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Experience with Human Lymphoblastoid Interferon in Acute Myelogenous Leukaemia (AML)

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Summary. *Fourteen patients with acute myelogenous leukaemia, who had either failed to enter remission or had relapsed following conventional chemotherapy, received human lymphoblastoid interferon (Hu IFN-αN) at a dose of 100 × 10^6 units/m^2 daily by continuous IV infusion for 7 days. Complete remission was not achieved in any of 10 patients evaluable for response, although a transient decrease in the degree of bone marrow infiltration was observed in two patients.*

Introduction

Interferon (IFN) has been demonstrated to have dose-dependent anti-proliferative activity in vitro against murine and human leukaemic blast cells [7, 11]. Both normal and leukaemic (chronic myeloid) clonogenic cells exhibit a decrease in granulocytic colony-forming capacity when exposed to IFNs α and β [3, 12]; IFN-β has been shown to inhibit both primary proliferation and self-renewal of blast progenitors in a colony-forming assay of myeloblasts [15]. Interferon inhibits the growth of transplantable ascitic tumours including L1210 [6, 8], delays the evolution of virus-induced murine leukaemias [4, 5], and prolongs survival in mice with AKR lymphoma/leukaemia [9].

Growth of human myeloblasts in short-term liquid culture is inhibited at the 50% level by exposure to lymphoblastoid Interferon (HuIFN-αN) at concentrations of 10^3 units/ml [1, 13]. This may be achieved in vivo by continuous infusion of HuIFN-αN at a daily dose of 50 × 10^6 units/m^2, and it has been established that the maximum tolerated daily dose for a 7-day infusion is 100 × 10^6 units/m^2/day [14]. These findings, and some indication from the phase I study that continuous infusion of high-dose interferon for 7 days had some anti-leukaemic activity, prompted the initiation of a formal phase II study.

Patients and Methods

1. Patients. Fourteen patients with AML, aged between 22 and 63, are included in this analysis. Eleven patients had relapsed following intensive short-term therapy comprising adriamycin, cytosine arabinoside, and 6-thioguanine, and three had been referred specifically for Interferon therapy, having failed to enter remission or relapsed following conventional therapy. Four patients are inevaluable for response, three having died within 3 days of starting Interferon therapy (2 of bronchopneumonia, 1 of septicaemia and cerebral haemorrhage) and one having withdrawn from the study after 24 h on deciding that he did not wish to have any further therapy.

2. Interferon. Hu IFN-αN derived from a Namalwa lymphoblastoid cell line (Wellcome Research Laboratories) had a specific activity ranging from 2.59 × 10^7 to 2.13 × 10^8/mg protein. All patients received 100 × 10^6 units/m^2 daily, when possible for 7 days, via a right atrial catheter. One patient subsequently received a second cycle, 3 weeks after completing the first.

3. Investigations. Full blood count, electrolytes, uric acid, urea, liver function tests, and serum calcium and phosphate were measured prior to therapy and daily thereafter. Bone marrow aspiration was performed prior to commencing Hu IFN-αN, 10 days after commencing IFN, and subsequently when clinically indicated.

4. Interferon Assay. Hu IFN-αN activity in serum was measured by reduction of viral RNA synthesis in WISH cells (Flow Laboratories) challenged with Semliki Forest virus prior to therapy and daily thereafter.

Results

a. Response (Table 1)

Circulating blast cells were present in the peripheral blood in seven of 12 patients prior to therapy. A fall was observed in three patients, in one of whom the degree of bone marrow infiltration also decreased from 33% to less than 5% blasts in association with eventual complete clearing of blasts from the blood. Complete remission was not achieved in this case however, because of persistent neutropenia and thrombocytopenia, and splenomegaly which had not been present prior to therapy. Splenectomy was subsequently performed when there was no obvious leukaemic infiltration of the bone marrow. The morphological appearance was that of a myeloproliferative disorder. Six weeks later blasts reappeared in the peripheral blood and bone marrow aspiration revealed increased infiltration. A Philadelphia chromosome was not present at any time.

In a second patient bone marrow infiltration was reduced from 10% in a normocellular marrow to less than 5%. The

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Table 1. Outcome of treatment with Hu IFN-αN

Patient	Pretreatment				Day 10				Day 21				Outcome
	Peri. blood		Bone marrow		Peri. blood		Bone marrow		Peri. blood		Bone marrow		
	WBC $\times 10^9$/l	Blasts	Cell.	Infil.	WBC $\times 10^9$/l	Blasts	Cell.	Infil.	WBC $\times 10^9$/l	Blasts	Cell.	Infil.	
1. H. V.	3.4	6%	Incr.	80%	1.0	0%	Incr.	85%	2.8	8%	Incr.	90%	Death
2. P. L.													
Cycle 1	2.2	0%	Normal	10%	1.0	0%	Normal	10%	2.1	0%	Normal	5–10%	Relapse at 3 months
Cycle 2	2.4	0%	Normal	10%	1.4	0%	Not done		1.5	0%	Normal	< 5% (*day 71)	
3. G. M.	57.5	56%	Incr.	95%	150.0 (*day 5)	84%	Not done		Patient died on day 5				
4. M. P.	5.4	0%	Incr.	15%	3.5	8%	Incr.	60%	2.4	13%	Incr.	65%	No response to alternative Rx
5. P. M.	4.0	28%	Incr.	95%	1.7	9%	Incr.	90%	3.5	24%	Incr.	95%	Response to alternative Rx
6. A. B.	8.2	3%	Incr.	33%	3.4	8%	Incr.	30%	7.3	0%	Normal	< 5%	No response to alternative Rx
7. C. C.	20.7	68%	Incr.	90%	165.0	89%	Not done		Patient died on day 12				
8. F. W.	1.4	13%	Normal	70%	1.3	16%	Normal	80%	1.7	13%	Normal	80%	No response to alternative Rx
9. S. J.	1.2	0%	Incr.	88%	1.4	2%	Incr.	95%	Patient died on day 12				
10. S. J.	116.9	40%	Incr.	73%	142.0	59%	Not done		Patient died on day 8				

Peri., peripheral; Cell., cellularity; Infil., infiltration; Incr., increased

criteria for complete remission could not be fulfilled because again, there was a lack of normal haemopoiesis with resultant peripheral neutropenia and thrombocytopenia. Overt relapse occurred after 3 months.

In the remaining eight patients there was no change in the morphological appearance of the bone marrow, and in five patients the circulating blast count increased during interferon therapy.

b. Clinical Toxicity

All patients became pyrexial and complained of anorexia, fatigue, and symptoms of influenza. Five patients became drowsy, two becoming confused and disorientated.

c. Haematological and Biochemical Toxicity

All patients became neutropenic and thrombocytopenic. Biochemical evidence of hepatic dysfunction (i.e., transient elevation of alkaline phosphatase and transaminases [SGOT]) was observed in nine of 10 patients.

d. Serum Hu IFN-αN Levels

Peak serum concentrations greater than 800 units/ml were achieved in the seven patients studied.

Discussion

The objective of this phase II study was to determine whether a 7-day infusion of Interferon at the maximum tolerated dose, yielding serum concentrations which are inhibitory to proliferation of myeloblasts in vitro, would induce complete remission of acute myelogenous leukaemia. The study was terminated after entry of only 14 patients, only 10 of whom were evaluable for response, when it became apparent that this aim was unrealistic. This view is supported by the lack of significant clinical responses seen in two patients receiving 200×10^6 units/m^2 daily in the phase I study [14].

Combining the results of the two studies reveals a complete remission rate of zero of 12. Seen within the context of recent phase II studies of high-dose cytosine arabinoside, yielding complete remission in more than 50% of cases refractory to this drug in conventional doses, the results are impressively negative [2, 10]. It is unlikely that Hu IFN-αN administered at a high dose for 7 days will be of practical relevance to the management of patients with acute myelogenous leukaemia. Whether or not alternative schedules and doses will have any potential advantage to patients presenting with AML or in remission remains to be determined.

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