Eur J Cancer Clin Oncol, Vol. 22, No. 11, pp. 1407–1411, 1986.
Printed in Great Britain

0277-5379/86$3.00+0.00
Pergamon Journals Ltd.

Letter to the Editor

Recombinant Leukocyte A Interferon and Cimetidine Treatment in Disseminated Melanoma

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INTERFERONS (IFN) comprise a class of glycoproteins with a wide range of biological activities, including anti-tumor effects [1–4]. In particular, inhibition of melanoma cell growth *in vitro* and *in vivo* indicates an anti-melanoma effect of IFN [5–7]. Despite promising experimental observations, leukocyte IFN therapy in melanoma has yielded only limited therapeutic success [8–10]. In a recent analysis of the results of 13 trials comprising a total of 324 melanoma patients treated with different preparations of IFN, an overall response rate of 11.1% (CR 3.1%, PR 8.0%; 11) was noted. Some investigators reported, although not unequivocally [12–14], that the anti-tumor effect of IFN can be enhanced by adding cimetidine [15–17], possibly via the inhibition of suppressor T-cells [18–20].

Table 1. *Treatment with recombinant leukocyte A interferon (rIFN-αA) and oral cimetidine in* 11 *patients with melanoma metastases*

Case age/sex	Performance status Karnofsky index	Prior therapy	Site of metastases prior to rIFN-αA	rIFN-αA therapy Dosage × 10^6		Days	Response
1. 41/male	50	PVD	liver, kidney	18	i.m.	10	PD (death)
2. 61/male	40	BCG	brain, liver	18	i.m.	14	PD (death)
3. 72/male	50	0	lung, brain, bone, cutaneous metastases	18	i.m.	20	PD (death)
4. 63/male	50	PVD	brain	18	i.m.	24	PD (death)
5. 48/male	40	PVD	liver	18	i.m.	30	PD (death)
6. 57/female	70	0	cutaneous metastases	18	i.m.	370	PR
7. 36/female	80	D, PVD, perfusion	cutaneous	18	i.m.	320	SD
		l-phenylalanine mustard	metastases, lung	4×/week	i.m.	80	PD
8. 90/female	60	0	cutaneous	18	i.m.	7	PR
			metastases	36	i.m.	27	PR
9. 61/female	70	BCG	cutaneous	18	i.t.	21	SD
		DNCB	metastases	18	i.m.	120	PR
				9	i.m.	220	CR
				0	0	180	CR
10. 54/female	60	D	cutaneous	18	i.m.	180	SD
			metastases	4×/week	i.m.	60	PD
11. 57/female	70	surgery	cutaneous	18	i.m.	82	SD
			metastases	18	i.m.	370	PD

P = cisplatin; V = vindesine; D = DTIC; i.m. = intramuscularly; i.t. = intratumoral; CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease.

Accepted 4 April 1986.
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This study was supported in part by Hoffmann–La Roche, Basel, Switzerland.

In the present study 11 patients with melanoma metastases were treated with recombinant leukocyte A interferon (Ro 22–8181, rIFN-αA; Hoffman–La Roche, Basel, Switzerland) and oral cimetidine (OC; Cimetag^R). Ro 22–8181 is a biosynthetic human leukocyte (α) IFN, which is comparable in its biologic effect to natural leukocyte IFN [21, 22]. Details of patients' characteristics, course of disease and results of therapy are presented in Table 1 and were mentioned in part elsewhere [23]. In all patients the primary melanoma lesion had been surgically excised. When the combined rIFN-αA/OC therapy was instituted, all patients had histologically or radiographically verified progressively growing measurable metastatic lesions. Treatment was started in all patients with intramuscular injections of 18×10^6 IU rIFN-αA(specific activity $2–4 \times 10^6$ IU/mg protein) at 5 days/week except patient No. 9 who initially received rIFN-αA intratumorally (Table 1). Oral cimetidine was given concomitantly in a constant daily dosage of 1000 mg, the rIFN-αA dosage was reduced (or increased in patient No. 8) individually according to tolerability of treatment and severity of side effects. Tumor responses to treatment were evaluated according to the recommendations of the WHO [24].

In general, three patients responded to, and three exhibited stable disease (SD) after combined treatment with rIFN-αA/OC (Table 1). No objective regressions were observed in patients Nos. 1–5 with visceral metastases and a Karnofsky index of $\leqq$ 50. Treatment responses—(or SD)—were found exclusively in patients with cutaneous or subcutaneous metastases—except patient No. 7 who had additional lung metastases—and exhibited a Karnofsky index of $\geqq$ 60%. In patient No. 9, we observed one complete response (CR) (Figs. 1, 2) which was histologically verified (Figs. 3, 4). Two patients exhibited partial responses (PR; Nos. 6 and 8) and three showed SD (Nos. 7, 10, 11), which was also true for 7 months for the lung metastases in patient No. 7. Discontinuation of treatment in patient No. 8 who had responded by an impressive reduction of the tumor mass on her right foot was immediately followed by a prompt relapse.

Table 2. Clinical toxicity and side effects of recombinant leukocyte A interferon from 18×10^6 IU/5 *times weekly*

Moderate:	Severe:
Anorexia	Fever, Flu
Diarrhoea	Fatigue
Nausea	Weight loss
Vomiting	Leukopenia
Myalgia	Liver toxicity
Thrombocytopenia	
Renal Toxicity	

Toxicity and side effects were experienced in various degrees in all patients with fever, flu-like symptoms and fatigue being the most common, usually at the very first or the first days after initiating the treatment or increase of the dosage (Table 2). Side effects were dose dependent, reversible and necessitated reduction of dosage in some patients but not discontinuation of treatment.

Although the limited number of patients obviously does not permit to draw a definitive conclusion, our study thus indicates that combined rIFN-αA/OC therapy seems to control or at least beneficially influence the course of cutaneous melanoma metastases, but seems to be of little value in the treatment of visceral metastases in patient with terminal disease state. Finally, despite the fact that the present study was not designed to evaluate the contributory effect of cimetidine to recombinant IFN treatment, comparison of our data with those of other studies using recombinant IFN alone in similar or even higher IFN dosages [10, 25] suggests a beneficial effect on the overall response rates by adding oral cimetidine to recombinant IFN treatment.

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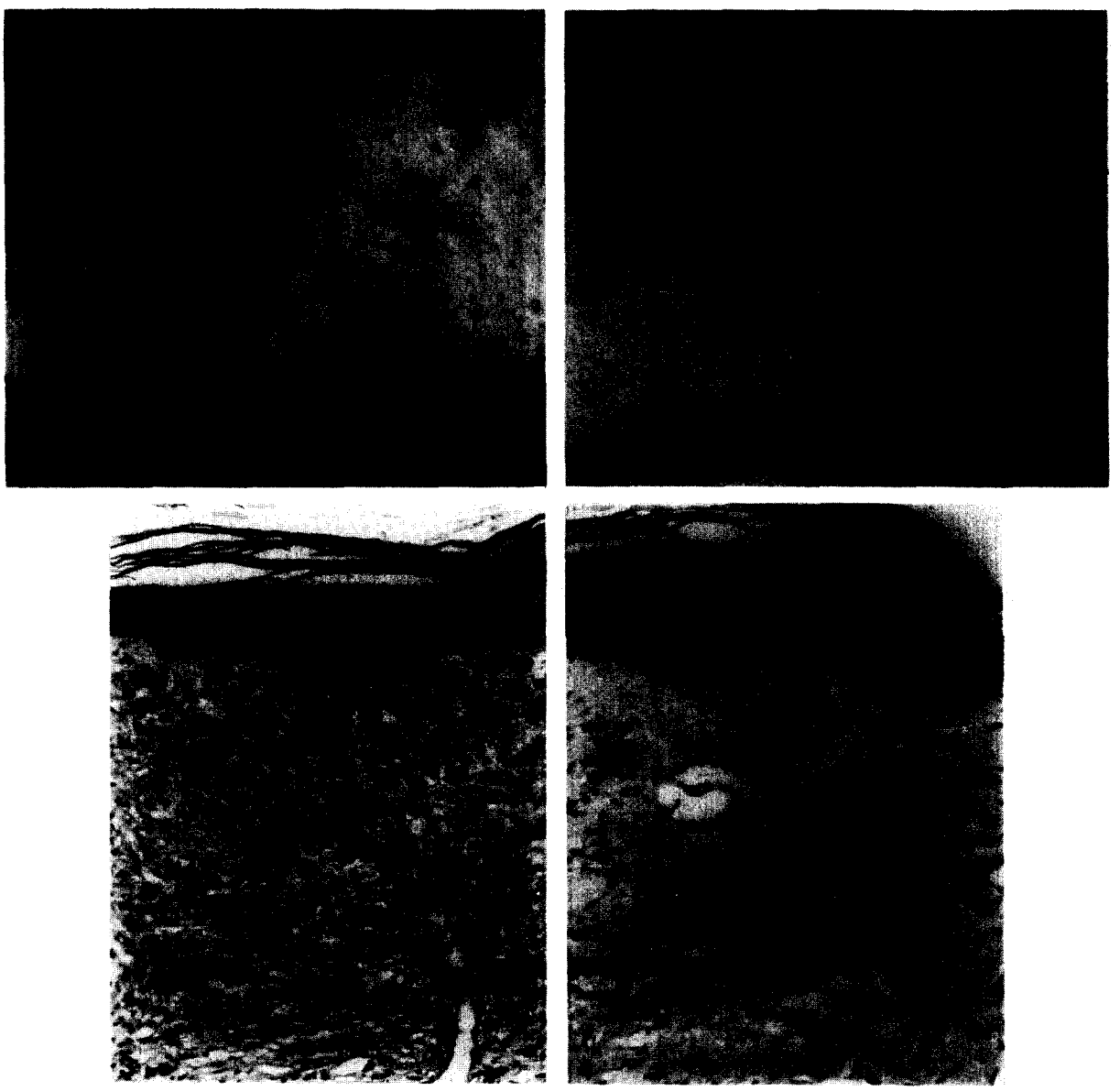

Figs. 1–4. *Patient No.* 9, *SF. Cutaneous melanoma metastases on the left upper leg before* (*Fig.* 1) *and after* 18 *months of rIFN-αA/OC treatment* (*Fig.* 2). *Response to treatment was histologically verified in that metastatic melanoma cells* (*Fig.* 3) *could not be identified in a biopsy specimen taken after treatment from the previously involved site* (*Fig.* 4).

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