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Phase II Study of Continuous Subcutaneous Interferon-Alfa Combined with Cisplatin in Advanced Malignant Melanoma

J. Richner, R.A. Joss, A. Goldhirsch and K.W. Brunner

Interferon-alfa (IFN-α) and cisplatin have shown synergism *in vitro* against tumour cell lines and optimal effects were observed with continuous and high IFN concentration. 20 patients with advanced malignant melanoma were treated with 10 MU IFN subcutaneously continuously, daily, plus cisplatin 50 mg/m² intravenously on days 8 and 9. Cisplatin was repeated every 4 weeks. The main toxic effects were myelosuppression, fatigue and weight loss. Toxicities always resolved completely after reduction/interruption of IFN and no life-threatening infection was observed. There were 1 complete and 6 partial responses. 6 patients had stable disease. Median time to progression was 7 months with a range of 16 to 2 months. The combined regimen of IFN-α and cisplatin is active in patients with multiple visceral and skeletal sites.
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INTRODUCTION

MELANOMA HAS a rising incidence, for which we lack effective treatment after definitive surgery. Chemotherapy has been of limited value in metastatic melanoma. Single agent treatment with dacarbazine, nitrosoureas or cisplatin have yielded response rates of 10 to 20% [1]. Encouraging reports of early results with combination chemotherapy regimens are rarely confirmed in sizeable series and the duration of response is generally short [2]. Interferons (IFN) have shown an inhibition of proliferation of melanoma cells *in vitro*. Objective regressions have been obtained in about 20%. The dose range was 10 to 50 MU interferon IFN three times weekly. Complete

responses are nearly one third. Responses can last for years [3].

Combinations of cytotoxic drugs with IFN-α have shown additive and occasionally synergistic antiproliferative effects on human tumour cell colony formation [4]. An optimal antiproliferative effect with continuous and high IFN concentrations has been shown on several tumour cell lines. A continuous subcutaneous application of IFN-α is feasible and better tolerated than intermitten subcutaneous treatment [5]. Cisplatin and IFN belong to two completely unrelated groups of drugs and the modes of action are presumably also different. Toxicities of these two drugs are different and the main side effects should not overlap. We investigated a combination of conventional doses of both agents with strict dose reduction roles for clinical or laboratory toxicity.

PATIENTS AND METHODS

Eligibility criteria included histologically proven diagnosis of malignant melanoma, recurrent or metastatic disease not amenable to curative surgery, measurable lesions with documented progression within 2 months prior to study entry, preferentially no previous systemic chemotherapy, ECOG performance status of ≤ 1, white blood cells (WBC) $> 3 \times 10^9$/l and platelets $> 100\,000 \times 10^9$/l and adequate organ function. Pretreatment with either ≤ one regimen of non-cisplatin chemotherapy or interferon or radiotherapy for localised lesions was allowed. Exclusion criteria were age > 70 years, creatinine-clearance < 60 ml/min and cardiac conditions incompatible with fever.

10 MU IFN-α2B (IFN-α) was delivered subcutaneously and continuously by a battery-operated syringe driver pump (Graseby MS26) and small Abbocath-T Teflon catheters. Catheters were changed once a week. Patients were instructed to dissolve and draw up IFN in a syringe and change this syringe daily. Collaboration of patients and their relatives was excellent and most of them enjoyed an active role in their treatments. 50 mg/m^2 cisplatin was administered on days 8 and 9 as a 30 min infusion and then repeated every 4 weeks. The first 5 patients received cisplatin as a single dose of 100 mg/m^2, but this dose had to be split thereafter due to renal toxicity (see results). Response and toxicity was evaluated by WHO criteria. The IFN-α dose was decresaed 50% at WHO grade 3 toxicity and discontinued at grade 4 toxicity. Cisplatin treatment was repeated every 4 weeks if WBC $> 3.0 \times 10^9$/l and platelets $> 100\,000 \times 10^9$/l or WBC $> 2.5 \times 10^9$/l and platelets $> 70\,000 \times 10^9$/l and follow-up values indicated an increase. Cisplatin dose was reduced 50% at a creatinine clearance of 40 to 60 ml/min and stopped at < 40 ml/min until recovery.

RESULTS

20 patients were entered into this study between November 1986 and September 1990 (Table 1). The median age was 42 years with a range of 30–69 years. 12 patients had a performance status of WHO grade 0, 8 patients were grade 1. 7 patients had adjuvant isolated limb perfusions with melphalan, one patient had a palliative perfusion for in-transit metastases. 2 patients had γ or α-interferon as experimental adjuvant therapy. 1 patient progressed under a palliative therapy of lomustine and vincristine and 1 patient had radiotherapy for localised bone metastases. 6 patients had single localisations, 4 lymph nodes, 1 lung and 1 liver. 8 patients had three or more tumour sites. 8 out of 20 patients had liver metastases, other visceral sites were pancreas, spleen, gall bladder and adrenal glands.

Table 1. Patients' characteristics

No. of patients	20
M/F	11/9
Median age, range	42, 30–69
Prior treatment	
Adjuvant isolated limb perfusion	7
Adjuvant IFN-α or IFN-γ	2
Palliative isolated limb perfusion	1
Palliative systemic chemotherapy	1
Radiotherapy	1
No. of sites	
1	6
2	7
≥ 3	7

All except 2 patients received at least two cycles of treatment. Therapy was stopped during the second cycle because of progressive disease in 3 patients and these incomplete cycles were not evaluated for toxicity. A 50% reduction of IFN-α was common (Table 2). Dose reduction to 5 MU IFN-α daily occurred in 58% of all cycles, and temporary interruption of therapy occurred in 42% of all cycles. Application of cisplatin was less affected by delay or reduction. 40 out of 52 cycles were given as planned. The main toxic effects were myelosuppression, fatigue and weight loss (Table 3). Leukopenia up to WHO grade 3 was frequently observed. The dose of IFN-α was reduced to 50% at grade 3 leukopenia only. Systemic infections were never observed. Platelet nadirs up to grade 3 occurred 2–3 weeks after cisplatin application. Anaemia was mild during the first treatment cycle, but increased during prolonged treatment. 4 patients received erythrocyte transfusions. 1 patient with a haemoglobin nadir of 57 g/l at his fourth cycle had normal values again after cessation of interferon. The first 5 patients entered in this trial received 100 mg/m^2 cisplatin as a single dose every 4 weeks. 2 patients had a substantial increase of plasma creatinine—332 and 702 μmol/l—after the first dose of cisplatin. 1 patient developed chronic renal failure under prolonged IFN-α treatment. The other patient recovered spontaneously under continuous IFN-α therapy. Further treatment cycles, with cisplatin dose splitting, were given to this patient without overt signs of renal toxicity. Intermittent proteinuria and/or microscopic haematuria were observed in 5 patients. Nausea

Table 2. Dose modifications of IFN-α-2B

	Treatment cycle No.					All cycles	
	1	2	3	4	5	No.	(%)
No. of cycles	20	15	11	5	1	52	(100)
IFN-α-2B							
50% reduction	10	8	9	3	—	30	(58)
Interruption	10	5	2	4	1	22	(42)

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Table 3. Toxic effects

	WHO grade				
	1	2	3	4	No. of patients
Leucocytes	—	7	10	—	17
Haemoglobin	3	5	3	1	12
Platelets	1	2	6	2	11
Nausea/vomiting	5	12	1	—	18
Central neurotoxicity	1	5	9	—	15
Weight loss*	5	7	5	—	17
Plasma creatinine	2	3	1	—	6
Alopecia	1	2	—	—	3
Rash	—	1	—	—	1
Diarrhoea	—	—	1	—	1

* Grade 1 < 5%, grade 2 = 5–10%, grade 3 > 10%.

and vomiting were alleviated in most patients with 5-hydroxytryptamine-receptor antagonists. The occurrence of fever was low, and chills were not observed. The most disturbing side effect was a pronounced fatigue or drowsiness. Patients lost interest in matters of daily life and preferred to stay in bed. A general slow-down in thinking, sometimes associated with mental confusion was common. 4 patients received steroids for recurrent grade 3 fatigue. Weight loss was a common initial side effect, but most patients could stabilise their weight at a lower level. 1 patient with a grade 3 weight loss had a large amount of ascites at start of treatment, which resolved completely during therapy. 1 patient developed a transient rash. Local skin infiltrations at the site of IFN-injection were common. They were asymptomatic and resolved within days of change of catheter site. One patient had a local skin infection at the injection site.

7 out of 20 patients responded to this cisplain/IFN-α combination, 5 had a response duration of 7 or more months. 1 patient had a complete response lasting for 9 months. He had large tumour masses in the spleen and colon which were removed surgically before study entry and he was treated for remaining cervical lymph node metastases. 6 patients had partial responses. The median duration of response was 9+ months (range 11+ to 2 months). One of these patients with large abdominal tumour masses (adrenal glands, gall bladder and retroperitoneal lymph nodes) had a partial response (PR) after four cycles and the residual tumour masses could be completely removed. Another patient with lung and lymph node metastases with a PR after the first cisplatin/IFN-α cycle was changed to vindesine/lomustine /IFN-α because of toxicity and had a complete response 5 months later. The other 4 patients with a PR had all multiple sites involvement and responded at all sites (patient no. 3 involvement of skin, liver and pancreas, patient no. 7 lymph nodes, large amounts of cytological positive ascites and pleural effusion, patient no. 12 skin and lung, and patient no.18 lung, liver and bone). All 3 patients with a primary or secondary CR, and one patient with a PR, received a maintenance therapy with 5–10 MU IFN-α subcutaneously alternate days for 12, 7+, 5+ and 5 months. Metastases of 6 patients were stable for a median duration of 5 months (range 10–2 months). 7 patients, including the pretreated one, had progressive disease. Responses have been seen at all sites (Table 4).

DISCUSSION

Patients with multiple metastatic sites of malignant melanoma have a short survival time and single agent chemotherapy produces a low response rate. IFN-α has limited activity in patients with metastasising melanoma, but responding lesions are mainly skin, subcutaneous and lymph node metastases [6]. Combinations of cisplatin and IFN-α have additive or synergistic effects in human tumour cell assays [4] and on xenografts of non-small cell lung-tumour in nude mice [7]. The mode of interaction is complex, and a proposed mechanism is that IFN-α might biochemically modulate the activity of anticancer drugs [8].

In the present study of 19 previously untreated patients with advanced malignant melanoma seven achieved a significant tumour reduction and 6 patients had stable disease. Median time to progression was 7 months with a range of 16–2 months. The combined regimen of IFN-α and cisplatin is active in patients with multiple visceral and skeletal sites. Toxicity is pronounced but manageable and life-threatening toxicities have not been observed. A subclinical renal toxicity of IFN-α was described for patients with chronic myelocytic leukaemia [11]. The initial renal toxicity in our study was lessened by splitting the initial single dose of 100 mg/m^2 cisplatin to two doses of 50 mg/m^2 on the following 2 days. A remaining subclinical toxicity was observed in some patients. Myelosuppression was accentuated but easily controlled through IFN-α modifications. Infections or life-threatening thrombocytopenias were not observed. Continuous treatment with IFN-α may potentiate a cisplatin induced myelosuppression. The most troublesome side-effects were grade 3 central neurotoxicities. The continuous subcutaneous application reduced the incidence of chills and fever, but could not prevent fatigue and malaise. A long-term treatment with 10 MU IFN-α continuous subcutaneous was only feasible in a minority of patients.

On-going phase-II trials [9, 10] with cisplatin/IFN-α combinations will provide further information about optimal combination schedules and relations between dose intensity and response. Several other combinations of cytostatic drugs and IFN-α have been investigated. Dacarbazine and IFN-α are active in patients with malignant melanoma. Results of two studies with 51 and 79 patients have been reported and response rates were 32 and 25% [12, 13]. A superiority of such combinations over single agent chemotherapy will be clarified by further phase III studies. We observed a response rate of 35% (95% confidence interval 15.4–59.2%) with cisplatin/IFN-α

Table 4. Site of disease and response

		Responses				
	No. of patients	CR	PR	NC	P	Median duration (CR and PRs, months)
Lymph nodes	12	2	1	5	4	7
Lung	10	—	5	3	2	7
Skin	6	—	2	2	2	3
Visceral						
Liver	8	—	3	2	3	9
Other	6	—	3	1	2	7
Bone	1	—	1	—	—	11+

CR = complete response, PR = partial response, NC = no change, P = progressive.

and more important, sustained responses and stable disease in patients with advanced metastasising melanoma. A cisplatin/IFN-α combination may be useful in younger patients as induction treatment followed by surgery for residual disease and maintenance treatment with IFN-α.

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Sequential Interleukin-2 and Alpha Interferon for Renal Cell Carcinoma and Melanoma

H. Thomas, C. Barton, A. Saini, A. Dalgleish and Jonathan Waxman

There is a theoretical basis for the synergy of interleukin-2 (IL-2) with other cytokines. We have investigated sequential treatment with IL-2 and α interferon. 1 of 22 patients with metastatic renal cell carcinoma had a partial response and one a minimal response to continuous infusion IL-2 but none of the 9 patients with melanoma responded. 16 of 17 patients with renal cell cancer, and 8 with melanoma, were then treated with α interferon. 2 patients with renal cell cancer responded to α interferon with sustained remissions of 30 and 40 months; both had responded to IL-2. The investigation of combination therapy with other cytokines is suggested, by these unusually long responses to α interferon.
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INTRODUCTION

REPORTS APPEARED in 1985 of the use of recombinant interleukin-2 (rIL-2) with lymphokine activated killer (LAK) cells in human malignancies [1]. Surprisingly high response rates were described in solid tumours unresponsive to conventional therapies. Renal cell carcinoma and melanoma were amongst the most responsive tumours within this group. rIL-2 and LAK cells therapy have significant morbidity and this relates to a capillary leak syndrome. These toxicities manifest in a myriad of ways [2]. The high response rate led other groups to investigate the possibility of modifying treatment related toxicity. Treatment was originally given by bolus injection of rIL-2 with infusions of LAK cells. Subsequently constant infusions of rIL-2 were given without LAK cells with the idea of generating LAK cells *in vivo* [3]. A similar order of response was reported with much less toxicity, but this view is contentious. Since these earlier reports, treatment with rIL-2 has been investigated at other centres and the response of renal cell cancer and melanoma is thought to be lower than originally described [4]. There is theoretical evidence that cytokines in combination may act synergistically, but the precise combination, and the optimal treatment regimen is not known. We now report our experience of rIL-2 infusional therapy followed by subcutaneous alpha interferon treatment in patients with metastatic renal cell carcinoma and melanoma.

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