Int 03

PHENOTYPIC ALTERATION OF LEUKEMIC HAIRY CELLS UPON INTERFERON- α TREATMENT IN VITRO
G.Gastl, W.Aulitzky, C.Martha, H.Tilg, E.Leiter, C.Gattringer, C.Huber

Hairy-cell leukemia is a B-cell tumor in which IFN- α has recently been shown to have a clear antitumor effect. In order to elucidate the action of IFN in HCL we studied the effect of human recombinant IFN- α 2 on purified peripheral blood hairy cells and a hairy cell leukemia line (HCL-1). Since IFN can promote cell differentiation of various tumor cell lines, morphological and immunophenotypic differentiating effects were studied in detail. In the presence of IFN- α the leukemic hairy cells lost most of their typical villous membrane projections and became non-adherent to glass and plastic surfaces. Surface marker analysis was carried out using the monoclonal antibodies FMC-7, OKIa1, Leu-M3, anti-Tac, Tol5, BMA 030, and Lyt3. Reactivity with the monoclonals Lyt3 and BMA 030 was found to be induced by IFN. In contrast, IL-2 receptor expression was down-regulated by IFN treatment. From these results we conclude that IFN- α 2 exerts a profound differentiating action on hairy cells in vitro.

Tab: HCL- in vitro effect of IFN- α 2 on surface marker expression (immunoperoxidase staining)

antibody	specificity	IFN- α ¹⁾	HC-1 ²⁾	HC-2 ²⁾
FMC-7	B-cells	-	++ ³⁾	+
		+	++	+
Leu-M5	Hairy cells	-	++	++
		+	++	++
BMA 030	T-cells	-	-	-
		+	++	++
Lyt3	T-cells	-	-	-
		+	++	++
anti-Tac	IL-2 receptor	-	-	++
		+	-	+(30%)

Universitätsklinik f. Innere Medizin, A-6020 Innsbruck

Int 04

EFFICACY OF GAMMA AND ALPHA INTERFERON (IFN) IN THE TREATMENT OF HAIRY CELL LEUKEMIA (HCL).
N. Niederle, O. Kloke, M.R. Nowrousian, H. Kruse and C.G. Schmidt.

Thirteen patients (pts) with HCL have been treated with γ - and/or α 2B-IFN. Pretreatment and follow-up evaluations included complete blood counts; staining with acid phosphatase resistant to tartrate; determination of liver and renal functions, LDH levels, serum electrolytes, clotting factors; bone marrow biopsy. To date, 11 pts - 10 men; median age 49 years (range 36-73); 22 months (range 2-49) after diagnosis - are evaluable for response. In 6 pts, treatment was started with γ -IFN (initial dose 4×10^6 U/m² sc every second day) lasting 2-7 months (median 5.5). Although the white blood cell counts slightly decreased during therapy from $3.3-49 \times 10^9$ /l (median 23×10^9) to $1.5-43 \times 10^9$ /l (median 8.4×10^9), no remission was obtained: median lymphocytes 89% vs 87%, 90% hairy cells (HC); median hemoglobin (Hb) levels 10.3 g% vs 11.1 g%; median platelet counts 111×10^9 /l (range $21-179 \times 10^9$) vs 145×10^9 /l (range $30-247 \times 10^9$); in bone marrow biopsies no decrease of HC. IFN- α 2B (initial dose $1-4 \times 10^6$ U/m²) was given to 5/6 pts pretreated with γ -IFN and another 5 pts without IFN pretreatment (splenectomy n=3, chemotherapy n=1). Dependent on the duration of treatment (2-8 months, median 4), there are so far: CR 1, PR 4, MR 5, SD 1 (median blood cell counts: leukocytes 4.2×10^9 /l, 51% lymphocytes; platelets 190×10^9 /l; Hb 12.2 g%; absence or decrease of HC in bone marrow biopsies of 5 pts). Side effects including fever, headache, nausea, myalgia, dryness of the mouth, and fatigue were severe only during the first days of therapy and did not differ significantly between the two IFN preparations. In conclusion, IFN- γ is unlikely to have any significant impact on the course of HCL, while IFN- α 2B does result in improvement of hematologic values and feelings of well-being in almost all patients.

Innere Universitätsklinik und Poliklinik (Tumorforschung), Hufelandstraße 55, D-4300 Essen 1.

Int 05

DETECTION OF URINARY ENZYME EXCRETION AS A PARAMETER OF THE NEPHROTOXICITY OF HUMAN- α -INTERFERON IN PATIENTS WITH CHRONIC GRANULOCYTIC LEUCEMIA (GCL)
E.Kurschel, U.Metz, N.Niederle

A previous study in 13 patients (pts.) with tumors of the colon or rectum, renal cancer and carcinoid tumors revealed no signs of acute or chronic renal toxicity. During a study on the effect of human- α -interferon in 13 pts. with chronic granulocytic leucemia we analysed the nephrotoxic potential of this agent. As particularly sensitive parameters in the detection of subclinical renal injury we measured the excretion of the following 5 enzymes: Lactate Dehydrogenase (LDH), Leucine aminylase (LAP), Gamma-Glutamyltransferase (GGT), Beta-Galactosidase (GAL), N-Acetylglucosaminidase (NAG). Additionally we analysed the protein excretion and the urinary sediment. In 10 of 13 pts. there was a significant increase in the excretion of LDH, LAP, GGT, and NAG; 6 pts. had a rise in the output of GAL, 6 pts. developed a proteinuria. According to our results in pts. with malignant lymphomas we must conclude that human- α -interferon is nephrotoxic in leucemia and related disorders. To date we have no explanation of the pathogenesis of the observed phenomena. But our results should lead to special attention on renal function studies in pts. treated with human- α -interferon. Further studies are warranted to find out whether preventive steps are necessary.

1. Metz, U., Kurschel, E., Niederle, N., Oehl, S.: Urinary enzymes in the detection of the nephrotoxic potential of recombinant human- α -Interferon, Renal Heterogeneity and Target cell toxicity, 267-270, 1985
2. Metz, U., Kurschel, E., Niederle, N., Scheulen, M.E.: Comparison of the nephrotoxic potential of recombinant human- α -interferon in patients with solid tumors and malignant lymphomas. American Journal of Kidney Disease (in press).

Innere Klinik und Poliklinik (Tumorforschung) der GHS Essen
Hufelandstr. 55, D-4300 Essen, FRG

Int 06

TREATMENT OF MYCOSIS FUNGOIDES BY RECOMBINANT LEUKOCYTE ALPHA-A INTERFERON AND VINBLASTINE
M.E. Scheulen, S. Öhl, M. Bamberg and M. Goos

The results of the treatment of mycosis fungoides by alpha-interferon are inconsistent. Synergistic effects of interferon with vinca alkaloids against human tumors have been suggested in clonogenic assay systems. Thus, we have initiated the treatment of patients with mycosis fungoides with Hoffmann-La Roche recombinant leukocyte alpha-A interferon and vinblastine in a phase I/II study to test anti-tumor effects and tolerance.

Since 2/84 six patients received recombinant leukocyte alpha-A interferon i.m. from a starting dose of 3×10^6 IU on day 1, to 9×10^6 IU on day 2, and up to 10×10^6 IU/m² the following days for 12 weeks, followed by 10×10^6 IU/m² x 3/week. In addition, vinblastine was administered i.v. once every three weeks from 0.05 to a maximum of 0.15 mg/kg.

Responses were seen in 5/6 patients: one complete response for five weeks which could not be maintained because of patient's rejection, three partial responses (5, 14, 49 weeks), and one minor response (5 weeks), respectively.

Except one patient who developed hypotonia and an acute toxic state with coma causing discontinuation of therapy, side effects were mild or moderate. Flu like symptoms were seen in all patients during initiation of therapy and could effectively be suppressed by acetaminophen. One patient was found to have elevated transaminases. After recovery he refused further treatment in complete remission.

In conclusion, combined treatment by recombinant leukocyte alpha-A interferon and vinblastine appears to be an effective regime in patients with mycosis fungoides. Further studies with a reduced interferon-dose are projected to decrease the side effects without reduction of antitumor efficacy.

West German Tumor Center, University of Essen Medical School, Hufelandstr. 55, D-4300 Essen 1