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A phase I study of rDNA alpha-2b interferon as a 6-week continuous intravenous infusion*

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Summary. Sixteen patients with advanced malignancy were treated with rDNA alpha-2b interferon using a continuous 6-week i.v. schedule. Patients received 1 μg, 3 mg, 5 mu and 7 mu/m^2/day via a portable infusion pump system, all therapy being on an outpatient basis. The dose-limiting toxicity occurring at 7 mg/m^2/day was lethargy and somnolence. Five million units (mu) was the maximum tolerated dose but significant nausea, anorexia and lethargy affected 4/5 patients at this level. A dose of 3 mu/m^2/day was well tolerated, producing little disturbance of normal activity in the majority of patients. Suppression of WBC and platelets was seen at all doses but was not dose-limiting. There was increasing severity of derangement of hepatic transaminases with increasing dose, and the occurrence of liver toxicity appeared to correlate with nausea, anorexia and lethargy.

Assay of serum interferon during the infusion showed that this system maintained a constant level of interferon in the blood. However, the increase did not show a linear pattern with increasing dose, suggesting saturation of metabolic inactivation at 7 mu/m^2/day.

We recommend that a dose of 3 mu/m^2/day be used in future studies of prolonged infusions of alpha-2 interferon.

Introduction

Since the advent of recombinant DNA (rDNA) technology, several phase I and II clinical studies have been performed with alpha-2 interferon [5, 15, 17]. The majority of these trials have used intermittent s.c. or i.m. schedules based partly on the kinetics of interferon [2, 14] and partly on pragmatism. However, the early experiments investigating the antitumor effects of interferon in transplanted mouse tumours showed that greater cell kill could be achieved if the drug was given daily rather than intermittently and that a total dosage given as a series of injections was more effective than as a single large dose [7]. In addition the antitumour effect was enhanced by giving as large as possible a dose with each injection [16].

These data suggest that interferon may be most effective when administered as a continuous infusion at the maximum possible dose. The development of accurate small-volume portable infusion pumps has made studies of prolonged drug infusions feasible [10].

This study investigates the toxicity of rDNA alpha-2b interferon (Intron A, Kirby-Warrick Ltd) administered as a 6-week continuous i.v. infusion. In addition the serum levels of interferon were monitored to determine whether or not stable concentrations of interferon could be maintained.

Patients and methods

Patients. The patients included in the study either had advanced malignancy which had failed to respond to conventional therapy or had completed planned chemotherapy and the interferon was used as a "maintenance" therapy. This latter group included patients with multiple myeloma who had entered a plateau phase [3] and also patients with melanoma who had entered partial remission following treatment with high-dose melphalan and DTIC. All patients had a WHO performance status of <3 and an estimated life expectancy of at least 3 months. Minimum haematological requirements were white blood count (WBC) $>3\times10^9$/l and platelets $>100\times10^9$/l. In addition, serum creatinine had to be <0.12 nmol/l with normal hepatic transaminases.

Interferon administration. The interferon was administered through a central venous line using either a Vygon Nutricath (Vygon, Laboratories Pharmaceutiques, Ecouen, France) or a Port-A-Cath system (Pharmacia Ltd, Milton Keynes, England). The drug was delivered using Pharmacia Acta-Pumps (Pharmacia Ltd, Milton Keynes, England) which could be conveniently carried on a waist belt. Preliminary studies had demonstrated that there was no reduction in interferon level in the pump reservoir over a period of at least 7 days. Thus interferon sufficient for 8 days therapy was reconstituted in 40 ml sterile water and added to the pump reservoir. Patients were seen every 7 days during treatment for haematological testing and refilling of the reservoir.

The starting dose for the study was 1 mu/m^2/day (1 mu) with subsequent patients entered at 3 mu/m^2/day (3 mu), 5 mu/m^2/day (5 mu) and 7 mu/m^2/day (7 mu).

Investigations. Investigations prior to the start therapy included full blood count, biochemical profile and liver function tests. These investigations were repeated weekly

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during therapy and 1 week following discontinuation of therapy. In addition all patients had a chest X-ray at the start and finish of treatment. Other X-rays and scans were performed as clinically indicated.

Interferon analysis. Blood samples were taken for interferon assay prior to start of therapy, at weekly intervals during therapy and 7 days post therapy in patients treated at 3, 5 and 7 mu.

Serum was separated immediately and stored at −20° C prior to assay. The analyses were carried out using a Boots Cell Tech Diagnostic Assay with NK2 monoclonal antibody by Dr. Sheila Jacobs, Schering Plough Corporation, USA.

Results

Sixteen patients were entered in the study and the patient characteristics are shown in Table 1. Two patients were studied at 1 mu, seven at 3 mu, five at 5 mu and two at 7 mu. Two patients did not complete the planned 6 weeks treatment because of rapid tumour progression, and a further patient discontinued therapy because of infection.

Subjective toxicity

The subjective toxicity is shown in Table 2. One of the two patients treated at 1 mu, 4/7 treated at 3 mu, 3/5 treated at 5 mu and both the patients at 7 mu experienced a flu-like syndrome commencing 6–12 h after the start of the infusion and lasting 24–48 h. There was no further subjective toxicity at the lowest dose. However, at higher doses there was progressively more nausea, anorexia and fatigue. These symptoms occurred in 3/7 patients at 3 mu, 4/5 patients at 5 mu and in both patients at 7 mu. A further three patients at 3 mu complained of fatigue but without associated nausea and anoexia. Nausea and anorexia exhibited a degree of tachyphylaxis but responded poorly to antiemetics and did not resolve completely until the infusion was discontinued. Fatigue, on the other hand, became progressively more severe throughout treatment, and at 7 mu was accompanied by marked somnolence, both patients sleeping for 6–8 h during the day as well as at night. The severity of these symptoms necessitated stopping the interferon infusion after 5 weeks in both patients.

All subjective toxicity resolved within 7 days of discontinuing therapy.

Haematological toxicity

Changes in the blood count were seen at all dose levels (Fig. 1) but were not dose-limiting. Maximum WBC suppression occurred during the first 7–14 days, counts remaining low until the infusion was discontinued. The lowest WBC values ($\times 10^9$/l) recorded in any patient at each dose level were 2.4 at 1 mu, 1.2 at 3 mu, 1.2 at 5 mu and 1.7 at 7 mu. Although in some patients therapy appeared to in-

Table 1. Patient characteristics

Patient	Age	Diagnosis	Previous treatment	Interferon dose (mu/m²/day)	Duration of interferon	Reason for discontinuation
ER	52	Myeloma	CT	1	6	Completed
RM	61	Myeloma	CT+RT	1	6	Completed
EP	63	Myeloma	CT+RT	3	4	Central line infection
TW	60	Melanoma	CT+RT	3	3	Disease progression
SM	37	Melanoma	CT	3	6	Completed
EA	46	Melanoma	CT	3	6	Completed
BD	56	Renal Ca	RT	3	6	Completed
MH	68	Myeloma	CT+RT	3	6	Completed
RS	50	Myeloma	CT+RT	3	6	Completed
RS	55	CLL	CT	5	6	Completed
JO	40	Melanoma	CT+RT	5	3	Disease progression
LH	32	Melanoma	CT+RT	5	6	Completed
KL	22	Melanoma	CT	5	6	Completed
CA	22	ALL	CT	5	6	Completed
AM	33	Melanoma	CT+RT	7	5	Toxicity
AB	55	Myeloma	CT+RT	7	5	Toxicity

CLL, chronic lymphotic leukaemia; ALL, acute lymphotic leukaemia; CT, chemotherapy; RT, radiotherapy

Table 2. Subjective toxicity

Interferon dose (mu/m²/day)	No. of patients	Number of patients				
		Flu-like syndrome	Nausea	Anorexia	Lethargy	Somnolence
1	2	1 (50%)	–	–	–	–
3	7	4 (57%)	3 (43%)	3 (43%)	6 (85%)	–
5	5	3 (60%)	4 (80%)	4 (80%)	4 (80%)	–
7	2	2 (100%)	2 (100%)	2 (100%)	2 (100%)	2 (100%)

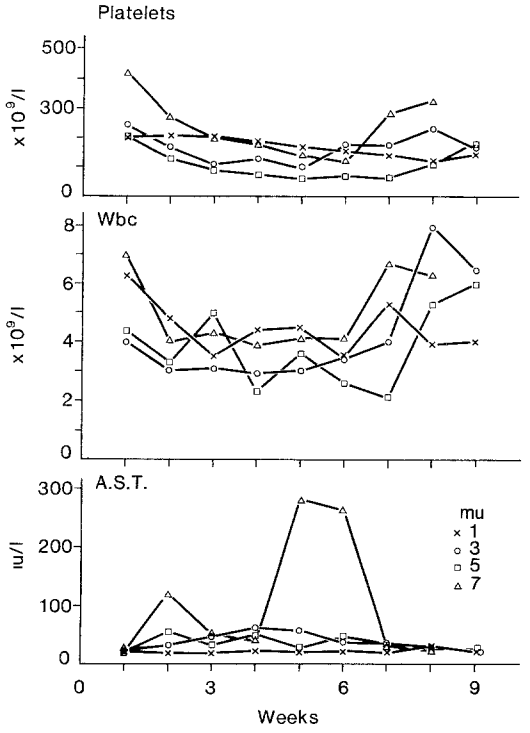

Fig. 1. Mean values for platelets, WBC and AST recorded weekly at 1, 3, 5 and 7 mu/m²/day

duce a proportionally greater fall in the neutrophil count than in the lymphocyte count, no consistent pattern emerged.

Thrombocytopenia occurred progressively throughout treatment. In 10/16 patients the lowest platelet count was recorded during the last week of therapy. The lowest counts ($\times 10^9$/l) seen were 110 at 1 mu, 48 at 3 mu, 36 at 5 mu and 84 at 7 mu.

The degree of myelosuppression was similar at all dose levels and appeared to be related more to the extent of prior therapy than to the dose of interferon administered. Both WBC and platelet count recovered rapidly on cessation of therapy.

Hepatotoxicity

There was no evidence of hepatic toxicity at 1 mu, but at higher doses progressively increasing derangement of liver function tests was observed (Fig. 1). Raised aspartate aminotransferase (AST) levels occurred in 6/7 patients at 3 mu, 4/5 at 5 mu and in both patients at 7 mu. At 5 mu and 7 mu the elevation was greater than twice the upper limit of normal in all affected patients but reached this level in only three of those affected at 3 mg.

Gammaglutamyl transferase was elevated in 4/7 patients at 3 mu (in two cases to greater than twice normal) and in 4/5 patients at 5 mu (in two cases greater than twice normal). Both patients receiving 7 mu experienced a rise of greater than twice normal.

Significant elevation of lactate dehydrogenase (>50% above the upper limit of normal) occurred in both patients treated at 7 mu but in none at lower doses.

Fatigue was seen in 12/16 patients during the study. Of these 12 patients nine had AST levels greater than twice the upper limit of normal. The remaining three patients also had elevated transaminases but to a lesser degree. The four patients who had no elevation of AST also experienced no anorexia, nausea or fatigue.

Enzyme levels returned to normal within 7 days of completing treatment.

Complications related to central venous access

Five patients were treated using the Port-A-Cath system and 11 using Nutricaths. There were no complications related to placement of the catheters, but two of the patients with Port-A-Caths developed septicaemic episodes (both due to *Staphylococcus aureus*). These occurred during the early part of the study and were probably due to leaving the Port-A-Cath needle in situ for more than 7 days. Subsequently these needles were changed weekly with no further problems. Both patients recovered from the infection, but in one case the interferon infusion was terminated.

The constant presence of the pump proved to be only a mild inconvenience, with four patients continuing to work normally throughout the study.

Pharmacokinetic study

Weekly samples were assayed for interferon levels in three patients at 3 mu, four at 5 mu and two at 7 mu. The individual data are shown in Table 3 and mean values displayed graphically in Fig. 2. The mean weekly area under the curve (AUC) was 35.3+/−11.6 IU/ml/week at 3 mu, 52.8+/−17.5 IU/ml/week at 5 mu and 136.4+/−39.0 IU/ml/week at 7 mu. The mean AUC therefore increased

Table 3. Weekly serum interferon levels

Patient	Dose (mu/m²/day)	Pre	Week						Post	AUC (IU/ml/week)	Mean weekly AUC
			1	2	3	4	5	6			
EA	3	0	42.1	54.3	42.3	79.2	38.7	54.5	0	283.8	47.3
MH	3	0	26.5	24.7	76.9	24.5	41.1	28.5	0	207.9	34.6
RS	3	0	13.4	26.9	38.8	28.9	19.1	35.2	0	144.6	24.1
RS	5	0	57.2	43.3	59.8	78.4	88.7	93.7	0	374.2	62.3
LH	5	0	42.9	37.1	26.3	10.1	38.8	13.0	0	166.6	27.7
KL	5	0	12.9	81.9	60.9	59.9	89.6	44.0	0	327.1	54.5
JO	5	0	64.9	86.4	99.2	0	–	–	–	200.9	66.9
AM	7	0	133.6	83.2	150.1	163.2	26.7	0	–	543.4	108.6
AB	7	0	176.0	197.3	186.0	186.4	150.0	0	–	820.4	164.0

Interferon concentration was measured in IU/ml

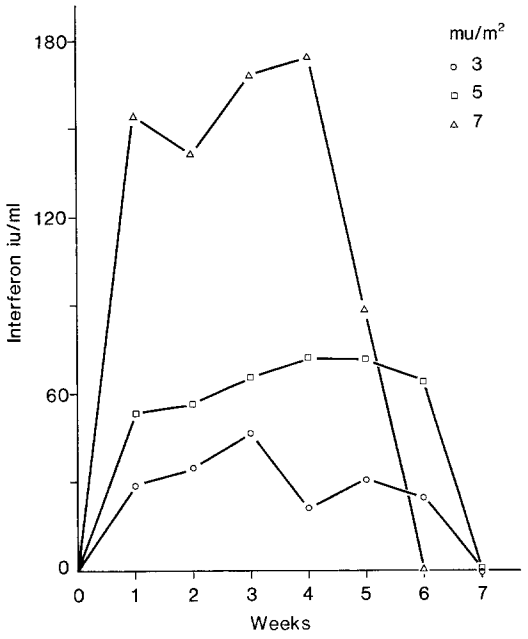

Fig. 2. Mean serum level of interferon in weekly samples at 3, 5 and 7 mg/m^2/day. Both patients treated at 7 mg stopped interferon after 5 weeks

by 49.5% from 3 mu to 5 mu and by 158% from 5 mu to 7 mu.

Among the patients treated at each dose level there was no consistent correlation between serum interferon concentration and the occurrence of objective or subjective toxicity.

Discussion

At present alpha interferon is most commonly administered as a subcutaneous injection two or three times weekly [4, 11, 18]. The biological half-life of interferon used in this fashion is of the order of 2–6 h [2, 14] and thus target sites will be exposed to continuously fluctuating levels of drug. One way of overcoming this is to use a continuous i.v. schedule, which also avoids the problem of erratic absorption from subcutaneous tissues. A number of continuous infusion studies of alpha interferon have been reported in recent years [12, 19]. However, these trials have used short-term infusions of 5–10 days, whereas it is becoming increasingly recognised that prolonged therapy is clinically more useful. Moreover, although doses of up to 100 mg/m^2/day have been said to be tolerable they have been attended by considerable toxicity and have necessitated hospital admission.

The purpose of this study was to assess the toxicity of alpha interferon administered on an outpatient basis as a prolonged continuous infusion. Moreover, we wished to identify a dose that would interfere as little as possible with the patient's normal life style. The results of the study show that although the two patients treated at 7 mg were able to continue the treatment for 5 weeks, side effects of lethargy and somnolence became progressively more severe and eventually resulted in discontinuation of therapy. Somnolence was not a problem at 5 mg, but nausea, anorexia and lethargy were significant problems in 4/5 cases and these patients all felt much better once the interferon was stopped. Even a dose of 3 mg was associated with significant subjective toxicity in three patients, and only 1 mg/m^2/day was entirely non-toxic. There was a close correlation between the incidence of nausea, anorexia and lethargy and disturbance of hepatic function. In the four patients with none of these side effects (two at 1 mg, one at 3 mg, one at 5 mg) there was no elevation of hepatic transaminases. It is possible, therefore, that hepatic toxicity is responsible for these side effects, although other authors have suggested that the fatigue syndrome may be a manifestation of neurotoxicity affecting predominantly frontal lobe functions [1, 8]. In this study definite evidence of CNS toxicity as demonstrated by somnolence was only seen at 7 mg. Such side effects have been shown to be accompanied by reversible EEG changes [13] and therefore appear to be due to a direct action of interferon rather than being secondary to liver damage. Moreover, Nethersell and Sikora [9] have found that hepatic side effects do not correlate with encephalopathy.

Consistent WBC and platelet suppression was seen during the trial but this was not dose-limiting. The degree of suppression, particularly thrombocytopaenia, appeared to be related more to the extent of prior chemotherapy than to the dose of interferon.

We recommend that future studies exploring a long-term i.v. schedule should use a dose of 3 mg/m^2/day alpha-2 interferon, with dose reduction if significant toxicity is encountered.

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