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Interferon in Acute Myelogenous Leukaemia: A Preliminary Report

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A. Introduction

Interferon has been shown to have an anti-proliferative effect on leukaemic blast cells in vitro [1, 3, 4]. In short-term liquid culture, 50% inhibition of growth is achieved at IFN-α concentrations of 10^3 units/ml using myeloblasts derived from patients with acute myelogenous leukaemia (AML) [5]. Pharmacokinetic studies in patients receiving IFN-α by continuous intravenous infusion (i.v.i) have shown that it is possible to achieve serum concentrations of 10^3 units/ml at daily doses greater than 30×10^6 units/m^2 [6].

A phase II study of IFN-α is currently in progress at St. Bartholomew's Hospital, to determine whether an anti-proliferative effect can be demonstrated in patients with acute myelogenous leukaemia.

B. Patients and Methods

I. Patients

Fifteen patients with acute myelogenous leukaemia, aged between 31 and 63, are included in this analysis. All had either relapsed following conventional chemotherapy or had demonstrated resistance to therapy comprising adriamycin, cytosine arabinoside and 6-thioguanine. Four patients died whilst receiving IFN-α (two of septicaemia, one of pneumonia and one of cerebral haemorrhage) and are therefore inevaluable.

II. Interferon

IFN-α from a Namalwa lymphoblastoid cell line (Wellcome Research Laboratories) had a specific activity ranging from 2.59×10^7 to 2.13×10^8 units/mg protein.

III. Dosage and Schedule

Between 50 and 200×10^6 units/m^2 of IFN-α were administered continuously for 5,7 or 10 days. Details of dosage and schedule are shown in Table 1.

Table 1. Dosage and schedule

Daily IFN-α dose ($\times 10^6$ units/m^2)	Duration of infusion (days)	No. of patients
50	10	3
100	7	10
200	5	2
Total		15

IV. In Vitro Study

Bone marrow and peripheral blood myeloblasts from patients who subsequently received IFN-α were cultured with IFN-α at concentrations of 10, 10^2, 10^3 and 10^4 units/ml. Growth was assessed at 3 days by viable cell counts under phase-contrast microscopy and uptake of tritiated thymidine.

% ↓ in control cell numbers	Interferon concentrations (units/ml)			
	10	10^2	10^3	10^4
Median	6.2	21.7	58.3	79.8
Range	0 – 18.3	1.6 – 33.4	21.6 – 72.5	31.0 – 88.0
% ↓ in thymidine incorporation	Interferon concentrations (units/ml)			
	10	10^2	10^3	10^4
Median	10.8	25.3	55.6	68.4
Range	0 – 16.3	3.7 – 36.2	17.0 – 58.1	33.2 – 85.0

Table 2. Growth inhibitory effect of IFN-α on myeloblasts in short-term liquid culture

V. Interferon Assay

Serum IFN-α concentrations were measured by reduction of RNA synthesis in V3 cells [2] challenged with Semliki forest virus.

C. Results

I. Anti-proliferative Effect

1. In Vitro

With increasing interferon concentrations, the degree of growth inhibition increased, 50% inhibition being observed at an IFN-α concentration of 10^3 units/ml (Table 2).

2. Clinical Response

Five patients showed no evidence of response. In four patients there was a marked fall in the number of circulating leukaemic blasts but no change in the degree of bone marrow infiltration. In two patients clearing of blasts from the peripheral blood was associated with a decrease in the degree of bone marrow infiltration to less than 5% blasts.

II. Clinical Toxicity

All patients became pyrexial and described symptoms of influenza. Eight patients complained of headache and two of nausea and vomiting. Six patients became drowsy and this symptom persisted for up to a week after the end of the infusion. Two patients receiving IFN-α at a dose of 200×10^6units/m^2 per day became disorientated and had grand mal fits. In view of this unacceptable CNS toxicity, which was associated with severe biochemical disturbances (see below), subsequent patients received 100×10^6 units/m^2 per day.

III. Haematological and Biochemical Toxicity

All patients became neutropenic and thrombocytopenic. Biochemical evidence of hepatic dysfunction, i.e. transient elevations of alkaline phosphatase and transaminases (SGOT) were observed in 10 out of 11 patients. Reversible hyperkalaemia and hypocalcaemia occurred in two patients receiving 200×10^6 units/m^2.

IV. Serum IFN-α Levels

Peak serum concentrations greater than 10^3 units/ml were achieved in all patients studied.

D. Discussion

Fifteen patients with acute myelogenous leukaemia received IFN-α at doses with resulted in serum concentrations that are inhibitory to myeloblasts in vitro. The clinical toxicity, cytopenia and hepatic dysfunction have previously been described [6].

Myeloblasts from all 15 patients showed evidence of growth inhibition in vitro at IFN-α concentrations which were subsequently acieved in the serum. This was not paralleled in vivo, only 2 of 11 evalu-

able patients showing any decrease in the degree of bone marrow infiltration. There was thus no correlation between the in vitro findings and clinical response.

These preliminary results suggest that IFN-α may have some activity in acute myelogenous leukaemia, and further patients are being entered into the study.

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