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Original Paper

A Phase II Study of Dacarbazine, Cisplatin, Interferon-α and High-dose Interleukin-2 in 'Poor-risk' Metastatic Melanoma

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Melanoma patients with very advanced disease have usually not been included in chemo-immunotherapy trials. We report on 22 melanoma patients, including 5 with reduced performance status (Karnofsky PS <70), 8 with metastatic ocular melanoma, 6 with brain metastases, and 4 who had pretreatment with interleukin-2. These were treated with a combination regimen of dacarbazine (250 mg/m², days 1–3), cisplatin (30 mg/m², days 1–3), interferon-α2a (IFN-α, 10 Mio IU/m² s.c., days 1–5) and IL-2 (i.v., 18 Mio IU/m² for 6, 12, 24 h, followed by 13.5 Mio IU/m² in 72 h). In the case of brain metastases radiotherapy was added. No grade IV toxicity occurred and no dose reductions were necessary. 21 patients were evaluable for response. 6 (29%) had disease progression, 5 (24%) had partial response and 10 (48%) had stable disease. Sites of response included skin, lymph nodes, muscle, lung, pleura, liver, pancreas, adrenal gland and brain. The described treatment schedule is safe and active even in patients with metastatic melanoma and poor prognosis. Copyright © 1996 Elsevier Science Ltd

Key words: melanoma, chemo-immunotherapy, interleukin-2, ocular melanoma, brain metastases
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INTRODUCTION

Introduction of immunotherapy for metastatic melanoma using interferon-α (IFN-α) and intravenous (i.v.) interleukin-2 (IL-2) has led to response rates of up to 40% [1]. Even more promising are results obtained from subsequent chemo-immunotherapy trials. Response rates up to 70% have been reported, and long lasting complete responses have been obtained in selected patients [2–5]. However, one of the main problems is the high toxicity of i.v. IL-2 administration. Both the multiple bolus schedule [6] and the 5 days-constant infusion [7] surpassed the maximum tolerated dose (MTD) in up to one third of patients [8, 9]. Using a modified regimen of IL-2 administration with an initially high and a subsequently low maintenance dose, we recently observed significantly less toxicity without diminishing clinical efficiacy [9]. Addition of dacarbazine or cisplatin to this regimen did not provoke severe toxicities and did not diminish immunological effects [10].

Patients with very poor prognosis have rarely been included in such immunotherapy trials. We report here on a cohort of patients with poor prognosis because of reduced performance status, metastatic ocular melanoma or brain metastases, who were treated in a phase II trial of chemo-immunotherapy.

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PATIENTS AND METHODS

Patient selection

Eligibility criteria included histologically or cytologically proven metastatic melanoma, bidimensionally measurable disease, a Karnofsky performance index of at least 40% and written informed consent. Exclusion criteria were pre-existing symptomatic cardiopulmonary, renal or liver disease and symptomatic brain metastases. The schedule was approved by the local Ethics Committees.

Response assessment

Response was assessed at week 8 after initiation of study treatment and thereafter at 3-monthly intervals. Partial response (PR) was defined as a more than 50% reduction of the sum of two perpendicular diameters in bidimensionally measurable tumours. Changes in size between a reduction of 50% and an increase of up to 25% was defined as stable disease (SD). An increase in tumour size of more than 25% or the appearance of any new tumour lesion was classified as progressive disease (PD).

Treatment schedule

Study treatment was started on days 1 and 29. On days 1–3 dacarbazine (250 mg/m^2) was given as a 30 min infusion, before cisplatin (30 mg/m^2) was administered over 1 h. 10×10^6 IU/m^2 IFN-α2a (Roche, Grenzach, Germany) was given subcutaneously (s.c.) on days 1–5. On days 3–8, after completion of chemotherapy, IL-2 (Chiron, Ratingen, Germany) was administered as a continuous infusion (18 Mio IU/m^2 i.v. in 6, 12, 24 h, subsequently, followed by 4.5 Mio IU/m^2 in 24 h for 3 days).

All patients with brain metastases received either stereotactic or whole brain irradiation with doses of 20 or 30 Gy, respectively. Radiation was performed before (n=4), or between the first and second cycle of chemo-immunotherapy (n=2). When brain irradiation was administered between the first and second cycle, corticosteroids for prophylaxis of brain oedema were omitted.

Serum tests

During treatment (weeks 1 and 5), serum was collected daily and investigated for levels of tumour necrosis factor (TNF-α), and soluble IL-2 receptor (sCD25),using commercially available enzyme linked immunosorbent assays (ELISA) (TNF-α, Medgenix, Ratingen, Germany; sCD25, T-Cell Sciences, Cambridge, Massachusetts, U.S.A.)

RESULTS

Patient characteristics

22 patients with metastatic melanoma (Table 1) who did not meet the usual inclusion criteria for phase II trials, because of the presence of brain metastases (n=6), primary ocular melanoma (n=8), prior administration of high-dose IL-2 and IFN-α without chemotherapy (n=4), or Karnofsky performance index below 70 (n=5) were included in this phase II study.

Table 1. Patient characteristics

	Origin of melanoma			
	Cutaneous	Ocular	Unknown	Total
No. of patients	11	8	3	22
Age (years)				
30–39	2	2	1	5
40–49	0	2	1	3
50–59	9	2	—	11
60–69	—	2	1	3
Prior treatment				
No therapy	0	0	0	0
Surgery	11	6	2	19
Radiation	1	4	1	6
Chemotherapy	3	0	2	5
Interferon-α	6	0	2	8
IL-2 s.c.	1	0	0	1
High-dose IL-2	3	0	1	4
Karnofsky score				
90–100%	3	5	1	9
70–80%	7	0	1	8
40–60%	1	3	1	5
Brain metastases	5	0	1	6
Bone metastases	4	1	1	6

IL-2, interleukin-2; s.c., subcutaneous.

Toxicity

In 22 patients, 50 treatment cycles were completed (median 2 cycles, range 1–4). No dose reduction was necessary. Toxicity evaluation of the first and second cycle of treatment is summarised in Table 2. No grade IV toxicity occurred, but 40% of cycles produced grade III nausea and vomiting. Haematological side-effects were tolerable without necessity for transfusions, but, 27% of patients experienced grade III thrombocytopenia and 17% suffered from grade III anaemia. In 79% of cycles, grade II hypotension occurred, and in 13%, weight gain, both attributed to IL-2 related capillary leak syndrome. Except dermatitis and lichenification of the skin, all side-effects were fully reversible within 3 days after cessation of treatment.

Remarkedly, despite omission of corticosteroids, none of the 6 patients with brain metastases experienced signs of elevated intracranial pressure.

Tumour response

21 of the 22 patients were evaluable for tumour response (Table 3). One patient with cutaneous melanoma who had experienced no grade III toxicities refused undergoing a second treatment cycle in the absence of disease progression and was therefore excluded from response evaluation. His reasons have been general symptoms, such as fatigue and anorexia under and after treatment, which he experienced much more severely than was objectively recorded.

5 evaluable patients (24%, 95% confidence interval 8–47%) had a PR after two cycles. This included 3 patients with cutaneous melanoma, 1 patient with ocular and 1 patient with primary melanoma of unknown origin. Two of the responding patients also had brain metastases with additional radiation therapy. Response durations were 4, 5, 7, 7 and 9 months. The current survival time of responders is 9+, 10, 12+, 13 and 14+ months (Table 4).

10 evaluable patients (48%) had SD after two cycles. Median survival of patients with SD was 8.5 months (range 3 to 17+ months). 6 evaluable patients (29%) had PD after two cycles. 4 patients with PD died within 1, 2, 2 and 4 months following initiation of immunotherapy.

Treatment of patients with a Karnofsky index of 60% or below needs special consideration (Table 5). 4 of 5 patients improved their general appearance under treatment, 3 of whom had been able to discontinue morphine analgesics for

Table 2. Toxicity of 41 cycles in percentage of 22 patients. Only first and second cycles have been evaluated

Toxicity (WHO grade)	0	I	II	III
Nausea/vomiting	20	11	29	40
Diarrhoea	29	20	31	20
Hypotension	5	16	79	0
Weight gain	77	10	13	0
Haematological				
Anaemia	2	42	54	2
Leucopenia	32	22	29	17
Thrombocytopenia	20	12	41	27
Liver	25	30	20	25
Kidney	12	37	46	5
Skin	10	13	51	26
Ototoxicity	95	0	5	0

Table 3. Response to treatment of 21 evaluable patients according to usually applied exclusion criteria

Response	All patients	Ocular melanoma	Karnofsky below 70%	Brain metastases	Pretreatment with high-dose IL-2
PR	5	1	1	2	1
SD	10	3	3	2	3
PD	6	3	1	2	0
Total	21	7	5	6	4

One patient with brain metastases also had pretreatment with high-dose IL-2.
PR, partial response; SD, stable disease; PD, progressive disease; IL-2, interleukin-2.

Table 4. Characteristics of responders

Patient no.	Primary tumour	Karnofsky index	*Previous treatment	Brain mets	Number of cycles	Location of metastases and response	Response duration	Survival
1	Cutaneous	90	None	Yes	3	Brain, lung, pleura, LN	4	10
2	Cutaneous	80	IFN-α, IL-2	No	3	LN, liver, adrenal	7	13
3	Cutaneous	90	None	Yes	4	Brain, lung, adrenal, muscle, LN	9	14+
4	Ocular	100	None	No	3	Liver	7	12+
5	Unknown	60	Dacarbazine, IFN-α	No	3	Lung, pancreas, adrenal, skin, LN	5	9+

LN, lymph node; brain mets, brain metastases; IL-2, high-dose interleukin-2; IFN-α, interferon-α, * previous systemic treatment; +, still alive.

Table 5. Characteristics of patients with initially low Karnofsky index

Patient no.	Primary tumour	Karnofsky before/after treatment	Brain mets	Number of cycles	Location of metastases	Response/duration	Survival	Comment
5	Unknown	60/80	No	3	Lung, LN, skin	PR/5	9+	Haemoptysis stopped, dyspnoea relieved
6	Ocular	40/60	No	3	Bone, muscle, LN, skin	SD/—	3	Morphines omitted for 2 months, died from sepsis
7	Unknown	60/70	No	2	Bone, liver, lienal, LN	SD/—	3	Morphines omitted for 2 months, died from meningitis carcinomatosa
8	Cutaneous	60/70	No	2	Bone, lung	SD/—	9	Morphines omitted for 3 months, died from brain metastases
9	Ocular	60/40	No	2	Lung, liver, lienal	PD/—	4	No benefit from treatment

LM, lymph node; brain mets, brain metastases; PR, partial response; SD, stable disease; PD, progressive disease. Response duration and survival is given in months. +, still alive.

painful bone metastases for 2, 3 and 6 months, respectively. One patient who had been repeatedly transfused for anaemia with a haemoglobin level below 7.0 g/dl had a PR and was able to carry out normal daily activities for over 5 months until she developed brain metastases. However, risk of occurrence of fatal complications seems to be higher in patients with initially low Karnofsky index. Patient 6 (Table 5) died from septic shock after a partially ulcerated bone/soft tissue metastasis with a volume of 2 l became infected with *E. coli*. Patient 7 who had otherwise SD throughout his body, suddenly developed dyspnoea of central origin and died. By autopsy, meningitis carcinomatosa was noted.

Serum levels of TNF-α and sCD25

Serum levels of TNF-α and soluble high affinity IL-2 receptor (sCD25) of 1 representative patient are displayed in Figure 1. While TNF-α serum levels, with a delay of one day, largely mimicked the dose intensity of the IL-2 continuous infusion schedule, the levels of sCD25 increased steadily throughout administration of IL-2. After IL-2 infusion was stopped, both TNF-α and sCD25 reached their baseline values within 3 days. Peak values for sCD25 and TNF-α were 10039 ± 3524 U/ml and 182 ± 97 pg/ml, respectively.

DISCUSSION

Toxicity

Administration of the described chemo-immunotherapy schedule is safe even in far advanced melanoma patients with Karnofsky index as low as 40% or with asymptomatic brain metastases. No grade IV toxicities were observed and only a minority of patients suffered from reversible grade III toxicities which were haematological, or affecting renal or liver function.

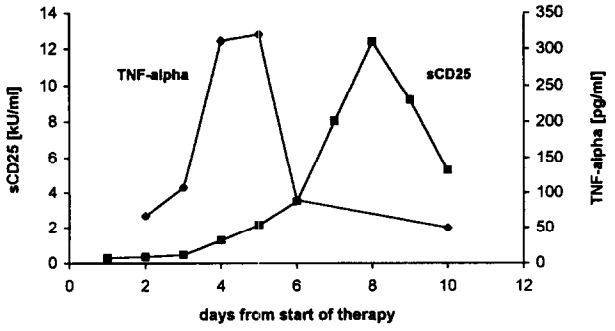

Figure 1. Serum levels of soluble interleukin-2 (IL-2) receptor (sCD25) and tumour necrosis factor (TNF-α) from one representative patient.

In general, toxicity was only slightly increased compared with toxicity due to immunotherapy with IFN-α and i.v. IL-2 alone [10].

Patients with brain metastases are usually excluded from treatment with IL-2, since severe neurological side-effects of high-dose bolus IL-2 treatment have been reported [11]. In this study, 6 patients with asymptomatic brain metastases were treated without development of any neurological side-effects. It could be possible that irradiation prior to immunotherapy or addition of chemotherapy to immunotherapy diminishes the CNS toxicity of IL-2 in patients with brain metastases.

Tumour response

A response rate of 24% (5 PR of 21 patients) is remarkable taking into account the negative selection of patients. Furthermore, only 29% of patients had PD after two treatment cycles. A similar percentage has been reported with other chemo-immunotherapy trials for metastatic melanoma in patient cohorts with better prognosis [2, 4, 12].

Of further interest is also that 1 of 7 patients with ocular melanoma had a PR and 3 had SD. To our knowledge, no phase II study has investigated the role of immunotherapy or chemo-immunotherapy in patients with ocular melanoma. In the few studies where patients with ocular melanoma have been included, extremely poor responsive rates have been observed [13, 14].

Also remarkable is the possibility of treating patients with a Karnofsky index of 60% or below. In 4 of 5 patients (Table 5), general appearance has improved and morphine analgesics or repeated transfusions were no longer required for periods between 2 and 6 months. However, even if the risk of fatal complications under treatment seems to be controllable, the risk of fatal complications according to the advanced stage of the disease seems to be substantial and needs special discussion with the patient. The patient should be aware that, in the worst case scenario, his very limited life span could be filled with several hospital stays. Alternatively, higher quality of remaining life and even an increase of the remaining life span is possible.

Addition of dacarbazine and cisplatin did not influence the kinetics of TNF-α and sCD25 as compared to the data published either for IFN-α/IL-2 immunotherapy alone [9] or if combined with a single dose of dacarbazine or cisplatin [10]. However, the peak value of serum TNF-α at 42 h was almost twice as high in this schedule as compared with immunotherapy with IFN-α and IL-2 alone, without induction of a higher cardiocirculatory toxicity.

In conclusion, combination of dacarbazine, cisplatin, IFN-α and high-dose IL-2 is a safe and active regimen even in patients with very advanced metastatic melanoma.

Note added in proof: A further patient with ten asymptomatic brain metastases up to 2 cm in diameter was subsequently treated according to this protocol. She received two cycles of treatment and after each cycle developed fully reversible grade II CNS toxicity for a period of 4 days.

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