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Interferon Alfa-2b in Acute- and Chronic-Phase Chronic Myelogenous Leukaemia: Initial Response and Long-Term Results in 54 Patients

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Fifty-four patients with Ph¹-positive chronic myelogenous leukaemia (CML) (48 with chronic-phase and six acute-phase disease) were treated with interferon alfa-2b subcutaneously (s.c.). The starting dose was 4 million units (MU)/m² body surface area daily. It was reduced in parallel with serially determined leucocyte counts, and minimal effective doses were given as maintenance after achieving remission. Haematological remissions were induced in 22 of the 48 patients (46%) with chronic-phase disease. Thirteen patients (27%) revealed partial haematological remission and another 13 no response to treatment. No complete remission could be induced, although minor or partial cytogenetic responses were seen in 16 patients (33%). Moreover, a bcr-abl reduction was detected on Southern blot analysis in two patients. In chronic-phase disease, results of treatment were influenced by elapsed time after diagnosis, extent of previous treatment and interferon dosage. No beneficial effects of interferon were detected in the six patients with acute-phase disease. Principal acute side effects were fever and flu-like symptoms at the beginning of the therapy, which usually subsided within 3-7 days. Chronic side effects, especially weakness and neuropathy, were less frequent but more severe and necessitated discontinuation of treatment in 10 patients. In summary, interferon alfa-2b seems to be an effective treatment in early chronic-phase CML. Long-term effects on the course of the disease, however, must be determined.
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INTRODUCTION

IN THE MAJORITY of patients, chronic myelogenous leukaemia (CML) manifests during the 3rd to 5th decades of life. The disease has been shown to result from clonal neoplastic transformation at the level of the pluripotent haematopoietic stem cells [1,2]. The resultant unrestrained proliferation leads to an accumulation of myeloid cells in bone marrow and peripheral blood. The predominant clinical picture is granulocytosis of promyelocytic to polymorphonuclear leucocytic character, with occasional blast cell formation. Associated features include anaemia, changes in platelet counts, hepatosplenomegaly and a decreased index of alkaline phosphatase in mature neutrophils in the peripheral blood [3-6]. The neoplastic haematopoietic cell clone is characterized by the Philadelphia chromosome (Ph¹) (a shortened chromosome 22 arising from a reciprocal translocation t(9;22)(q34;q11) with chromosome 9) in more than 90% of the patients [7-10]. The Ph¹ translocation results in a transposition of the c-abl oncogene from chromosome 9 to chromosome 22. The fusion with the bcr gene generates a hybrid bcr-abl locus which is transcribed into an 8.5 kb mRNA and translated to a 210 KD protein with associated tyrosine kinase activity [11-18].

CML usually progresses through two distinct clinical phases. The initial chronic phase may last several years and is commonly asymptomatic, although constitutional symptoms or symptoms of hepatosplenomegaly may occur. The chronic phase terminates in the acute phase (accelerated phase, blast crisis) which usually lasts 3-6 months [19]. It is characterized by profound systemic effects such as fever and weight loss, refractory splenomegaly, progressive leucocytosis with a rising proportion of peripheral blasts and promyelocytes, and cytogenetic clonal evolution. The development of acute-phase disease may be heralded by gradual resistance to previously effective chronic-phase treatment [3-5,20].

Allogeneic bone marrow transplantation has, up to now, been seen to be the only curative procedure for CML [21-26]. This treatment, however, is restricted to patients under the age of 50 years with human leucocyte antigen (HLA) compatible donors. Recently, interferons have been shown to possess marked inhibitory activity on normal and leukaemic myeloid precursors [27-31]. In clinical trials, alpha interferon was shown to be capable of controlling myeloid proliferation in CML patients with chronic-phase disease [32-36]. Moreover, a persistent decline of Ph¹-positive bone marrow and peripheral blood cells was detected in some cases [35,37]. We report long-term results of a study initiated in 1984 to evaluate the clinical effects of interferon alfa-2b in patients with CML.

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PATIENTS AND METHODS

Patient eligibility criteria

Patients were entered into this study from April 1984 to March 1987. All patients presented with CML confirmed by characteristic blood and bone marrow smears and lowered leucocyte alkaline phosphatase, and were positive for the Philadelphia chromosome. Excluded were patients with cardiomyopathies, atrial fibrillation, patients having received antiarrhythmic or cardiotoxic drugs within 3 months prior to study, and those who had received cytoreductive therapy, steroid hormones, radiation, immune therapy or any investigational drug, including interferon or interferon inducers, within the previous 4 weeks. Patients with other underlying medical conditions which could not be adequately controlled, pregnant women, patients having undergone major surgery within the previous 28 days or suffering from uncontrolled infections, and patients with a history of pulmonary embolism or coagulopathies were also excluded. The study was performed after approval by the local Human Investigations Committee and all patients gave informed consent prior to treatment.

Treatment

Recombinant human interferon alfa-2b, produced and purified by Schering-Plough (Kenilworth, N.J., U.S.A.), was available as a lyophilized powder. Patients were treated with daily s.c. injections at a single starting dose of initially 4 million units (MU)/m^2 body surface area. After acute side effects had subsided, usually after 3 to 7 days, treatment was continued on an outpatient basis [36]. Dosage was adjusted in accordance with serially determined blood cell counts. The first decrease was performed only after an initial white blood cell (WBC) count reduction of more than 50%. The minimal effective dose to keep WBC counts well below 10,000/μL was given as maintenance after normalization of WBCs.

Evaluation

Pretreatment and follow-up evaluations were performed at regular intervals and included physical examination, complete blood counts, blood chemistry and coagulation profile. Ultrasonic measurements of hepatic and splenic size were repeated every 2 to 3 months, and bone marrow aspirations to perform cytogenetic studies and identification of haematopoietic progenitor cells were performed every 4 to 6 months. Side effects were determined at regular medical check-ups, as well as being registered in questionnaires completed by all patients each day of the induction period. The intensity was graded in accordance with WHO criteria. Side effects were considered chronic if they lasted for longer than 4 weeks after the induction of treatment.

Responses to therapy were evaluated by standard criteria [32]: complete remission (CR) was defined as haematological remission plus suppression of the Ph^1 chromosome in all analyzable metaphases and/or suppression of the bcr-abl marker band in Southern blots. Haematological remission (HR) was defined as normalization of total and differential leucocyte counts, platelet counts and serum lactate dehydrogenase (LDH) levels, as well as disappearance of all clinical symptoms of disease, including splenomegaly. Partial haematological remission (PHR) was defined as a greater than 50% reduction in total leucocyte counts, which should also be decreased to less than 20,000/μL, but without normalization of differential counts. Treatment failure (no response, NR) included reduction of total leucocyte counts to values higher than in PHR as well as stable and progressive disease (PD). Secondary resistance to interferon was defined as a progressive increase of WBC counts, in the absence of overt infections or acute-phase disease, to a value over 20,000/μL for at least 4 weeks after previous HR or PHR, despite administration of the maximum tolerable interferon dose (at least 3 MU/m^2).

Chromosome analysis

Cytogenetic response was evaluated according to the criteria described by Talpaz *et al.* [32]: no response if Ph^1 chromosomes persisted in all analyzable metaphases; minimal response with Ph^1 chromosome reduction to 35-95% of metaphases; partial response with Ph^1 chromosome reduction to 5-34% of metaphases and complete response with total elimination of Ph^1-positive metaphases.

Southern hybridization

High molecular weight DNA was extracted from Percoll (Seromed, Berlin, Germany) purified white blood or bone marrow cells using the proteinase K/SDS procedure with phenol and chloroform extractions as well as ethanol precipitation [38]. The DNA was digested with restriction enzymes following the suppliers' suggestion, run on 1% agarose gels and blotted onto nylon membranes (Hybond N, Amersham, Braunschweig, Germany). The filters were hybridized to a 2.0 kb Bgl II - Hind III fragment specific for the 5' end of the bcr region [39]. The probe was labelled with the Amersham multiprime kit to specific activities of 3×10^8 - 1×10^9 cpm/μg DNA. Filters were hybridized as described elsewhere [40], washed under stringent conditions and exposed to Kodak X-Omat films for 2 to 7 days at -80°C.

RESULTS

Patient characteristics

Fifty-four patients with Ph^1-positive CML were treated: 48 had chronic-phase and six acute-phase disease (Table 1). All patients were evaluable for response and toxicity. The 32 males and 22 females had a median age of 36 years (range 14 to 64 years). Performance status according to the WHO scale was 0 in 30 patients, I in 23 patients and II in one patient. Elapsed time after diagnosis was 1 to 253 months with a median of 13 months. Specific pretreatments included busulfan in 39 patients, hydroxyurea in seven patients, splenectomy in three patients, bone marrow transplantation in two patients, splenic irradiation in one patient and cytosine-arabinoside in one patient. Thirteen patients received no treatment prior to interferon.

Induction therapy

Chronic phase. No CR could be induced in 48 patients with chronic-phase disease (Table 2). HR, however, was found in 22 patients (46%) and PHR in 13 patients (27%), while another 13 patients showed no response to interferon alfa-2b. Time until PHR ranged from 4 to 40 weeks (median 7 weeks) and time until HR ranged from 5 to 26 weeks with a median of 12 weeks. Of the 35 patients with HR or PHR, a significant decrease in peripheral leucocytes (from 17.1-333 x 10^6/μL to

Table 1. Patient characteristics

Ph¹-positive patients (*n*)	
- chronic phase	48
- acute phase	6
Male/female	32/22
Age (years)	14-64 (median, 36)
Performance status (WHO)	
- 0	30
- I	23
- II	1
Time after diagnosis (months)	1-253 (median, 13)
Prior treatment (*n*)	
- Busulfan	39
- Hydroxyurea	8
- Splenectomy	3
- Bone marrow transplantation	2
- Radiation (spleen)	1
- Cytosine-arabinoside	1
- None	13

3.3 - 9.9 x 10^6/μL) and platelets (from 68 -1,550 x 10^6/μL to 30 - 341 x 10^6/μL), as well as in serum LDH levels (from 180 - 1019 U/L to 87 - 240 U/L) was detected (Fig. 1). Splenomegaly regressed or disappeared in all 35 responding patients.

Of the 48 patients with chronic-phase disease, 16 had no specific treatment prior to interferon (13 patients) or were treated for less than 6 months (three patients). In this subgroup, the time elapsing from diagnosis to interferon treatment was from 1 to 33 months (median 3 months). HR was achieved in 13 patients (81%) and PHR in two patients (13%). Only one patient (6%) failed to respond to therapy (Table 3). Among the remaining 32 patients with previous therapy for more than 6 months (time from diagnosis to interferon treatment 7 to 81 months, median 18 months), HR was achieved in nine (28%), PHR in 11 (34%), and 12 patients (38%) failed to respond to therapy.

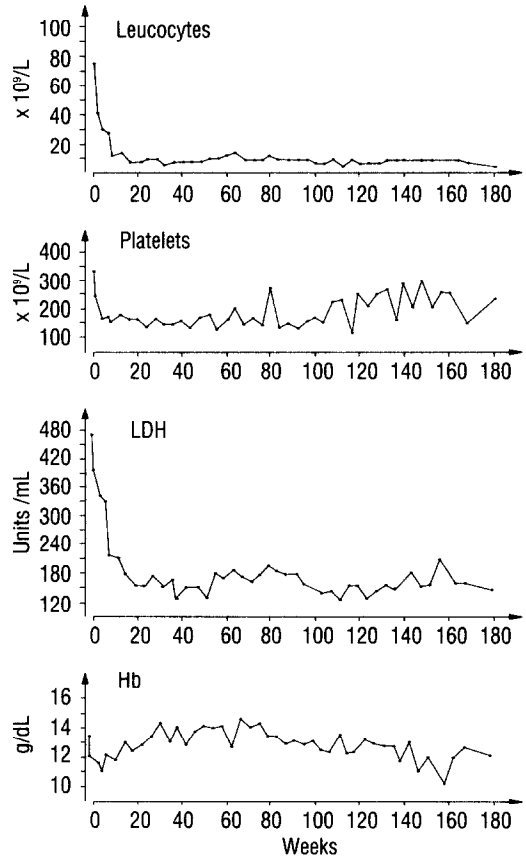

Fig. 1. Course of time vs. median blood parameters in 35 chronic-phase CML patients responding to interferon alfa-2b treatment (LDH = lactate dehydrogenase; Hb = haemoglobin).

Acute phase. Of the six patients with acute-phase disease, no significant effects of interferon treatment on leucocyte or platelet counts, LDH levels or splenomegaly were noted. Therefore, interferon therapy was discontinued within 6 weeks for all patients.

Table 2. Response to interferon alfa-2b in 48 patients with Ph¹-positive chronic-phase CML

	Patients			Weeks to response	Months of treatment
	(*n*)	(%)	(95% Confidence interval)	Median (range)	Median (range)
CR	0	0			
HR	22	46	(32-60)	12 (5-26)	14 (3.5-50+)
PHR	13	27	(14-40)	7 (4-40)	9 (2-52+)
NR	13	27	(14-40)		2 (1-3.5)

CR = Complete response: haematological remission plus suppression of the Ph¹ chromosome.
HR = Haematological response: normalization of total and differential leucocyte counts, platelet counts and LDH levels plus disappearance of clinical symptoms, including splenomegaly.
PHR = Partial haematological response: greater than 50% reduction in total leucocyte counts, which should be decreased to < 20 x 10^9/L; no normalization of differential counts.
NR = No response (including a reduction of leucocyte counts to higher levels than PHR, stable disease, and progressive disease).

Table 3. Response according to pretreatment in 48 patients with chronic-phase CML

	No prior therapy or less than 6 months (n = 16)		Prior therapy for more than 6 months (n = 32)	
	(n)	(%)	(n)	(%)
HR	13	81	9	28
PHR	2	13	11	34
NR	1	6	12	38

Abbreviations: See Table 2.

Cytogenetic analysis

Repeated chromosome analyses (2-8, median 3 in a single patient) before and during treatment were carried out in 37 patients, including all 22 patients achieving HR (Table 4). A reduction of Ph¹-positive metaphases was demonstrated in 16 patients (33%) including one partial response and 15 minimal responses. Eleven of these patients had HR and five PHR.

Fifteen of the 16 patients with no previous treatment or less than 6 months' treatment were evaluable for cytogenetic analysis. One patient (6%) achieved a partial response and eight patients (50%) minimal responses. Of the 32 patients with pretreatment periods of more than 6 months, 22 were evaluable for cytogenetic response, with only seven showing a minimal response (22%).

Molecular analysis

Sequential analyses (2-9, median 3) of the bcr-abl rearrangement with Southern hybridization were performed in 36 of the 48 chronic-phase patients. In one patient, the bcr-abl band disappeared after 9 months of treatment and remained undetectable for 23 months. Another patient showed a marked reduction of the marker band while in HR. No other reductions of the bcr-abl band were seen.

Follow up

After induction of HR, maintenance doses ranging from 1 MU every other day to 10 MU daily (median 3 MU daily) were given to keep blood cell counts within normal limits. A frequent observation during maintenance therapy was relapse of disease at low interferon doses with re-establishment of remission status after increasing the maintenance dosage (Fig. 2).

The median duration of interferon treatment was 14 months, ranging from 2 to 52+ months, in responding patients. Broken down into subgroups, the median duration of therapy was 9.5 months in responders with prior therapy of more than 6 months (range 2 to 52+) and 21 months in responders with no or minimal pretreatment (range 3.5 to 50+). Interferon therapy was discontinued when progressive disease with WBC counts

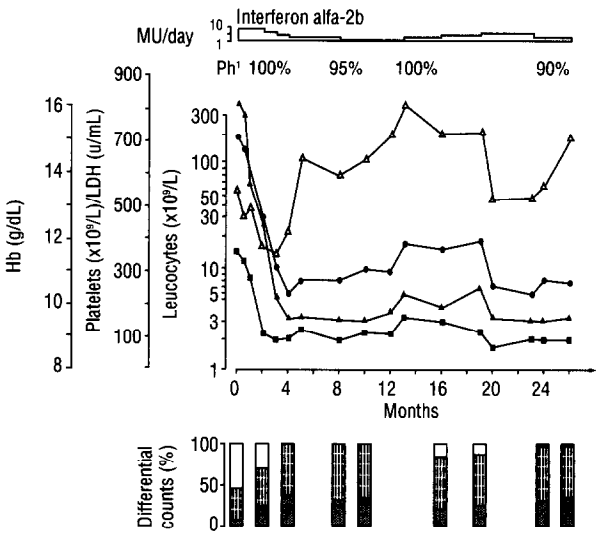

Fig. 2. Influence of interferon dosage (interferon alfa-2b) on leucocyte and differential counts, platelets, Hb and LDH values in a patient with chronic-phase CML. Haematological remission was reinduced by increasing the interferon alfa-2b maintenance dosage. (▲ = LDH; ● = leucocytes; △ = haemoglobin; ■ = platelets.) (See Fig. 1 for abbreviations.)

above 20,000/μL occurred or when side effects required cessation of therapy.

Among the HR patients, three have received interferon treatment for between 27 and 50 months and are continuing on therapy. Moreover, two PHR patients are still on schedule after 48 months and 52 months of therapy. Therapy had to be discontinued for the remaining 43 patients (Table 5). Primary or secondary disease progression was the reason for discontinuance in 20 patients and bone marrow transplantation (BMT) during HR or PHR in another eight patients. Ten patients had to be taken off interferon due to toxicities

Table 4. Cytogenetic response to interferon alfa-2b (37 of 48 patients, including all patients with HR, were investigated)

Cytogenetic response	Total group (n = 48)		No prior treatment or less than 6 months (n = 16)		Prior treatment for more than 6 months (n = 32)	
	(n)	(%)	(n)	(%)	(n)	(%)
Complete	–	–	–	–	–	–
Partial	1	2	1	6	–	–
Minimal	15	31	8	50	7	22

(Table 5). Therapy was also stopped at the request of another three patients. One patient in PHR died of viral myocarditis, probably unrelated to CML or interferon treatment, and one patient in HR was lost to follow up.

Four of the 20 patients with progressive disease developed blast crisis while on interferon therapy — two lymphoid, one myeloid, and one patient developed myeloblastomas. Remission status of the two patients at diagnosis of lymphatic metamorphosis was HR or NR, respectively. The patients with myeloid transformation were in HR and PHR. Interestingly, both acute phases developing during HR were primarily confined to solitary bone lesions.

Secondary treatment consisted of BMT, cytostatic drugs, gamma interferon with or without alpha interferon, or alpha interferon plus tumour necrosis factor (TNF) alpha (Table 5). Up to now, 24 of the chronic-phase patients have died. Survival time from diagnosis was 13 to 124+ months, median 51+ months.

Table 5. Follow up on 48 patients with CML and interferon alfa-2b treatment

	Patients (*n*)
Still under therapy (treatment duration)	5 (27-52; median, 48 months)
No further treatment due to:	43
- Progressive disease	20
- primary resistance	5
- chronic phase	4
- acute phase	1
- secondary resistance	15
- chronic phase	12
- HR/PHR	6/6
- acute phase	3
- HR/PHR	2/1
- Bone marrow transplantation	8
- Toxicity	10
- peripheral neuropathy	8
- weakness	1
- pancytopenia	1
- Patient's decision	3
- Death in remission	1
- Lost to follow up	1
Secondary treatment	
- BMT	15
- Gamma IFN	7
- Gamma IFN + alpha IFN	7
- TNF alpha + alpha IFN	3
- Cytostatic drugs	23

Side effects

Side effects could be differentiated into acute (during the first weeks of treatment) and chronic (beginning more than 4 weeks after starting treatment) toxicity. Acute side effects were usually mild to moderate and no grade IV toxicities were seen. They generally appeared within 1 to 8 hours after the initial dose of alpha interferon and subsided in almost every patient within 3 to 7 days of therapy, without a dose modification being necessary. The most common adverse reactions included fever, chills, headache, fatigue, dry mouth, nausea and vomiting, muscle and bone pain, mild hypotension, eye pain and loss of appetite (Table 6).

Table 6. Acute side effects during interferon alfa-2b therapy in 48 patients with chronic-phase CML

			Severity (WHO) No.			
	n	%	I	II	III	IV
Fever	48	100	1	42	5	–
Chills + flu-like symptoms	48	100	22	16	10	–
Headache	38	79	18	14	6	–
Fatigue	37	77	22	10	5	–
Dry mouth	22	46	6	15	1	–
Nausea + vomiting	21	44	17	4	–	–
Muscle + bone pain	17	35	11	4	2	–
Hypotension	15	31	14	1	–	–
Eye pain	15	31	13	2	–	–
Loss of appetite	13	27	9	4	–	–
Confusion	5	10	4	1	–	–
Stiff neck	4	8	2	2	–	–
Cough	4	8	2	2	–	–
Diarrhoea	3	6	2	1	–	–
Night sweat	3	6	2	1	–	–
Hot flushes	2	4	1	1	–	–
Skin sensitivity	2	4	2	–	–	–
Visual disturbances	2	4	1	–	1	–
Nightmare	1	2	1	–	–	–

Chronic side effects dominated after subsidence of acute effects and often persisted for weeks or even months. The most common were fatigue and weakness, anorexia, hair loss and neuropathy (Table 7). Chronic side effects necessitated discontinuation of treatment in 10 patients. Eight of these patients developed progressive and uncontrollable neuropathy-like symptoms, one patient had severe weakness and one patient progressive pancytopenia.

Table 7. Chronic side effects during interferon alfa-2b therapy in 48 chronic-phase patients

			Severity (WHO) *n*			
	n	%	I	II	III	IV
Fatigue and weakness	26	54	16	7	3	–
Weight loss	16	33	9	6	1	–
Muscle + bone pain	13	27	6	5	2	–
Hair loss	10	21	9	1	–	–
Neuralgia + polyneuropathy	9	19	–	2	7	–
Depression	3	6	–	3	–	–
Itching	1	2	1	–	–	–
Pancytopenia	1	2	–	–	1	–

No severe, longer lasting changes in excretory or parenchymal liver enzymes, coagulation factors, creatinine values or serum electrolytes were detected during this study (Table 8).

Table 8. Changes in laboratory parameters in 48 patients with chronic-phase CML during treatment with interferon alfa-2b

			Severity (WHO) *n*				
	n	%	0	I	II	III	IV
SGOT	28	58	6	17	4	1	–
SGPT	33	68	5	14	12	2	–
Alkaline phosphatase	15	31	6	7	1	–	1
LAP	45	94	5	25	13	2	–
Bilirubin	2	4	1	1	–	–	–
Urea	2	4	1	1	–	–	–
Uric acid	14	29	13	1	–	–	–
Creatinine	19	40	14	5	–	–	–
Sodium	2	4	2	–	–	–	–
Potassium	2	4	1	1	–	–	–
Calcium	1	2	1	–	–	–	–
Fibrinogen	18	37	16	2	–	–	–

DISCUSSION

The present study was undertaken to evaluate the therapeutic effectiveness of alpha interferon in patients with CML, a disease that can be palliated but not cured by conventional therapies. In accordance with other groups [32,34,41,42], our data demonstrate a significant efficacy of alpha interferon in controlling chronic-phase disease. Haematological response rates of 73% (46% HR, 27% PHR) correspond well to studies utilizing similar doses and are superior to treatment results following lower interferon doses [34,41,42]. The clinical dose-response relationship correlates well with *in vitro* data [43-45], indicating that higher induction and maintenance doses (near the maximum tolerable doses) are necessary to improve long-term results.

Better results in the sense of haematological remissions (94%) and cytogenetic improvements (56%), moreover, were observed in the 16 patients where a shorter period had elapsed since diagnosis (median 3 months; range 1-33) and where no or rather short pretreatment periods had occurred. No or minimal pretreatment and short elapsed time from diagnosis to start of treatment have also been described by other investigators as positive factors for the outcome of interferon treatment in CML [33,34,41].

No significant effect of interferon treatment was seen in the six patients with acute-phase disease. These results are in accordance with data reported in the literature [46,47], although occasional reports to the contrary do exist [34,48].

Acute side effects of interferon administration, e.g., fever, flu-like symptoms and myalgias (Table 6), were more pronounced during the first days of interferon application, but usually disappeared completely within 1 week. Paracetamol and/or indomethacin served to prevent these symptoms effectively. No patient's therapy had to be stopped or reduced because of acute side effects. During the first days of treatment, the patients learned readily to prepare and inject interferon subcutaneously, making it possible to continue therapy on an outpatient basis.

Chronic side effects were less frequent than acute ones but far more of a problem. Fatigue and weakness were the most frequent adverse reactions (54%), although they caused discontinuation of treatment in only one patient. In another patient, therapy had to be stopped due to progressive pancytopenia. Neurological side effects consisted of a combined polyneuropathic pain along the lower spine and the ischiatic nerve root, and diffuse muscle and bone pains. Eight patients had to stop treatment due to these problems. Although similar side effects are described frequently, no underlying causative mechanism has been found so far, even with the broad range of neurological investigations used (personal, unpublished data).

Median duration of remission (14 months; range 2 to 52+) and median survival time after diagnosis (51+ months; range 13 to 124+) were similar to data published previously [32,33,41]. This study offers no answer to the question as to whether interferon treatment has any impact on long-term survival of chronic-phase CML patients. To reach conclusive results, prospective randomized studies with longer follow up periods and larger patient populations are required [49].

Another major problem in long-term interferon treatment is secondary resistance developing in previously responsive patients. In this study, secondary resistance during interferon therapy developed in 15 patients (eight in HR, seven in PHR), with 12 of these patients remaining in chronic-phase disease and three progressing to acute-phase disease. In this context, anti-interferon alfa-2b antibody formation seems to be of minor relevance. In 26 of these patients, serially performed anti-interferon antibody analysis (ELISA and bioassay for up to 12 analyses during 40 months in a single patient) revealed high antibody titres in only one patient at the time of treatment failure (data in preparation).

It is of interest to notice, however, that some patients responded later to combined therapy with alpha interferon plus either gamma interferon or TNF alpha, although they did not respond to gamma interferon or TNF alpha alone [50-52]. In view of these results, and the multiple, well-documented synergistic effects of alpha interferon with gamma interferon or TNF alpha *in vitro*, future studies are warranted to evaluate the efficacy of these combinations in primary or secondary alpha interferon-resistant patients, as well as for primary therapy [45,51,53-56].

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Evolving Modalities of Treatment with Interferon Alfa-2b for Ph^1-Positive Chronic Myelogenous Leukaemia

Enrica Morra, Giuliana Alimena, Mario Lazzarino, Anna Marina Liberati, Enrico Montefusco, Paolo Bernasconi, Marco Mancini, Emilio Donti, Serena Merante, Ferdinando Dianzani, Fausto Grignani, Carlo Bernasconi and Franco Mandelli

We have administered interferon alfa-2b, alone or in combination with chemotherapy, to 126 Ph^1-positive chronic myelogenous leukaemia patients. Of 71 early chronic phase (CP) patients (< 12 months from diagnosis), 41 (58%) obtained a complete haematological response (CHR). Daily interferon was more effective than intermittent administration. In previously untreated patients, the response was significantly influenced by risk status at diagnosis. Thirty-four out of 71 (48%) patients improved cytogenetically, the median of Ph^1+ mitoses declining from 100% to 66% with complete Ph^1-suppression in one case. Of 46 late CP patients (> 12 months from diagnosis), 32 (70%) achieved CHR with interferon alone or combined with chemotherapy. All 10 patients with disease well controlled by chemotherapy obtained stable CHR with interferon alone. Of 36 partial responders to conventional chemotherapy, 22 (61%) obtained CHR on interferon plus low-dose hydroxyurea. Ph^1 mosaicism was reached by 16 (35%) late CP patients (median Ph^1+ cells 75%). Of nine accelerated phase patients on interferon plus chemotherapy, one attained CHR, and two responded partially. At a median follow up of 36 months, of 41 CHR patients in early CP, 15 are controlled on interferon, 12 have had autologous bone marrow transplantation (BMT), and two allogeneic BMT. Blastic transformation (BT) has occurred in eight of 41 CHR patients (19%) versus 17 of 30 (57%) non-responders and partial responders to interferon. At a median follow up of 22 months, of 32 late CP patients obtaining CHR, 26 remain on interferon, one had allogeneic BMT, one had autologous BMT, and one developed BT (versus five out of 14 with less than CHR). These studies confirm the haematological and cytogenetic efficacy of interferon in CML and indicate that the disease status at the start of treatment is critical in determining the success of therapy.
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INTRODUCTION

DURING the last 20 years neither conventional chemotherapy, nor more aggressive chemotherapy have substantially modified the natural evolution of chronic myelogenous leukaemia (CML) [1, 2]. The suppressive effect on the Ph^1-positive clone, sometimes observed after intensive chemotherapy, is usually transient [3, 4]. To date, only allogeneic bone marrow transplantation (BMT) has led to the stable, complete suppression of the Ph^1 cells with restoration of normal haemopoiesis. This approach, however, is limited to a minority of CML patients [5]. Since 1983, several studies with partially purified human alpha interferon and with recombinant interferon have demonstrated significant activity in CML patients, leading in some cases to the partial or complete

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