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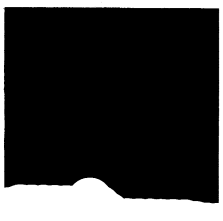

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Interferon-alpha2b for Early Phase Chronic Lymphocytic Leukemia with High Risk for Progression – First Results of a Randomized Multicenter AIO-Study[1]

Key Words
Interferon-alpha2b
Chronic lymphocytic leukemia
Early phase

Summary
Background: In prior pilot studies Interferon-alpha2b (IFN-alpha) was shown to be effective in B-cell type chronic lymphocytic leukemia (B-CLL). Therefore, the benefit of an IFN-alpha-therapy in early phase B-CLL is assessed with respect to freedom from progression and long term survival in a randomized multicenter study. *Material and methods:* Patients with early phase B-CLL (Binet A) and high risk for progression (diffuse bone marrow infiltration plus serum level of thymidinkinase >5 U/l plus/or lymphocyte doubling time <12 months) are randomized into an IFN-treatment group (arm A) or a watch and wait group (arm B). Patients who do not share the risk parameters are documented in another watch and wait arm C. Dosage of IFN-alpha is 3 x 5 Mill. IE per week. *Results:* Out of 14 evaluable patients im arm A two patients achieved a complete remission (normalization of blood cell counts, no lymph nodes palpable) and three patients attained a partial remission. Three patients have stable disease, and one out of four patients with progressive disease was in need of chemotherapy. Ten out of 15 evaluable patients in arm B have stable disease, but five others had progressive disease with four patients in need of chemotherapy. None of the 24 evaluable patients in arm C had progressive disease with need of chemotherapy. *Conclusion:* These preliminary results seem to prove the validity of the risk parameters and show the possible benefit of an IFN-treatment in early phase B-CLL at high risk for progression.

[1] Presented as 'Actual Contribution' at the Common Meeting of German and Austrian Societies of Hematology and Oncology, Innsbruck, October 10 – 13, 1991

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Schlüsselwörter
Interferon-alpha2b
Chronische lymphatische Leukämie
Frühphase

Zusammenfassung
Hintergrund: In Pilotstudien hat sich Interferon-alpha2b (IFN-alpha) als effektiv in der Behandlung der chronischen lymphatischen Leukämie vom B-Zelltyp (B-CLL) erwiesen. In einer randomisierten multizentrischen Studie wird deshalb der Nutzen einer Interferonbehandlung bezüglich Progressionsfreiheit und Langzeitüberleben geprüft. *Material und Methodik:* Patienten mit einer unbehandelten B-CLL im Frühstadium (Binet A) und hohem Progressionsrisiko (diffuse Knochenmarkinfiltration plus Serumspiegel der Thymidinkinase >5 U/l plus/oder Lymphozytenverdopplungszeit < 12 Monate) werden einer IFN-Behandlungsgruppe (Arm A) oder einer Beobachtungsgruppe (Arm B) zugeteilt. Patienten, die das Risikoprofil nicht erfüllen, werden in einem weiteren Beobachtungsarm C dokumentiert. Die Dosierung von IFN-alpha besteht aus 3x5 Mill. IE pro Woche. *Ergebnisse:* Von 14 auswertbaren Patienten im Arm A haben zwei Patienten eine klinische komplette Remission (Normalisierung des Blutbildes, keine Lymphadenopathie) und drei Patienten eine partielle Remission erreicht. Drei Patienten sind in einer stabilen Phase und vier Patienten waren progredient, wovon jedoch nur ein Patient zytostatisch behandelt werden mußte. Bei zwei weiteren Patienten wurde die Therapie wegen Nebenwirkungen vorzeitig abgebrochen. In Arm B sind zehn von 15 auswertbaren Patienten in einer stabilen Phase, und vier von fünf progredienten Patienten mußten zytostatisch behandelt werden. Von 24 evaluierbaren Patienten im Arm C erlitt keiner eine therapiepflichtige Progression. *Schlußfolgerung:* Diese vorläufigen Daten unterstützen nicht nur das Stratifizierungskonzept, sondern weisen auch auf einen therapeutischen Nutzen des IFN-alpha in der Frühphase der B-CLL hin.

Introduction

The majority of previously untreated patients with early phase B-cell chronic lymphocytic leukemia (B-CLL, stage Binet A) expects a long-lasting indolent course of the disease. Long time survival of these patients does not differ from that of an age and sex matched control population [1]. However, approximately 30% of the patients will have progressive disease within two years after establishment of diagnosis. Diffuse bone marrow infiltration [2], lymphocyte doubling time > 12 months [3], and serum levels of thymidine kinase > 5 U/l [4] have been identified as risk factors for progression. In pilot studies, interferon-alpha2b (IFN-α) has been shown to be efficient for B-CLL [5, 6]. In Binet stage A disease a decrease of circulating malignant B-lymphocytes was achieved. In addition, IFN-α treatment induced an increase in serum immunoglobulin levels [7]. The possible benefit of an IFN-α treatment of Binet stage A B-CLL at high risk for progression is therefore being examined in an ongoing randomized multicenter study. The goals of the study are freedom from progression and from chemotherapy, and overall survival.

Material and Methods

Inclusion criteria and study design: Patients who are not older than 75 years and having a morphologically and immunophenotypically proven, previously untreated B-CLL in stage Binet A were included into the study. The lymphocyte count to had be below 100,000/µl. The patients had to give their written informed consent. Patients with a diffuse bone marrow involvement and a lymphocyte doubling time <12 months, and/or a serum thymidine kinase level > 5 U/l were allocated to the high risk group. They were randomized into study arm A (IFN-a therapy) or study arm B (wait and watch). Patients with diffuse bone marrow involvement but without an additional risk factor as well as all patients with nodular bone marrow infiltration are allocated to the low risk group receiving no treatment (study arm C, wait and watch).
Patient characteristics: Until September 1, 1991, 100 patients were enrolled into the study. Risk factors were known from 63 patients. Sixteen patients were randomized into arm A, and 19 patients into arm B. Twenty-eight patients did not fulfill the criteria for being at high risk for progression and were therefore included in arm C. In the high risk group, the mean lymphocyte doubling time was 4.1 months compared to 27.4 months in the low risk group. The mean serum level of thymidine kinase was 11.0 U/l in the high risk and 4.6 U/l in the low risk patients.
Therapy: High risk patients randomized into study arm A are treated with IFN-α (Intron A®) subcutaneously. The planned dosage per week is 3x5 Mio IE IFN-α. Dose modification for individual reasons like toxic side effects is possible. In case of increasing lymphocyte counts during IFN-α treatment, dose escalation up to 3x8 Mio IE IFN-α is planned.

Results

Two out of 14 evaluable patients of the IFN-treatment group achieved a complete remission defined as normalization of peripheral blood counts and absence of enlarged lymphnodes. Three patients attained a partial remission and three other patients had stable disease. In four patients progression occurred and one of them was in need of chemotherapy. Due to toxic side effects (fever, nausea, depression) the treatment was

Table 1. Treatment results

	High risk/ IFN-α treatment (n = 16)	High risk/ no treatment (n = 19)	Low risk/ no treatment (n = 28)
Evaluable	14	15	24
Complete remission	2		
Partial remission	3		
Stable disease	3	10	21
Progression[1]	4	5	3
Need for chemotherapy	1	4	0
Off study due to toxicity	2		

[1] Progression is defined as increase of lymphocytes over 100,000/μl, or occurrance of new enlarged lymphnodes, or increase of prior enlarged liver/spleen/lymphnodes

Table 2. Toxicity of IFN-α (WHO grading > II)

	n
Fever	2
Arthralgia/myalgia	1
Diarrhea	1
Nausea/vomiting	0
Weight loss	1
Hair loss	0
Depression	2

stopped in two patients. Ten out of 15 evaluable patients of the high risk group without IFN-α treatment have stable disease, whereas five patients had progressive disease, with four of them in need of chemotherapy. In contrast, none of the 24 patients in the low risk group was in need of chemotherapy.
The treatment results and toxicities of IFN-α are summarized in tables 1 and 2, respectively.

Discussion

These preliminary results seem to show the benefit of an IFN-α treatment of early stage B-CLL at high risk for progression. Antileucemic effects of IFN-α had been reported earlier in pilot studies on B-CLL [5, 6, 7]. It has been shown, that IFN-α is more effective in early stage than in late stage disease [8]. In this still ongoing randomized trial the effectiveness of IFN-α appears to become evident. While four out of 14 patients treated with IFN-α had progressive disease, only one of them was in need of chemotherapy. In the high risk group, however, five out of 15 patients had progressive disease and four of them needed chemotherapy. Moreover, the randomization concept seems to be confirmed as none of the patients without risk factors were in fact in need of specific therapy. These preliminary data support the validity of the risk factors, i.e. diffuse bone marrow infiltration, short lymphocyte doubling time, and high levels of serum thymidine kinase. Whether IFN-α could decrease the use of chemotherapy and prolong overall survival requires a greater number of patients and follow-up investigation of this ongoing trial.

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