

α Interferon in Myelodysplasia

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A. Patients and Methods

I. Myelodysplastic Patients

The FAB classification was employed in categorising MDS patients. Seventeen patients were studied initially – six with refractory anaemia (RA), six with RA with excess blasts (RAEB), one with transforming RAEB (trRAEB) and four with chronic myelomonocytic leukaemia. Of these, eight were suitable for α IFN therapy (3 RA, 3 RAEB, 1 trRAEB, 1 CMML). Treatment was commenced as 3 MU of Wellferon daily for up to 6 months. This dosage was reduced in the presence of thrombocytopenia.

II. Cell Phenotype

Peripheral blood mononuclear cells and neutrophils were separated using Ficoll/Hypaque centrifugation, and the neutrophils were further purified by dextran sedimentation.

Mononuclear antibody analysis was performed by an indirect immunofluorescent technique employing FITC-labelled goat anti-mouse immunoglobulin. Results were read on an FACS analyser. A spectrum of lymphocyte markers were used to characterise subsets, and several myeloid antibodies were used to stain neutrophils.

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III. NK Assay

A standard ^{51}Cr -release assay was employed using K562 cells as targets. Various ratios of effectors-to-target cells were used, and cells were incubated at 37°C for 4 h. ^{51}Cr released from lysed cells was measured in the supernatant as a measure of cytotoxicity. The standard formula for % cytotoxicity was employed.

B. Results

I. Clinical Response to α IFN

One patient with RAEB showed a drop in marrow blast count from 18% to 0% over 6 months. The patient with CMML showed a fall in peripheral monocyte count from $>15 \times 10^9/l$ to $3 \times 10^9/l$ but became neutropenic. The other six patients showed no improvement in transfusion requirements or marrow. Interestingly, no infective episodes were observed, in contrast to a previous report on α IFN used in MDS.

II. Cell Phenotype

Percentage positivity of NK cells was not substantially different from normal before therapy and did not change during therapy (Table 1). Lymphocyte subsets were not found to be markedly abnormal before or after therapy. Mature neutrophils expressed the immaturity marker (CD33) in $18\% \pm 4\%$ (compared with $4\% \pm 1\%$ in normals).

III. NK Function

NK function was generally low in all 15 patients studied. The addition of α IFN in vitro enhanced this, however.

Table 1. Phenotypical NK cells in different forms of myelodysplasia

Diagnosis	No. of patients	IFN therapy ^a	% positive (± 1 SEM)		Absolute no. of positive cells $\times 10^9/l$ (± 1 SEM)	
			Leu7	CD16	Leu7	CD16
RA	4	—	13 \pm 3	17 \pm 3	0.1 \pm 0.1	0.3 \pm 0.1
	3	+	15 \pm 3	19 \pm 5	0.2 \pm 0.1	0.2 \pm 0.1
RAEB	6	—	25 \pm 4	19 \pm 4	0.3 \pm 0.1	0.2 \pm 0.1
	3	+	26 \pm 6	20 \pm 6	0.3 \pm 0.1	0.2 \pm 0.1
trRAEB	1	+	11	27	0.4	0.8
CMML	4	—	4 \pm 1	11 \pm 5	0.7 \pm 0.3	1.6 \pm 0.9
	1	+	9	8	0.5	0.4
Normal	10	—	14 \pm 2	21 \pm 3	0.4 \pm 0.1	0.6 \pm 0.1

^a — Patient not receiving IFN; + patient receiving IFN

During α IFN therapy there was no consistent increase in NK cytotoxicity. When patients were studied sequentially, no consistent pattern emerged. One responder demonstrated increased activity, whilst the other demonstrated reduced activity. Nonresponders showed either enhancement or inhibition.

C. Discussion

A previous study of α IFN in MDS using 3 MU three times weekly revealed no clinical response. The present study suggests that a higher dosage may be effective occasionally in RAEB.

Although defective NK cytotoxicity was enhanced in vitro by α IFN, when α IFN was administered clinically it had no consistent effect on NK function. This phenomenon was independent of the percentage of NK cells present, which was in fact within normal limits. As NK cells may be implicated in haematopoiesis, we feel the effects of therapeutic α IFN are not mediated via these cells in MDS. Further, cold-target inhibition experiments using purified myeloid marrow cells showed no reduction in NK cytotoxicity.

We conclude that, although NK function is defective in MDS, the occasional beneficial effects of α IFN therapy are not mediated by this immunological mechanism.