1. Response to therapy. CR: complete response, PR: partial response, SD: stable disease, PD: progressive disease.

Table 2. Characteristics of responding patients

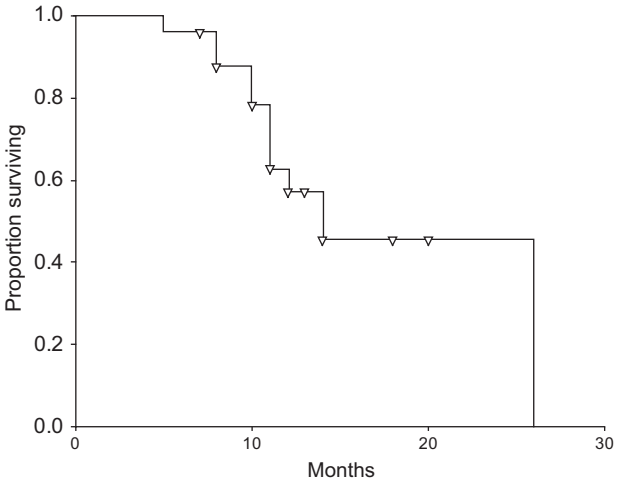
Age (years)/gender	*Metastatic site*	*Response*	*PS*	*Duration (months)*	*Survival (months)*
30/female	Skin, node	PR	1	10	14
61/male	Skin	PR	1	9+	12+
62/female	Lung	CR	1	12+	14+
61/female	Node, liver	PR	1	4+	7+
35/female	Node, lung	PR	0	10	12
54/male	Lung	CR	0	16+	18+
44/female	Skin, node, liver	PR	1	9	26
51/male	Liver	PR	1	10	20+
57/male	Skin, lung	PR	1	9	13+
44/female	Node, lung	PR	0	8	11+
40/female	Node, lung	PR	1	10+	12+

PS: ECOG performance status. For the rest of the abbreviations see Figure 1

Table 3. Treatment toxicity

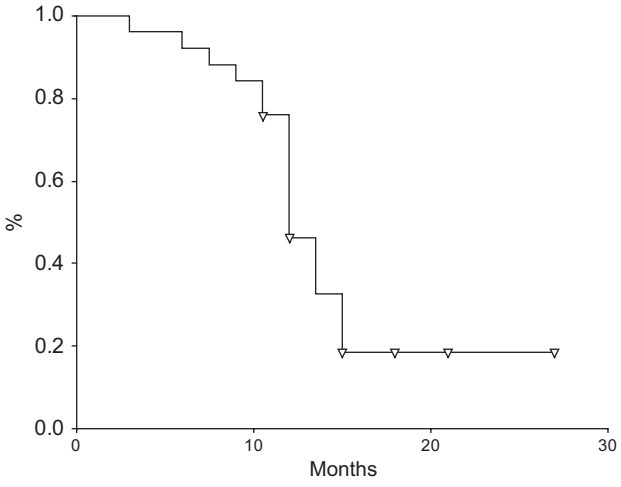
Toxicity	*Grade*				
	0	*1*	*2*	*3*	*4*
Hematological (patients, n)					
Hb	10	7	7	1	0
Plt	15	3	4	3	0
WBC	2	6	8	5	4
ANC	2	5	10	4	4
Non hematological (patients, n)					
Nausea/vomiting	2	5	12	6	0
Fever	8	6	5	5	1
Arthralgia/myalgia	5	8	5	6	1

Hb: hemoglobin, Plt: platelets, WBC: white blood cells, ANC: absolute neutrophil count



	Survival time	Standard error	95% CI
Mean:	17.66	2.05	(13.64 - 21.69)
Median:	14.00	3.32	(7.50 - 20.50)

Figure 2. Overall survival.



	Survival time	Standard error	95% CI
Mean:	9.60 (Limited to 18.00)	0.92	(7.80 - 11.39)
Median:	8.00	0.47	(7.08 - 8.92)

Figure 3. Time to progression.

Discussion

The response rate in this study was 44%. In two prospective randomized trials, a therapeutic advantage in response rate or in the duration of response has been reported with the combination of IFN and dacarbazine compared to dacarbazine alone [10]. The results of our study matched a later phase III study by Falkson et al. [6]. However, it should be emphasized that response rates were higher with combined IFN-α and chemotherapy. Extra toxicity was not observed, at least with the IFN-α doses used.

The sequence of application of dual-component chemotherapy and immunotherapy seems to play a role in achieving high response rates. Alternating biochemotherapy regimens produced poorer response rates compared to concurrent biochemotherapy programs [11].

A more convenient schedule of drug administration in which chemotherapy was used concurrently with immunotherapy showed an overall objective response rate of 64% (21% CR and 43% PR) [12]. However, chemotherapy with dacarbazine, vindesine and cisplatin with interleukin (IL)-2 and IFN-a is invariably accompanied by substantially increased and potentially hazardous toxicity [13], and without significant benefit in patients treated with biochemotherapy [14].

In the 1980s and 1990s the trend was to increase the dose of chemotherapy in order to maximize response rates in cancer [15,16].

The treatment applied in this study had acceptable toxicity profile and a high objective response rate. The experience with such a treatment was positive, though the survival analysis indicated that the disease remained incurable (without any plateau in the actuarial survival curve).

In view of the small number of the patients enrolled, we may conclude that no standard systemic therapy can be defined for metastatic melanoma. Patients should be carefully selected and appropriate treatment should be individualized. Individualization of treatment starts at the bedside, not with genome [17].

Conclusion

It is not yet possible to define standard therapy for metastatic melanoma. However, concurrent chemoimmunotherapy still represents a good option for patients with disseminated disease and good performance status. Therapeutic approaches with less toxicity and regimens able to improve overall survival rates are highly desired in the treatment of advanced malignant melanoma.

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