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.

1. Lucas VS, Huang AT. Chemotherapy of Melanoma. In: N Siegler ed. *Clinical Management of Melanoma*. The Hague, The Netherlands, Martinus Nijhoff, 1982, 381–404.
2. Luikart SD, Kennelaley GT, Kirkwood JM. Randomized phase III trial of vinblastine, bleomycin, and cis-dichlorodiammine-platinum versus dacarbazine in malignant melanoma. *J Clin Oncol* 1984, 2, 164–168.
3. Kirkwood JM, Ernsthoff M. Melanoma: Therapeutic options with recombinant interferons. *Sem Oncol* 1985, 12, Suppl. 5, 7–12.
4. Welander C, Morgan T, Homesley H, *et al.* Combined recombinant human interferon alpha2 and cytotoxic agents studied in a clonogenic assay. *Int J Cancer* 1985, 35, 721–729.
5. Ludwig Ch, Stoll H, Obrist R, *et al.* Improved tolerance of interferon by continuous subcutaneous infusion. *Proc Am Soc Clin Oncol* 1986, 5, 234.
6. Dorval Th, Palangie T, Jouve M, *et al.* Clinical Phase II Trial of recombinant DNA interferon (interferon alfa 2b) in patients with metastatic malignant melanoma. *Cancer* 1986, **58**, 215–218.
7. Carmichael J, Ferguson R, Wolf C, *et al.* Augmentation of cytotoxicity of chemotherapy by human alfa-interferons in human non-small cell lung cancer xenografts. *Cancer Res* 1986, **46**, 4916–4920.
8. Wadler S, Schwartz E. Antineoplastic activity of the combination of interferon and cytotoxic agents against experimental and human malignancies: a review. *Cancer Res* 1990, **50**, 3473–3486.
9. Oratz R, Dugan M, Walsh C, *et al.* Phase II trial of r-α2b-interferon and cisplatin in metastatic malignant melanoma. *Proc ASCO* 1989, **8**, 288.
10. Margolin K, Doroshow J, Akman S, *et al.* Treatment of advanced melanoma with cisdiamine dichloroplatinum and alpha interferon. *Proc ASCO* 1990, **9**, 277.
11. Kurschel E, Metz-Kurschel U, Hofmann W, *et al.* Untersuchungen zur Erfassung der Nephrotoxizität von humanem Alpha-2b-Interferon. *Klin Woschr* 1987, **65**, 667–672.
12. Thomson DB, McLeod RC, Hersey P. Phase I/II Study of tolerability and efficacy of recombinant interferon with dacarbazine in advanced malignant melanoma. *Proc ASCO* 1987, **6**, 208.
13. Bajetta E, Negretti E, Giannotti B, *et al.* Phase II study of interferon alpha-2a and dacarbazine in advanced melanoma. *Am J Clin Oncol* 1990, **13**, 405–409.

Acknowledgement—We thank Dr. H.P. Egger from Essex Chemie AG, Lucerne for the provision of recombinant Interferon-Alfa-2B.

Eur J Cancer, Vol. 28A, No. 6/7, pp. 1047–1049, 1992.
Printed in Great Britain

0964–1947/92 $5.00 + 0.00
Pergamon Press Ltd

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.
Eur J Cancer, Vol. 28A, No. 6/7, pp. 1047–1049, 1992.

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.

Correspondence to J. Waxman.
J. Waxman, H. Thomas, C. Barton and A. Saini are at the Department of Clinical Oncology, Royal Postgraduate Medical School, Hammersmith Hospital, Du Cane Road, London W12 0HS; and A. Dalgleish is at St. George's Hospital, London, U.K.
Revised 18 Oct. 1991; accepted 18 Nov. 1991.

PATIENTS AND METHODS

22 patients with metastatic renal cell carcinoma and 9 patients with metastatic melanoma were treated. The patients' characteristics are described in Table 1.

Treatment with rIL-2 (Glaxo) was given as infusional therapy in albumin for 5 days each week for 4 weeks. The initial dosage was 400 μg/m² per 24 h which was increased by 100 μg daily to clinical and biochemical tolerance. If patients developed WHO grade 3–4 toxicity, treatment was discontinued. Minor toxicities such as flu-like symptoms or gastrointestinal disturbance were managed by the use of the appropriate medications and rIL-2 dosages were not changed. WHO grade 2 change in renal or hepatic function was treated by discontinuing therapy until these changes had resolved. Treatment was then reinstituted at a dosage of 100 μg/m² less than that causing symptoms and maintained at that level. During treatment each patient was carefully monitored by daily fluid balance, weight, renal function, hepatic function, full blood count and symptom recordings. When the protocol was originally planned, if treatment was without major toxicity and there were no signs of disease progression, a further course of treatment should be given 4 weeks after the first course of rIL-2. Four weeks after completing rIL-2 therapy all patients were restaged. All patients were then treated with α interferon (Roche) given at a dosage of 3 mega units subcutaneously three times a week. The patients responses were described as complete, partial, where there were greater than 50% reduction in measurable disease or minimal with 25–50% reduction in measurable disease.

RESULTS

2 patients responded to rIL-2. A patient with renal cell carcinoma had a 50% reduction in her pulmonary and subcutaneous metastases but this lasted only 1 month. 1 patient with para-aortic metastases from renal cell carcinoma had a minimal response to treatment with a 25% reduction in the nodal mass. 1 patient with melanoma had disease stabilisation.

4 patients with renal cell carcinoma and 1 patient with melanoma died during the first four treatment weeks of progressive disease. These patients had poor performance statuses. The median total tolerable daily dosage was 1072 μg (range 200–1500 μg). There was no significant difference between the total daily dosage in renal cell carcinoma which was 1070 μg and melanoma which was 1074 μg. The median duration of treatment was 3.1 weeks (range 1–6 weeks) and was identical in the renal cell and melanoma patients. Only 2 patients received two courses of rIL-2.

Table 1. Patients' characteristics

	Renal cell carcinoma	Melanoma
Median age (range) years	53 (18–76)	49 (33–59)
Sex		
F	6	3
M	16	6
Karnofsky performance score	71%	83%
Disease site		
LD	11	2
LN	8	6
H	3	3
P	7	3
C	2	3
B	2	1

LD = local disease, LN = lymph nodes, H = hepatic, P = pulmonary, C = cutaneous, B = bone.

Table 2. Treatment toxicity (WHO grade 3 or 4)

	Overall	Renal cell	Melanoma
Diarrhoea	8	7	1
Mucositis	2	2	—
Renal	16	12	4
Fluid retention	24	15	9
CNS	5	4	1
Skin	13	9	4
Hepatic dysfunction	5	3	2
Pyrexia	19	11	8
Infection	6	4	2
Ascites	1	1	—
SVCO	1	1	—
Eosinophilia	6	4	2
Nausea	8	5	3
Coagulopathy	4	4	—
Hypovolaemia	9	6	3

Treatment toxicity was considerable, seen in all patients and is described in Table 2. The toxicities were significant enough for treatment to be discontinued in 16 patients, 12 of whom had renal cell carcinoma and 4 had melanoma. Major cardiovascular toxicities did not occur because of careful monitoring of weight and fluid balance.

Following radiological reassessment, 16 of 17 patients with renal cell cancer and 8 with melanoma were treated with alpha interferon. Treatment with α interferon continued until disease progression was demonstrable. 1 patient refused treatment with interferon and received medroxyprogesterone acetate. In renal cell carcinoma a complete response to alpha interferon was seen in the patient with lung and subcutaneous tissue metastases who had had a transient partial response to rIL-2. This patient's remission has lasted for 30 months. The patient who had had a minimal response in para-aortic nodes has had a further partial response to interferon for 40 months. No patients with melanoma responded to α interferon. There were no significant side effects from interferon.

DISCUSSION

There were two prolonged responses lasting 30 and 40 months to α interferon following rIL-2 treatment and these are of interest even in the context of a disease with a long natural history. The duration of response and disease stabilisation is greatly in excess of that expected for the interferons where the median duration of a complete response is 8 months [5].

The synergy of cytokines was first described for alpha interferon and IL-2 in a sarcoma model. Different combinations have different antitumour effects and in animal models, rIL-2 with γ interferon had less activity than with α or β interferon [6]. There have been reports of the combination of α, β and γ interferon with IL-2 in renal cell cancer or melanoma. In these studies, in contrast to our own, these agents have been administered concomitantly rather than sequentially. Only small numbers of patients have been treated in this way. The response to such regimens is similar to that expected for single agent treatment with rIL-2 [7–10]. In our study the possibility of cytokine

synergy is indicated by the prolonged second responses to α interferon. The duration of response to alpha interferon given after rIL-2 is 3–5 times longer than that expected.

This information provides an anecdotal basis for the continued search for the possibility that rIL-2 in combination with other biological response modifiers may lead to an increased response as compared with single agent treatment. The dosage, schedule of administration and the combination of agents to be used is unknown but is under investigation in many centres.

1. Rosenberg SA, Lotze MT, Muul LM. Observations on the systemic administration of autologous lymphokine-activated killer cells and recombinant interleukin-2 to patients with metastatic cancer. *N Engl J Med* 1985, **313**, 1485–1492.
2. Rosenberg SA, Lotze MT, Yang JC, *et al.* Experience with the use of high-dose interleukin-2 in the treatment of 652 cancer patients. *Ann Surg* 1989, **210**, 474–485.
3. Paciucci PA, Holland JF, Ryder JS, *et al.* Immunotherapy with interleukin-2 by constant infusion with and without adoptive cell transfer and with weekly doxorubicin. *Cancer Treat Rev* 1989, **16**(Supp A), 67–81.
4. Waxman J, Thomas H. Is the outlook changing for patients with renal cell cancer? *Eur J Cancer* 1990, **26**, 860–862.
5. Horoszewicz JS, Murphy GP. An assessment of the current use of human interferons in therapy of urological cancers. *J Urol* 1989, **142**, 1173–1180.
6. Truitt GA, Brunda MJ, Levitt D, Anderson TD, Sherman MI. The therapeutic activity in cancer of IL-2 in combination with other cytokines. *Cancer Surv* 1989, **8**, 875–889.
7. Hyung Lee K, Talpaz M, Rothberg JM, *et al.* Concomitant administration of recombinant human interleukin-2 and recombinant interferon alpha 2A in cancer patients: A phase I study. *J Clin Oncol* 1989, **7**, 1726–1732.
8. Hirsh M, Lipton A, Harvey H, *et al.* Phase I study of interleukin-2 and interferon alfa-2a as outpatient therapy for patients with advanced malignancy. *J Clin Oncol* 1990, **8**, 1657–1663.
9. Farace F, Mathiot C, Brandelyn M, *et al.* Phase I trial with recombinant interleukin-2 (rIL-2): immune activation by rIL-2 alone or following pretreatment with recombinant interferon-gamma. *Clin Exp Immunol* 1990, **82**, 194–199.
10. Kirchner H, Korfer A, Palmer PA, *et al.* Subcutaneous interleukin-2 and interferon-alpha 2b in patients with metastatic renal cell cancer: the German outpatient experience. *Mol Biother* 1990, **2**, 145–154.

Eur J Cancer, Vol. 28A, No. 6/7, pp. 1049–1051, 1992.
Printed in Great Britain

0964–1947/92 $5.00 + 0.00

Phase I Study Comparing Continuous Infusion of Recombinant Interleukin-2 by Subcutaneous or Intravenous Administration

M.G. Leahy, D. Pitfield, S. Popert, C.J. Gallagher and R.T.D. Oliver

22 cancer patients entered a randomised phase Ib trial comparing the effects of low-dose recombinant interleukin-2 (300 μg/m², approximately equivalent to 6.4 × 10⁶ cetus units or 38 × 10⁶ U per day) given continuously by intravenous or subcutaneous infusion. At 48 h after two 5-day courses, median lymphocyte levels (× 10⁹/l) were 6.0 (387% increase) in the subcutaneous arm (n = 9) and 5.9 (369% increase) in the intravenous arm (n = 8). Liver and renal toxicity were similar in the two groups. One minor response lasting 4 months occurred in 12 renal cancer/melanoma patients receiving subcutaneous treatment and one durable complete remission continuing at 30 months and one minor response lasting 10 months occurred in 6 renal cancer/melanoma patients receiving intravenous treatment.
Eur J Cancer, Vol. 28A, No. 6/7, pp. 1049–1051, 1992.

INTRODUCTION

INTERLEUKIN-2 (IL-2) produces 3–5% complete durable responses in patients with metastatic renal cell cancer and melanoma, and partial remissions in a further 15–20%, in multiple clinical trials [1]. However, though most of this work combined IL-2 with lymphokine-activated killer cells (LAKs), there has been little evidence that LAKs add much to response rate [2, 3], and these early studies used maximum tolerated doses of IL-2 given by intravenous boluses leading to considerable toxicity [2], which necessitated intensive therapy unit support, and some drug-related fatalities. Furthermore, animal studies suggest that efficacy may actually be reduced at high doses [4] and, *in vivo*, subcutaneous dosing leads to longer biological effects than intravenous dosing [5]. More recent studies of IL-2 have focused on less intensive, intermittent schedules with increased duration of treatment [6] though there has not been any direct comparison of the two approaches. Prompted by some evidence that the level of rebound lympho-

Correspondence to M.G. Leahy.
The authors are at the Royal London Hospital Medical College, Department of Medical Oncology, Whitechapel, London, U.K.
Received 7 Oct. 1991; accepted 24 Dec. 1991.