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A toxicity study of recombinant interferon-gamma given by intravenous infusion to patients with advanced cancer

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Summary. Eighteen patients with solid tumours were treated with human recombinant interferon-gamma at escalating dose levels starting at 1×10^6 units/m^2 per infusion and rising through 3×10^6, 6×10^6, 9×10^6 and 22×10^6 to a maximum of 110×10^6 units/m^2 per infusion. The IV infusions were given three times a week over a 4-week period.

Side effects were seen in all patients, but were mild except at the highest dose. Acute dose-related effects included pyrexia, tiredness, thirst, chills and rigors. Chronic dose-related effects included anorexia, lethargy, weakness, disorientation, a trace of proteinuria and minimal rises in liver enzymes. In addition, effects were observed which were not related to dose. These included headache, nausea and vomiting, backache, myalgia, flatulence and a mild, transient reduction in neutrophils and erythrocytes.

At the highest dose level dose-limiting toxicity was observed, consisting in severe tiredness and anorexia, hypotension, disorientation and changes on the electrocardiograph.

Overall, toxicity was similar to that seen with preparations of interferon-alpha, except that no tolerance to the effects of interferon-gamma was noted. We observed less hepatic and haematological toxicity, but also recorded flatulence, handcramps and electrocardiograph changes, which have not been reported with interferon-alpha.

When given according to this regimen, doses of 22×10^6 units/m^2 per infusion of recombinant interferon-gamma were generally well tolerated by the patients.

Introduction

Since the discovery of interferon in 1957 [14] it has been shown that the substance has both antiviral and antiproliferative activity [3, 10, 19, 28].

Three groups of interferons have now been identified: interferon-alpha, derived from leucocytes; interferon-beta, from fibroblasts; and most recently, interferon-gamma, which is derived from lymphocytes.

Most clinical studies to date have used alpha and beta interferons. Early trials suffered from material which was of low purity and small quantity. The side effects noted were attributed to the impurities in the preparation, and the sometimes disappointing results in malignant disease were blamed on the small quantities of material available. Recently, genetic engineering techniques have made relatively large amounts of highly purified interferons available. The side effects previously noted with the impure preparations are still present with the recombinant interferon-alpha (rIFN-α) material, implying that they were due to the interferon rather than to the impurities.

Many trials with both purified and recombinant interferons have also shown some evidence of efficacy, notably in myeloma [12, 17], breast cancer [4, 12, 18], renal cancer [8, 20], lymphomas [12, 25] and melanoma [5].

Interferon-gamma is the most recently identified type of interferon, and has now become available for clinical research. Evidence from animal studies and tissue culture work suggests it may have a greater antiproliferative effect than either interferon-alpha or -beta [2, 7, 9].

We have completed a toxicity examination of human recombinant interferon-gamma (rIFN-γ) in patients with solid tumours, in order to assess the side-effects of the drug, correlate them with the dose given and determine a maximum tolerated dose.

Materials and methods

Recombinant interferon-gamma was supplied by Biogen S. A., Geneva. The material was produced from *E. coli* using genetic engineering techniques, resulting in large quantities of rIFN-γ which were purified and supplied in both liquid and lyophilised forms. The liquid material was supplied in 2-ml vials. The activity was 1×10^6 units/ml in one batch and 1.5×10^7 units/ml in the other. The lyophilised material was supplied in 100- and 500-µg vials.

In all forms the material was of $>95\%$ purity, the pyrogen content was <5 ng/ml, and the specific activity was $1.5-5 \times 10^7$ units/mg protein, according to batch. The assay used was Hep 2 cells with Mengo virus [1, 11].

Before use, the interferon was thawed and made up to a manageable volume with 5% dextrose. It was administered by means of mini-pump system which we have found to be well tolerated by the patients [27].

Eighteen patients, nine men and nine women, with an age range of 34–75 years and a mean age of 60 years, were treated (Table 1). All patients suffered from histologically proven malignant disease with no further conventional therapy available, and all gave fully informed written consent. The trial was approved by the ethical committee of King's College Hospital.

The patients were all relatively fit (Karnovsky per-

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Table 1. Details of patients entered into trial

Pt no.	Sex	Age	Tumour type
1	F	58	Adenocarcinoma of ovary
2	F	62	1. Adenocarcinoma of breast 2. Adenocarcinoma of ovary
3	M	62	Squamous cell carcinoma, bronchus
4	M	36	Adenocarcinoma of stomach
5	F	70	Squamous cell carcinoma, bronchus
6	M	52	IgA Myeloma
7	F	54	Adenocarcinoma of breast
8	F	62	Squamous cell carcinoma, bronchus
9	M	34	Adenocarcinoma of unknown origin
10	F	73	Adenocarcinoma of ovary
11	M	53	Hodgkins lymphoma
12	M	57	Adenocarcinoma of kidney
13	F	61	Adenocarcinoma of colon
14	M	71	Hepatocellular carcinoma
15	M	75	Squamous cell carcinoma, penis
16	F	62	Adenocarcinoma of breast
17	M	72	Small cell carcinoma, bronchus
18	F	67	Adenocarcinoma of breast

formance score $>60\%$), with no evidence of serious renal, cardiovascular or hepatic dysfunction (except for the hepatoma patient). No patient had received any other treatment for their condition during the previous month; nor were they taking any drugs which might have interfered with the assessment of rIFN-γ, e.g. steroids, aspirin or the nonsteroidal anti-inflammatory drugs. Patients excluded from the trial included those with abnormal haematology, biochemistry or liver function (Table 2), as well as those with leukaemia or central nervous system disease.

Patients with a history of penicillin allergy were also excluded, as the preparation contained minute amounts of ampicillin which was used in the manufacturing process (<7.8 ng/ml).

The standard regimen was three 6-h IV infusions per week, on alternate days, for 4 weeks.

Patients were entered into the trial at different dose levels, and remained at the dose started on throughout the 4-week period unless a reduction in the dose was indicated (see below). The dose levels used were 1×10^6, 3×10^6, 6×10^6, 9×10^6, 22×10^6 and 110×10^6 units/m^2 per infusion (Table 3). Patients 1–6, 10 and 11 received liquid material, while the rest received lyophilised material throughout treatment. The decision to move up a dose level for the next patient was made on observing no serious side effects in at least two patients at the previous level. Halving of the dose or termination of treatment prematurely was decided on the basis of an overall assessment of the toxicity seen in the patient concerned.

Table 2. Laboratory exclusion criteria

Haemoglobin	<10 g/dl
Total white cell count	$<3.0\times10^9$/l
Neutrophil count	$<1.5\times10^9$/l
Platelet count	$<100\times10^9$/l
Urea	>9.5 mmol/l
Creatinine	>165 µmol/l
Bilirubin	>60 µmol/l
Transaminase	>130 IU/l
Alkaline phosphatase	>290 IU/l

All patients were treated as in-patients for the 1st week, and then as out-patients for the next 3 weeks. Patients with signs of improvement or stable disease at 4 weeks were offered up to a further 12 infusions.

Before treatment, all patients gave a history and had a general examination, full blood count, urea and electrolytes, liver function tests, prothrombin time, chest X-ray (CXR) electrocardiograph (ECG), urinalysis and urine microscopy performed. These tests were repeated frequently during the 4-week period, and were also repeated 4 weeks after the end of the course. One patient at each dose level also had serial electroencephalographs (EEGs) at fortnightly intervals.

In addition, blood was taken for autoantibody levels before the start of interferon therapy, then every 2 weeks until the end of treatment, and finally 4 weeks after the end of treatment. Autoantibodies measured included those to gastric parietal cells, thyroglobulin and thyroid microsomes, and also anti-ds.DNA, rheumatoid factor, and antinuclear factor. Serum immunoglobulin levels were also measured at the same intervals.

During and after each infusion, vital signs were measured frequently, and the subjective symptoms were also recorded.

Results

Of the 18 patients entered into the trial, 14 completed the treatment at the specified dose level. No patient at the maximum level completed the course at that dose. Patient 16 had one infusion, and then refused to have any further treatment. Patient 17 had six infusions at 110×10^6 units/m^2 per infusion and the dose was then reduced to 55×10^6 units/m^2 per infusion because of hypotensive episodes and right bundle branch block on ECG. Patient 18 had two infusions at 110×10^6 units/m^2 per infusion and the dose was then reduced to 55×10^6 units/m^2 per infusion because of her mental confusion. She was withdrawn from the trial after a further two infusions because she had an unrelated medical condition requiring in-patient care, and died suddenly 2 weeks after her final dose from a massive pulmonary embolus. Her prothrombin times had been normal

Table 3. Doseage of rIFN-γ

Pt no.	Dose per square metre given at each infusion	Total no. of doses received at 3 per week	Weeks of rIFNγ treatment	Total dose of rIFNγ received over treatment period
1	1	12	4	12×10^6 u/m^2
2	1	12	4	12×10^6 u/m^2
3	3	24	8	72×10^6 u/m^2
4	3	12	4	36×10^6 u/m^2
5	3	24	8	72×10^6 u/m^2
6	3	11	3.6	33×10^6 u/m^2
7	6	24	8	144×10^6 u/m^2
8	6	12	4	72×10^6 u/m^2
9	6	12	4	72×10^6 u/m^2
10	9	12	4	108×10^6 u/m^2
11	9	24	8	216×10^6 u/m^2
12	9	12	4	108×10^6 u/m^2
13	22	12	4	264×10^6 u/m^2
14	22	12	4	264×10^6 u/m^2
15	22	16	5.3	352×10^6 u/m^2
16	110	1	0.3	110×10^6 u/m^2
17	110/55[a]	6 at 110 then 6 at 55	4	990×10^6 u/m^2
18	110/55[a]	2 at 110 then 2 at 55	1.3	330×10^6 u/m^2

[a] Dosage of rIFN-γ halved during treatment

throughout treatment. Patient 6 received only eleven infusions, the second being omitted due to a low total white cell count.

Clinical signs

Pyrexia was universal and of a similar pattern at each administration and at all doses. About 2–4 h after the start of the infusion the temperature rose suddenly, to reach a maximum (Tmax) at 4–6 h. It then fell slowly over the next few hours, and was usually normal at 18 h, except at the higher dose levels, when it was normal by 28 h.

The rise in temperature was accompanied by chills or rigors depending on the Tmax reached, and at the point when the chills ended the patients felt hot and were noted to be flushed. At doses of up to 9×10^6 units/m^2 per infusion there was a statistically significant relationship between dose and both the Tmax reached and the duration of the pyrexia. At 9×10^6 units/m^2 per infusion "saturation" occurred, and there were no further significant rises in either Tmax or duration of pyrexia with higher doses. Several patients regularly had pyrexias of > 39 °C, and the highest temperature recorded was 40.3 °C.

No tolerance was observed to the rise in temperature over the 4-week course, nor was any tolerance seen in those patients who went on to receive further treatment.

A sinus tachycardia of 100–110 bpm was occasionally seen in patients 8, 10, 12, 15 and 17, which coincided with the Tmax. Mild hypertension, never more than 50 mmHg (systolic) and 30 mmHg (diastolic) above normal, was occasionally seen in patients 3 and 12. This occurred when the temperature began to rise, but lasted less than 1 h.

Hypotension was seen in patient 17 at the highest dose level. The blood pressure dropped from 120/80 mmHg to 90/40 mmHg about 6 h after the start of the infusions. This ended when his dose was halved.

Three patients became disoriented during treatment. In patients 8 and 15 this occurred once only, while their temperatures were raised, and lasted less than 1 min. In case 18, disorientation lasted 3 days, and ended after one dose was omitted and the dose level was halved.

Weight loss occurred in most patients. In 11 cases the weight loss was $< 5\%$ of the body weight, and in 3 cases (nos. 12, 14 and 15), between 5% and 10% of the body weight. Patients 2 and 10 put on weight during the trial, but both these patients were redeveloping ascites. Patients 16 and 18 were not evaluable as they did not finish treatment.

Symptoms

Symptoms were graded from 1 (mild) to 4 (very severe). At the end of treatment the scores for each symptom were summed, and an overall sequence reflecting both frequency and severity was drawn up (Table 4).

The symptoms were mainly acute in nature, occurring during the infusion and continuing on from it, but recovering by the next day. Exceptions to this were lethargy, anorexia and weakness, which increased over the second 2 weeks of the course and were not directly related to any individual infusion.

Acute tiredness (tiredness occurring during the infusion or continuing on from it) was seen in most cases. Seven patients said it was their most troublesome symptom, and at the highest dose level it was very severe, patient 18 sleeping for most of the infusion, though easily roused.

Anorexia was common at 9×10^6 units/m^2 per infusion and above. It may in part have been due to the other gastrointestinal complaints, the tiredness and the tastechange, and it probably contributed to the weight loss. It was more common in the second 2 weeks of treatment, and again was more severe at the higher dose levels.

Lethargy, like anorexia, was worse at the higher dose levels, and also in the second 2 weeks. Patient 17 was spending much of his time on nontreatment days in bed while receiving the highest dose level.

Headache was frequent, but severe only in patients 5 and 17. Neither patient had suffered from headaches before, but both continued to have headaches after the end of treatment. Patient 17 was subsequently shown to have previously unsuspected cerebral metastases, but no explanation was found for the continuing headaches of patient 5; indeed this was the only example in the trial of a symptom which was probably caused by rIFN-γ and did not disappear completely when treatment finished.

Interferon-gamma also caused nausea and vomiting in the majority of patients treated. This was particularly noted in those with underlying gastrointestinal disease. Often patients vomited when their temperature was rising, and in some cases the vomiting was not accompanied by nausea.

Weakness was only seen at doses of 9×10^6 units/m^2 per infusion and above, but was very severe at the higher dose levels.

Myalgia and backache were fairly common, and were relatively mild except in patient 7, who suffered from severe aches in the backs of the legs during most of the infusions.

Upper respiratory tract symptoms included sore throat, nasal congestion and cough. There was no change in viral titres or microbiology to suggest that these were due to infection.

Thirst and dry mouth were seen in the patients with higher temperatures, and were therefore grossly dose-related. Flatulence, however, was a common symptom during the second 3 h of the infusion and showed no dose relationship.

Anxiety, unsteadiness, hand cramps and taste change (particularly to alcohol) were each seen in only two patients, and no deductions about dose relationship can be made.

No tolerance was seen to any of these symptoms throughout the 4 weeks, but all symptoms, except the mild headache in patient 5, disappeared completely within 1 week of finishing the course.

Table 4. Symptoms in order of frequency

Symptom	Patients mentioning (max. 18)	Patients mentioning as worst symptom	Dose-related
Coldness/chills	18	0	Yes[a]
Acute tiredness	16	7	Yes
Anorexia	13	1	Yes
Lethargy	14	1	Yes
Headache	13	2	No
Nausea	11	4	No
Vomiting	11	0	No
Myalgia	10	2	No
Thirst/dry mouth	10	0	Yes[a]
Flatulence	10	0	No
Backache	9	0	No
URT symptoms	9	0	No
Indigestion	6	0	No
Weakness	5	1	Yes
Anxiety	2	0	–
Unsteadiness	2	0	–
Hand cramps	2	0	–
Taste change	2	0	–

URT, upper respiratory tract
[a] Directly related to Tmax. and therefore grossly dose-dependent

In addition to those mentioned above, the following symptoms were each reported on one or two occasions by one patient only: lacrimation, generalised itching, visual symptoms and palpitations.

Laboratory findings

The haematology results showed an immediate, statistically significant, but mild and transient decrease in the total white cell count (WCC), due mainly to a decrease in neutrophils. The decrease was often maximal after the second infusion, and then rose to near pretreatment levels after the first week (Table 5). The minimum WCC reached was not significantly dose-related. The lowest WCCs recorded were in patient 6 (1.6×10^9/l), patient 17 (2.1×10^9/l), and patient 18 (1.9×10^9/l). Patient 6 had always had low WCCs, particularly during past chemotherapy, and his normal WCC was around 3.5×10^9/l. In all cases the reduction in the WCC was transient, returning to pretreatment values at the end of the course and beginning to recover 48 h after the start of each infusion.

There was a similar but less marked decrease in the red cell count (RCC) during the 1st week, which then plateaued at a reduced level until the course ended, when it returned to pretreatment values. Falls in haemoglobin and packed cell volume mirrored this decrease.

No platelet counts of $< 100 \times 10^9$/l were seen during the trial, nor were any abnormal prothrombin times recorded except in the hepatoma patient, whose abnormal prothrombin time was disease-related.

Results of the blood chemistry investigations showed no significant changes in urea and electrolytes, but at higher doses some decreases in albumin were recorded, the maximum drop being from 40 g/l before treatment to 31 g/l after 4 weeks' treatment. This may have been due in part to the anorexia, but the mild proteinuria (see below) probably contributed to it. There were also slight rises in urate levels in some patients, but none developed gout.

Blood glucose levels in patients 1 and 6 were slightly raised during treatment, but both had a strong family history of non-insulin-dependent diabetes mellitus. As the samples taken were not fasting samples the relevance was not known. Glucose tolerance tests were therefore incorporated into the protocol, but no changes in glucose tolerance were observed on treatment with rIFN-γ.

Mild changes in liver function were observed at the highest dose levels. Patients 17 and 18 had transient, mild rises in aspartate transaminase (highest value: 92 IU/l) and gamma glutamyl transferase (highest value: 57 IU/l). The levels of both fell to normal after the rIFN-γ course ended. Patients 13 and 14 had abnormal liver enzymes before and during treatment, which slowly increased and did not return to pretreatment values. Patient 13 was known to have multiple liver secondaries, and patient 14 had a large hepatoma. Apart from patient 14, whose bilirubin rose slowly throughout the treatment period and was disease-related, there were no changes in bilirubin during the trial.

A trace of proteinuria, never greater than 0.3 g/l was often seen in patients at 22×10^6 and 110×10^6 units/m^2 per infusion. Urine microscopy revealed hyaline casts in the urine of patient 17 on one occasion, but no other abnormalities.

The EEG performed in patient 1 at the 4-week stage showed excessive slow-wave activity and evidence of a space-occupying lesion in the left temporal lobe. The pre-

Table 5. Mean haematological parameters over time

Day	Pre	4	8	15	22	28	56
Hb	13.9	13.0*	13.2*	13.2*	12.9*	13.1*	13.4
RCC	4.86	4.48*	4.64*	4.65*	4.46*	4.56*	4.83
PVC	0.431	0.390*	0.404*	0.406*	0.388*	0.398*	0.417
WCC	5.93	4.16*	5.69	5.77	5.29	4.87*	6.18

Hb, haemoglobin (g/dl); RCC, red cell count ($\times 10^{12}$/l); PCV, packed cell volume; WCC, total white cell count ($\times 10^{9}$/l)
* Significantly different from baseline (Pre) ($P<0.01$) according to repeated measures analysis of variance

treatment and 2-week EEGs had been normal. Clinically she was tired, but there were no focal neurological signs. A fourth EEG at 8 weeks was again normal. No EEG results are available at the highest dose level, as neither patient who had pretreatment EEGs finished the course. All EEGs in patients at 3×10^6, 6×10^6, 9×10^6 and 22×10^6 units/m^2 per infusion were normal.

From the ECG measurements, patient 3 was found to have a few atrial ectopics on two occasions, and patient 5, to have occasional ventricular ectopics on one ECG. In neither case were there any clinical effects; nor was any treatment required. Patient 17 developed an ECG picture of right bundle branch block (RBBB) at 110×10^6 units/m^2 per infusion, at the same time as he began to have hypotensive episodes. Following halving of the dose the hypotensive episodes stopped, but the ECG picture continued abnormal until the end of rIFN-γ treatment, when it returned to normal.

Results of the autoantibody and immunoglobulin studies showed no significant changes in autoantibodies or immunoglobulin levels in any patient throughout the study period.

Discussion

Recombinant IFN-γ caused acute and chronic dose-related syndromes, as well as other, non-dose-related effects.

The acute syndrome consisted of pyrexia, chills or rigors, thirst and tiredness; whereas the chronic syndrome included anorexia, lethargy, weakness and disorientation. Superimposed on these effects were heachaches, nausea and vomiting, backache and myalgia, flatulence and other, less common, effects which did not seem to be dose-related. No tolerance to any of these effects was seen.

Recombinant IFN-γ also caused a transient decrease in neutrophils and eryhtrocytes, as well as mild rises in aspartate transaminase and gamma glutamyltransferase at the highest dose level. Mild proteinuria was also observed at the higher dose levels. None of these abnormalities was severe enough to be dose-limiting.

The occasional ectopic beats seen on ECG are of doubtful significance, but the RBBB in patient 17 appeared to be linked to rIFN-γ treatment.

The significance of the EEG abnormality in patient 1 is not known. Other groups have reported slow-wave changes in patients treated with IFN-α [23, 26], but these have always been worse at higher doses.

At all doses up to and including 22×10^6 units/m^2 per infusion these signs and symptoms were generally well tolerated. At 110×10^6 units/m^2 per infusion dose-limiting toxicity was seen, which included ECG changes, hypotension, disorientation, and severe tiredness and anorexia. Even after the dose was halved to 55×10^6 units/m^2 per infusion subjective symptoms were severe.

At 22×10^6 units/m^2 per infusion the dose-related effects of chills and rigors, tiredness, anorexia, weakness and lethargy were moderate to severe, but in general they were well tolerated by patients 13 and 15, who were relatively fit (Karnovsky values 90% and 80%, respectively). They were less well tolerated by patient 14, who was more incapacitated by his disease (Karnovsky 60%) at the start of treatment. Non-dose-related effects were not seen at any greater frequency or severity at this dose level than any other. No ECG changes or hypotension were seen at 22×10^6 units/m^2 per infusion.

Patients 3, 5, 7 and 11 went on to receive a further 4 weeks' treatment at the same dose and regimen. Patient 15 had a further four infusions before withdrawing because of anorexia, tiredness and weakness.

In comparison with trials using purified and recombinant IFN-α the effects of rIFN-γ appear to be similar, but with a few important differences. No tolerance to any of the symptoms produced by rIFN-γ was seen, whereas in trials with IFN-α tolerance to acute signs and symptoms developed in about 1 week [15, 25, 29].

Effects mentioned in past trials with IFN-α which we have not seen with rIFN-γ include partial alopecia [13], reactivation of herpes lesions [12, 13, 25], peripheral tingling and numbness [13, 18], and injection site tenderness [13]. Effects we have recorded with rIFN-γ which have not, to our knowledge, been reported with IFN-α include flatulence, cramps in the hands in the absence of biochemical abnormality, and RBBB on ECG, all of which disappeared at the end of treatment.

Haematological and hepatic toxicity were less severe than with IFN-α when compared at similar doses, but this may have been an effect of our method of administration.

The IV route was chosen for two reasons. First, the exact mechanism of the antiproliferative effect of the interferons is still poorly understood; low serum levels may be all that is required for a full antiproliferative effect, but until that is clarified high blood levels are the logical aim, particularly in a toxicity study, where we are looking for a maximum tolerated dose. Secondly, recombinant IFN-γ, lacking the glycosylated section possessed by the natural substance, is comparatively poorly taken into the bloodstream after IM injection in animal studies [6].

An infusion was chosen rather than a bolus because when drugs such as the interferons, with very short pharmacological half-lives, are used, an infusion may enhance antiproliferative activity by providing available drug to interface with tumour cells entering the mitotic cycle over a longer period [16]. It has also been shown that when infusion are given a larger dose of interferon-alpha can be tolerated by the patients [22].

We found that prophylactic paracetamol blocked the pyrexial response to rIFN-γ and also prevented all the other acute symptoms, including nausea and vomiting, though it had little effect on the chronic symptoms. Since it so effectively masked the effects we were studying it was used as infrequently as possible. As we do not know exactly how interferons exert their antitumour action, it is possible that by blocking the side effects we may also be blocking any antitumour effect potentially present [15, 24], particularly as it has been shown that fever itself may have some antitumour action [21].

Although this was primarily a toxicity study, we attempted to seek evidence of efficacy in all patients studied.

Only one patient showed a significant improvement with rIFN-γ treatment, and this was maintained for only 3 weeks. Patient 15 was a 75-year-old man with a squamous cell carcinoma of the penis and bilateral inguinal lymphadenopathy. As a result he suffered from severe oedema of both legs, with difficulty and pain in walking. After 2 weeks of treatment the right inguinal nodes had shrunk from 5×2 cm to 2×1 cm. All oedema disappeared, and he had no pain on walking. Although he continued with interferon therapy for a further 3 weeks, at the end of that time the disease had recurred and his clinical situation was approaching that before he started interferon.

The future role of interferons as anticancer agents may be in combination chemotherapy with other types of interferons, other lymphokines, or conventional cytotoxic drugs. This trial has shown that at doses of up to 22×10^6 units/m^2 per infusion with this regimen recombinant interferon-gamma is relatively non-toxic and well tolerated by the patients, and trials of its efficacy are warranted.

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