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A Phase I Study of Human Lymphoblastoid Interferon Administered by Continuous Intravenous Infusion

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Summary. *A phase I study of human lymphoblastoid interferon (IFN-α) was undertaken in patients with acute leukaemia and other malignancies. The pharmacokinetics of intravenous IFN-α were also investigated.*

IFN-α was administered to two patients by intravenous (IV) bolus injection at a dose of 5×10^6 U/m²; and to a further 37 patients (40 cycles) by continuous intravenous infusion (IVI) for 5, 7, or 10 days at doses ranging from 5 to 200×10^6 U/m²/day. Pyrexia, general malaise, anorexia, and rigors were observed at all dose levels; three patients became hypotensive. Myelosuppression occurred in all patients, including seven without bone marrow infiltration. Transient rises in alkaline phosphatase and transaminases (SGOT) were observed in patients receiving daily doses greater than 30×10^6 U/m². Dose-limiting central nervous system toxicity, hyperkalaemia, and hypocalcaemia were encountered at 200×10^6 U/m².

In six patients with acute leukaemia there was a fall in the number of circulating leukaemic blasts and in one patient with acute myelogenous leukaemia (AML) the degree of bone marrow infiltration decreased from 99% to less than 5% with cellularity returning to normal. Serum levels of IFN above 1,000 U/ml were achieved with daily doses above 30×10^6 U/m² given by IVI. The maximum safely tolerated daily dose, 100×10^6 U/m² administered for 7 days, is appreciably higher than that used in most previous studies, although even at this level considerable toxicity may be encountered.

Introduction

In 1957, Isaacs and Lindenmann [13] published the initial observations on interferon, a substance they had demonstrated to be a naturally occurring anti-viral agent. A number of interferon sub-types have since been described and shown to possess antiproliferative and immuno-regulatory properties in addition to their ability to confer an anti-viral state [1, 26].

In vitro and in vivo studies with mouse L1210 cells [6] and in vitro studies with myeloblasts cultured with IFN [2, 17, 21] have demonstrated a dose-dependent growth-inhibitory effect. IFN has been shown to inhibit both primary proliferation and self-renewal of blast progenitors in a colony-forming assay of myelogenous blast cells [25].

Objective responses have been reported in patients with myeloma, breast cancer and follicular lymphoma [8, 16, 18] receiving IFN-α (leucocyte) at empirical doses of $3-10 \times 10^6$ U daily, administered by intramuscular injection (IM) for approximately 1 month. Anecdotal reports suggest some activity in acute leukaemia [9, 10]. With a view to possibly incorporating IFN-α into the management of patients with AML, a phase I study was commenced at St Bartholomew's Hospital in November 1980. Continuous IVI was selected as the schedule of choice because of the practical problem of thrombocytopenia in patients with acute leukaemia and the theoretical advantage of prolonged exposure of the blast cells to IFN.

The objectives of the study were to determine the maximum safely tolerated dose, toxicity and pharmacokinetics of IV IFN-α administered by continuous infusion.

Patients and Methods

1. Patients. Thirty-nine patients agreed to take part in the study. All but five had demonstrably failed 'conventional therapy'. Clinical details are given in Table 1. One patient developed signs of central nervous system (CNS) leukaemia (subsequently confirmed at autopsy) 6 h after commencing IFN-α and is therefore inevaluable in terms of toxicity.

2. Interferon. Human lymphoblastoid IFN derived from Namalwa cells (Wellcome Research Laboratories, Beckenham, Kent, Great Britain) had a specific activity ranging from 2.59×10^7 to 2.13×10^8 U/mg protein.

3. Study Design. The first two patients received 5×10^6 U/m² by IV injection over 5 min through the side arm of a fast-running saline infusion. Subsequent patients were treated

Table 1. Patients ($n = 39$)

Diagnosis	No. of patients
AML	23
ALL	5
CLL	1
Myeloma	1
Follicular lymphoma	2 (1[a])
Oat cell carcinoma of bronchus	2 (1[a])
Adenocarcinoma of bronchus	1
Colorectal cancer	2[a]
Melanoma	1[a]
Laryngeal papillomatosis	1

[a] No previous chemotherapy

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Table 2. Dosage and scheduling

IFN-α dose ($\times 10^6$ U/m^2/day)	Duration (days)	No. of patients[a]
5	5	4
5	10	2
7.5	5	3
10	5	3
15	5	4
20	10	2
25	5, 10	2
30	5	3
50	10	5
100	5	4
100	7	4
200	3, 4, 5, 5	4

[a] Three patients received more than one cycle

by continuous IVI at doses escalating from 5 to 200 $\times$ 10^6 U/m^2 per 24 h for 5, 7, or 10 days. Details of dosage and schedule are shown in Table 2.

IFN-α was discontinued after 4 days in a patient receiving 5 $\times$ 10^6 U/m^2 at his own request due to his intolerance of pyrexia and general malaise. IFN-α infusions were also discontinued after 3 and 4 days in two of the four patients receiving 200 $\times$ 10^6 U/m^2, both patients having experienced unacceptable CNS toxicity and hyperkalaemia. Seven patients died whilst receiving IFN-α, one of presumed pulmonary emboli (autopsy was refused), four of septicaemia (1 with cerebral haemorrhage), and two of bronchopneumonia. All were critically ill at the outset of the infusion.

4. Investigations. Prior to therapy, the following investigations were performed: full blood count, urea and electrolytes, liver function tests, serum calcium, phosphate and uric acid, and bone marrow aspirate when appropriate. Subsequently, blood counts were repeated daily; urea and electrolytes, liver function tests, calcium, and phosphate were assessed thrice weekly in patients receiving less than 100 $\times$ 10^6 U/m^2, and daily in those receiving 100 and 200 $\times$ 10^6 U/m^2. Repeat bone marrow aspirates were performed 10 days after initiation of therapy and subsequently when clinically indicated.

Blood samples (5 ml) for serum IFN-α levels were taken prior to starting the infusion, at 2, 4, 8, and 12 h on day 1, and once or twice daily thereafter. Aliquots of serum were stored at $-20°$ C before assay.

5. Interferon Assay. IFN-α activity in serum was measured in a biological assay by the reduction of viral RNA synthesis in V_3 cells [3] challenged with Semliki Forest virus. The assay was calibrated against British reference standard 69/19 (obtained from the National Institute of Biological Standards and Controls, London, Great Britain).

Results

a) Clinical Toxicity (Table 3)

1) Bolus IV Injection. Both patients receiving 5 $\times$ 10^6 U/m^2 became pyrexial and experienced rigors 30 min after the first injection. Patient 2 complained of symptoms of hypotension 20 min after the second injection of IFN-α and this was confirmed on examination (BP: 80/40 mm Hg). With IV fluids and hydrocortisone the blood pressure was restored and the patient was able to be discharged the following day with no adverse sequelae.

Table 3. Clinical toxicity

Symptoms	Frequency
General malaise, Anorexia	All patients
Pyrexia	41/42
Rigors	28/42
Headache	14/42
Joint pains	2/42
Hypotension	3/42

Table 4. Influence of IFN-α infusions on the peripheral blood of seven patients with normal bone marrows

Daily IFN dose ($\times 10^6$ U/m^2)	Duration (days)	Lowest WBC ($\times 10^9$/l)	Day of nadir	Lowest platelet count	Day of nadir	Day of recovery[a]
5	10	1.6	7	116	7	12
30	10	1.5	6	142	7	11
50	10	2.2	9	147	9	11
50	10	2.3	7	64	10	23[b]
100	5	2.2	7	76	7	13
100	5	0.8	6	38	10	22[b]
200	5	1.2	6	55	6	15

[a] Neutrophils, 1.0 $\times$ 10^9/l; platelets, 100 $\times$ 10^9/l
[b] Previous chemotherapy

2) Continuous IV Infusion. All patients complained of general malaise and anorexia, the majority describing symptoms of influenza. At doses lower than 50 $\times$ 10^6 U/m^2 the degree of subjective disturbance was greatest on day 1 and subsequently diminished. In patients receiving more than 50 $\times$ 10^6 U/m^2 subjective symptoms tended to increase. The majority of patients experienced rigors within 4 h of starting IFN-α. In all cases these were abolished by administration of hydrocortisone. The last 10 patients in the study received hydrocortisone (100 mg) prior to starting therapy and a further 200 mg at 2 h. Rigors did not occur in these patients.

All but one patient became pyrexial within 12 h of starting the infusion. At doses lower than 50 $\times$ 10^6 U/m^2 the height of the fever was greatest on day 1 but the degree of pyrexia was not dose-related. In patients receiving 50, 100, and 200 $\times$ 10^6 U/m^2 the initial temperature rise was greater (maximum 41° C) and the fever persisted for the duration of the infusion.

Three patients became hypotensive. The first, who had received 5 $\times$ 10^6 U/m^2, has been described above. One patient treated at 20 $\times$ 10^6 U/m^2 became hypotensive (blood pressure 80/50 mm Hg) 6 h after starting the IFN-α infusion, which was discontinued. The blood pressure recovered spontaneously within 2 h. The infusion was recommenced 24 h later at a dose of 15 $\times$ 10^6 U/m^2. No further hypotensive episodes occurred.

The third patient had a syncopal attack 48 h after completing a 5-day IFN-α infusion at 100 $\times$ 10^6 U/m^2. He was found to be hypotensive (blood pressure 70/45 mm Hg) for approximately 10 min but recovered spontaneously.

Minimal alopecia occurred in one patient after receiving 50 $\times 10^6$ U/m^2 daily for 10 days, followed 3 weeks later by 100 $\times$ 10^6 U/m^2 for 5 days.

Table 5. Details of haematological changes in the six patients in whom any response was observed

Diagnosis	Daily IFN-α dose ($\times 10^6$ U/m^2)	Duration (days)	Absolute blast count	Bone marrow
AML	5	5	7.32 → 1.04	
ALL	15	5	7.08 → 0.05	Hypercellular,
AML	25	10	47.3 → 0.6	> 90% blasts,
AML	30	10	3.2 → 0.8	no change
ALL	200	5	171.3 → 0.25	
AML	50	10	118.8 → 0	Hypercellular, 99% blasts, normocellular, < 5% blasts

At 200×10^6 U/m^2 CNS toxicity became apparent, with three of four patients becoming drowsy and disorientated. Grand mal fits were observed in two patients on days 3 and 5, respectively. Drowsiness but to a lesser degree was also observed in patients receiving 100×10^6 U/m^2. One patient (treated at 200×10^6 U/m^2) developed conjunctivitis, which did not appear to be infective in origin and resolved with prednisolone eye drops.

b) Haematological Toxicity

The majority of patients in the study had bone marrow infiltration with leukaemia or lymphoma and were therefore cytopenic before receiving IFN-α. Subsequent blood counts are therefore impossible to evaluate in terms of haematological toxicity. In seven patients without bone marrow infiltration, pancytopenia occurred at 5 days (lowest WBC, 0.8×10^9/l; lowest platelet count, 38×10^9/l) (Table 4).

Recovery of platelets and neutrophils occurred within 1 week of stopping the IFN-α infusion in previously untreated patients but was slower in patients who had received prior chemotherapy.

c) Biochemistry

1) Hepatic Toxicity. In patients who received 50, 100, and 200×10^6 U/m^2 marked but transient elevations in alkaline phosphatase and transaminases (SGCT) were observed (maximum values 239 and 1,506 U/l, respectively). IFN-α was never discontinued solely because of biochemical evidence of hepatic dysfunction and in all cases these parameters returned to pre-treatment values within 10 days of stopping the IFN-α infusion.

2) Metabolic Changes. At 200×10^6 U/m^2, severe hypocalcaemia (lowest corrected serum calcium 1.35 mmol/l) and hyperkalaemia (maximum serum potassium 7.0 mmol/l) were noted in three patients with acute leukaemia on days 3, 4, and 5. These biochemical changes were not attributable to any other cause and did not occur in a patient with rectal cancer who received the same dose for 5 days. Transient rises in urea and creatinine were observed in the same three patients (maximum urea 16.3, maximum creatinine 0.22).

d) Response

In six patients with acute leukaemia (3 AML, 3 ALL) there was a fall in the number of circulating leukaemic blasts without any change in the degree of bone marrow infiltration (Table 5). In one patient who received 50×10^6 U/m^2 for 10 days, clearing of blasts from the peripheral blood was associated with a decrease in the degree of bone marrow infiltration from 99% blasts (hypercellular) to less than 5% blasts (normocellular). A mass on the anterior chest wall decreased in size during the IFN-α infusion but never regressed completely. The patient was therefore not in complete remission. Three weeks later a further infusion at 100×10^6 U/m^2 was administered for 5 days but peripheral blood and bone marrow relapse occurred at 3 months.

e) Pharmacokinetic Study. (Table 6)

1) Bolus IV Injection. In the two patients who received IFN-α by IV injection at 5×10^6 U/m^2, peak serum levels between 10^2 and 10^3 were achieved at 30 min (Fig. 1), with a half-life of approximately 8 h.

2) Continuous IV Infusion. Baseline serum IFN-α levels were within the range of pre-treatment levels seen in patients with other malignancies (F. Balkwill, unpublished work) prior to 31/34 infusions. In three patients (CW, HdH, AG) higher pre-treatment serum levels were observed. In two patients these may reflect prior treatment with IFN-α completed 8 and 3 weeks previously, respectively. The third patient had not previously received IFN-α and was not suffering from any obvious virus infection.

Maximum serum levels were achieved more slowly with IVI IFN-α than IV bolus IFN-α, but peak levels had been reached by 24 h during the majority of infusions. At daily doses between 5 and 10×10^6 U/m^2 serum levels of IFN-α were between 100 and 800 U/ml, between 10 and 50×10^6 U/m^2 they were approximately 10^3 U/ml, and at 100 and 200×10^6 U/m^2 they were between 10^3 and 10^4 U/ml, one peak value being above 10^5 U/ml. Mean peak serum levels were calculated for each patient from 48 h to the end of the infusion, and are shown in Fig. 2. Once peak levels were achieved, they were usually maintained at the same order of magnitude for the duration of the infusion. However, two types of inconsistency were observed. Firstly fluctuating levels, sometimes of a one log difference were seen in several patients. The pattern of fluctuation suggests that this may have been related to the infusion being stopped for a period whilst syringes were changed, although this cannot be proven.

Secondly, there was considerable variation in the levels achieved in patients receiving the same dose of IFN-α. This was particularly obvious at 100×10^6 U/m^2/day, at which dose the levels achieved were consistently inappropriately low in three of seven patients.

IFN-α was not detected in the urine of 13 patients studied while receiving between 20 and 200×10^6 U/m^2. In two patients samples of cerebrospinal fluid (CSF) were obtained

Table 6. Serum IFN-α levels in patients receiving IFN-α by continuous IV infusion

Pt.	Infusion no.	IFN dose $\times 10^6$ U/m^2	no. of days	Day 1			Day 2		Day 3		Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 11
				0	4	12	0	12	0	12	0	0	0	0	0	0	0	0
JB	1		10	29	80	240	200	240	176	280	176	88	652	128	196	88	92	64
DM	2			36	–	72	58	–	192	–	249	–	–	102	118	115	119	118
AK	3	5		5	–	251	80	380	486	200	272	800						
PW	4		5	5	90	143	116	131	128	290	329	227						
DB[a]	5			35	240	68	88	312	140									
CR	6	7.5		22	42	120	156	74	136	58	86	84						
RF	7	7,5	5	5	5	12	18	28	92	36	20	25	18					
WC	8			22	96	200	112	185	200	512	352	264	288					
SJ	9	10	10	16	64	74	90	102	34	124	480	74	244					
CF	10			4	68	100	192	360	116	73	200	252						
SC	11			24	776	1,664	1,632	1,648	848	435	1,728	824	704					
JR	12	15	5	6	84	1,472	1,600	362	832	–	2,810	232	–					
DH	13			5	78	30	60	440	400	–	384	560	840					
LE	14			19	–	300	200	200	216	–	480	256	272					
ON	15	20	10	35	–	1,184	1,280	–	2,240	–	1,744	6,280	3,650	3,546	1,104	1,682	2,176	1,280
RN	16		5	53	190	90	272	332	336	100	320	1,312	520					
EA	17	25	10	30	2,272	1,136	2,560	327	1,556	–	4,608	434	1,648	237	131	1,760	768	49
JC	18		5	>10	>1,000	>1,000	>1,000	–	>1,000	–	>1,000	80	18					
EG	19	30	7	10	140	232	160	560	–	–	640	1,120	160	640	1,081			
CW	20		10	34	1,824	2,549	4,480	1,124	2,912	–	477	3,584	8,896	1,488	3,456	9,408	1,264	3,412
HdH	21			26	585	1,728	1,845	400	2,912	–	8,448	2,176	1,405	7,936	960	960	1,104	438
IP	22	50	10	8	65	202	398	501	410	–	280	310	452	391	374	1,420	1,200	419
FP	23			10	10	–	115	–	126	–	160	704	754	1,120	1,582	1,088	–	–
BdH	24			432	–	128,000	71,680	–	51,200	–	66,560	760	209					
FC	25	100	5	48	2,208	40,960	4,976	–	4,192	–	7,360	2,912	5,888	4,992				
TP	26			18	1,840	563	2,120	960	995	728	1,632	566	552	2,439	40			
HS	27			38	792	1,230	2,154	–	6,144	–	7,808	16,000	1,725					
DH[a]	28			10	–	–	128	–	110	–	81							
CH[a]	29	100	7	20	377	409	767	–	626	–	68							
FW	30			16	562	–	1,400	–	742	235	1,158	1,093						
AG	31		5	10,400	1,024	–	2,944	1,008	4,160	3,712	1,450	1,269	441	70	144			
CW	32	200	3	2,624	–	2,816	6,254	–	5,077	–	7,526	1,792						
AD	33		4	31	–	26,540	3,217	–	3,840	–	2,884	4,009	8,789					
DS	34		5	112	–	3,891	3,296	1,926	2,406	–	3,520	3,251						

[a] Patient died whilst receiving IFN-α

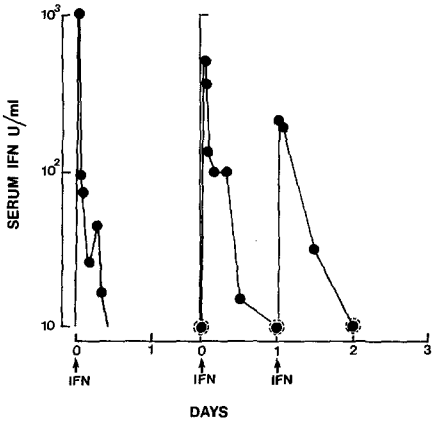

Fig. 1. Serum IFN-α levels in patients receiving IFN-α by IV bolus injection (*dotted line* represents undetectable levels)

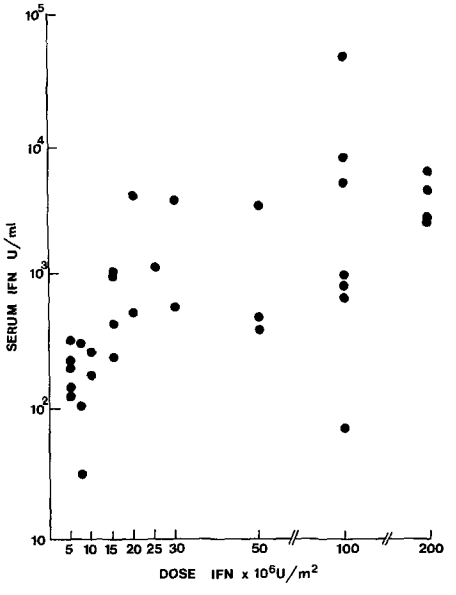

Fig. 2. Mean peak serum IFN-α levels in patients receiving IFN-α by continuous IV infusion

during the IFN-α infusion. In one of these patients 50 U/ml were detected 20 h after the start of an infusion at a dose of 100×10^6 U/m^2. In the second patient a CSF sample taken when the blood level was 2,500 U/ml revealed less than 10 U/ml.

Discussion

Escalating doses of IFN-α were administered by continuous IVI. The maximum safely tolerated dose administered over 7 days appears to be 100×10^6 U/m^2 per day, although considerable side-effects may be seen even at this level. Unacceptable CNS toxicity, hyperkalaemia and hypocalaemia were the dose-limiting factors at 200×10^6 U/m^2, a much higher daily dose than used in most previous studies. To date, the majority of patients have been treated with IFN-α (leucocyte) at doses over a range of $3-12 \times 10^6$ U daily [5, 8, 11, 12, 16, 18–21, 24]. Strander et al. originally proposed 3×10^6 U as the maximum dose that could be administered daily on an out-patient basis [24]. Merigan [19] suggested 7.5×10^6 U/day for ambulatory patients and Priestman [20], using lymphoblastoid IFN-α, concluded that 2.5×10^6 U/m^2 was a suitable dose for administration on an out-patient basis.

Most of the clinical toxicity observed in this study has previously been reported in patients receiving leucocyte and lymphoblastoid IFN-α administered by IM injection [5, 8, 11, 12, 16, 18–20, 24] at doses substantially lower than those used in this study, in patients treated with relatively high doses of IV leucocyte IFN [9, 10], and in a phase I study of poly · ICLC, an IFN inducer [15].

Several studies have suggested that tolerance develops with diminution in toxicity over a period of days [8, 12, 20]. This was confirmed at doses lower than 50×10^6 U/m^2. However, at high doses fever persisted for the duration of the infusion and subjective symptoms increased, though it is difficult to evaluate the significance of fever in severely neutropenic patients who are at risk of contracting infection.

Hypotension, observed in three patients, has previously been described by Emodi et al. [4] following IV injection of an impure leucocyte IFN preparation, by Priestman [20] in patients receiving IM injections of lymphoblastoid IFN, and following administration of poly · ICLC [15] at doses that induce serum IFN levels comparable to those observed in this study.

CNS toxicity to the degree found in three patients receiving 200×10^6 U/m^2 has not previously been reported, though confusion was observed by both Priestman [20] and Scott et al. [23] at considerably lower doses. The conjunctivitis observed in one patient receiving 200×10^6 U/m^2 was analogous to that seen in some patients treated with high-dose cytosine arabinoside [14].

In those patients in whom myelosuppression could be evaluated, the degree and duration of cytopenia were greater than that observed with leucocyte IFN [8, 20]. This is probably accounted for by the higher doses used, but in two patients also reflects prior chemotherapy (Table 4).

In keeping with several previous studies [8, 20, 24], patients who received 50, 100, and 200×10^6 U/m^2 developed transient abnormalities of liver function. The severe hyperkalaemia and hypocalcaemia together with transient rises in urea and creatinine which occurred in three patients treated at the maximum dose could not be ascribed to tumour lysis and have not previously been described. Grollman [7] has demonstrated ion fluxes across cell membranes in vitro; H. Rozengurt (personal communication), on the other hand, found no effect on the sodium/potassium pump mechanism at IFN levels up to 1,000 U/ml. However, in the three patients concerned, peak serum IFN levels considerably higher than 1,000 U/ml were achieved.

There has long been controversy as to whether the clinical side-effects are due to contaminants in the IFN preparation. Scott et al. [23], comparing the clinical toxicity of partially purified IFN-α (leucocyte) with that of a preparation purified by passage through a monoclonal antibody affinity chromatography column, found similar toxic effects with both preparations. This suggests that the side-effects are fundamental properties of the IFN molecule. Further support for this concept comes from a phase I study of IFN derived by recombinant DNA techniques from *E. coli* [11]. Similar side-effects were observed.

The pharmacokinetic study showed that constant high levels of circulating IFN could be achieved by infusion. In the patients receiving IFN-α by IV bolus injection, high peak levels were achieved but IFN-α was cleared rapidly. As the daily dose was escalated, progressively higher levels were seen in most patients receiving IFN by infusion. However, much variability was seen both in the levels achieved during individual infusions and between patients treated at the same dose level. These inconsistencies may reflect the problems of measuring serum levels of a biological substance, the use of a biological assay, and the difficulties of administering continuous infusions. Alternatively the differences may reflect an inherent variation between individuals in respect to their metabolism, binding and clearance of interferon.

The results at doses lower than 10×10^6 U/m^2 concur with the published data for leucocyte IFN in terms of peak levels [5, 8, 23]. However, in these studies IFN was administered by IM injection and levels therefore fluctuated to a greater degree than in the present study. Daily doses of 100 and 200×10^6 U/m^2 were associated with mean levels greater than 10^3 U/ml and peak levels greater than 10^4 U/ml. Such high levels have not previously been reported, though Hill et al. observed serum levels up to 2,400 U/ml in patients treated with approximately 50×10^6 U/m^2/day given in four IV doses [10]. Mean peak levels of more than 10^3 U/ml have also been induced with poly · ICLC [15]. Horning found mean serum levels in excess of 10^3 U/ml at 4 h [11] in patients receiving IM recombinant leucocyte IFN at doses greater than 100×10^6 U/m^2. Biologically active IFN was not found in the urine of patients in the present study or in that reported by Scott et al. [23].

In one patient receiving 100×10^6 U/m^2, low levels of IFN-α were found in the CSF 20 h after the start of the infusion. In another patient, however, in spite of high serum levels, IFN was not detected in the CSF. Priestman [20] assayed CSF from two patients receiving lymphoblastoid IFN-α and none was detected. Other studies have shown CSF levels to be lower than serum levels when IFN is administered systemically [22].

Doses higher than 15×10^6 U/m^2 were associated with peak serum levels greater than 10^3 U/ml in the majority of patients. In vitro, IFN-α concentrations of 10^3 U/ml result in 50% inhibition of growth in myeloblasts derived from patients with AML [21].

The maximum safely tolerated dose appears to be 100×10^6 U/m^2, and it is possible to administer IFN-α by

continuous IVI at this dose for 7 days. Whether this represents an optimal dose and schedule for the treatment of patients with acute myelogenous leukaemia has yet to be determined.

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