

---

# Contributions to Oncology Beiträge zur Onkologie

Vol. 46

Series Editors

*H. Huber, Wien; W. Queißer, Mannheim*

**KARGER**

---

Basel · Freiburg · Paris · London · New York · New Delhi · Bangkok · Singapore · Tokyo · Sydney

---

# Cytokines in Cancer Therapy

Volume Editors

*L. Bergmann, P. S. Mitrou*, Frankfurt

89 figures and 71 tables, 1994

Published with the kind support of Biotest Pharma GmbH

**KARGER**

---

Basel · Freiburg · Paris · London · New York · New Delhi · Bangkok · Singapore · Tokyo · Sydney

## Contributions to Oncology Beiträge zur Onkologie

---

### Drug Dosage

The authors and the publisher have exerted every effort to ensure that drug selection and dosage set forth in this text are in accord with current recommendations and practice at the time of publication. However, in view of ongoing research, changes in government regulations, and the constant flow of information relating to drug therapy and drug reactions, the reader is urged to check the package insert for each drug for any change in indications and dosage and for added warnings and precautions. This is particularly important when the recommended agent is a new and/or infrequently employed drug.

---

### All rights reserved.

No part of this publication may be translated into other languages, reproduced or utilized in any form or by any means, electronic or mechanical, including photocopying, recording, microcopying, or by any information storage and retrieval system, without permission in writing from the publisher.

- © Copyright 1994 by S. Karger GmbH, Postfach, D-79095 Freiburg and  
S. Karger AG, Postfach, CH-4009 Basel  
Printed in Germany by Konkordia Druck GmbH, D-77815 Bühl  
ISBN 3-8055-5809-0

---

# Contents

Preface .....	IX
 <i>Cytokine Network</i>	
Balkwill, F. R.; Naylor, M. S. (London, UK): The Cytokine Network .....	1
Seliger, B.; Lohmann, S.; Huber, C. (Mainz); Pfizenmaier, K. (Stuttgart, FRG): Regulation of Major Histocompatibility Complex Class I Gene Expression in Oncogene-Transformed Mouse Fibroblasts.....	11
 <i>Interferons and Tumor Necrosis Factor in Malignancies</i>	
Kloke, O. (Essen, FRG): Combinations of Interferon- $\alpha$ with Other Cytokines as Initial and Second-Line Therapy of Chronic Myelogenous Leukemia .....	24
De Fabritiis, P., et al. (Rome, Italy): The Role of Alpha-Interferon in Patients with Chronic Myeloid Leukemia Autografted in Chronic Phase.....	30
Hehlmann, R., et al. (Mannheim, FRG): Interferon- $\alpha$ in the Treatment of CML: Comparison of Busulfan versus Hydroxyurea versus Interferon- $\alpha$ .....	39
Freund, M.; Kleine, H.-D.; Heußner, P.; Poliwoda, H. (Hannover, FRG): Clinical Significance of Interferons in the Treatment of Malignant Lymphomas .....	53
Knauf, W. (Berlin, FRG), et al.: Interferon- $\alpha$ in the Treatment of B-Cell Chronic Lymphocytic Leukemia .....	71
Eggermont, A. M. M. (Rotterdam, The Netherlands), et al.: High-Dose Tumor Necrosis Factor- $\alpha$ in Combination with Interferon- $\gamma$ and Melphalan in Isolated Perfusion of the Limb for Irresectable Soft Tissue Sarcomas: A Highly Effective Approach to Achieve Limb Salvage .....	81
Doll, M.; Huber, C.; Seliger, B. (Mainz, FRG): Potentiation of Growth Inhibition and Modulation of Differentiation in Human Malignant Glioblastomas by Combined Treatment with Recombinant Human Interferon- $\alpha$ and - $\gamma$ .....	89
Weisch, H. J. C., et al. (Frankfurt a. M., FRG): Immunotherapy and Chemotherapy in Anaplastic Thyroid Carcinoma – An Experimental Study.....	99

*Interleukin-2 in Cancer Treatment*

Smith, K. A. (Hanover, N. H., USA): Endocrinologic Principles in the Therapeutic Use of Interleukin-2.....	105
Lotzová, E. (Houston, Tex., USA): Activation and Therapy with Cytotoxic Lymphocytes: Current Dilemmas and New Directions.....	109
Whiteside, T. L. (Pittsburgh, Pa., USA): Tumor-Infiltrating Lymphocytes: Potential and Limitations to Their Use in Antineoplastic Therapy.....	124
Weidmann, E., et al. (Pittsburgh, Pa., USA): The T-Cell Receptor $\beta$ Chain Variable Region Repertoire in Fresh and Cultured Lymphocytes Isolated from Human Malignant Melanomas.....	133
Bergmann, L. (Frankfurt a. M., FRG): Interleukin-2 and Its Combination with Other Cytokines in Cancer Therapy.....	143
Favrot, M. C. (Lyon, France), et al.: Early and Late Intravenous Interleukin-2 Infusion after Autologous Bone Marrow Transplantation: Report of Multicentric French Studies.....	156
Klingemann, H.-G.; Gong, H.-J.; Eaves, C. J.; Phillips, G. L. (Vancouver, B. C., Canada): Immunotherapy in Marrow Transplantation – Interferon Early after Transplantation or IL-2-Activated Bone Marrow.....	168
Cavallo, F., et al. (Turin, Italy): The Local Availability of IL-2 Induces the Immune Recognition of an Otherwise ‘Nonimmunogenic’ Tumor.....	175
Guida, M., et al. (Bari, Italy): Subcutaneous rIL-2 in Advanced Melanoma and Kidney Carcinoma: Clinical and Biological Aspects.....	182
Keilholz, U. (Heidelberg, FRG), et al.: Treatment of Metastatic Melanoma with Interferon- $\alpha$ and High-Dose Interleukin-2.....	191
Bergmann, L., et al. (Frankfurt a. M., FRG): Daily Alternating Administration of Interferon- $\alpha$ 2b and Interleukin-2 Bolus Infusion in Two Different Dose Levels by Metastatic Renal Cell Cancer. Results of Two Phase II Studies.....	201
Atzpodien, J.; Kirchner, H.; Poliwoda, H. (Hannover, FRG): Treatment Strategies Employing Chemoimmunotherapy in Patients with Metastatic Renal Carcinoma.....	211
Huland, E.; Heinzer, H.; Schwaibold, H.; Huland, H. (Hamburg, FRG): Inhalation of Natural Interleukin-2: Effectivity and Toxicity in Patients with Pulmonary Metastases of Renal Cell Carcinoma.....	218
Schwuléra, U. (Dreieich); Huland, E. (Hamburg); Struff, W. G.; Lissner, R. (Dreieich, FRG): Antibody Formation to Interleukin-2 in Renal Cell Carcinoma Patients with Pulmonary Metastases Treated by Aerosol Therapy. Comparison of Western Blot and Enzyme-Linked Immunosorbent Assay Data.....	224
Knüver-Hopf, J. (Springe, FRG), et al.: No Antibody Formation in Cancer Patients Treated with Natural Interleukin-2 in Combination with Recombinant Interferon- $\gamma$ ...	232
Weber, F. (Cologne, FRG), et al.: Local Application of Lymphokine-Activated Killer Cells and Natural Interleukin-2 in Malignant Glioma Therapy.....	238
Schmitt, K. (Frankfurt a. M., FRG), et al.: Real-Time Biospecific Interaction Analysis of Immobilized Interleukin-2 Receptor $\beta$ -Chain Peptides with Polyclonal Antibodies.....	243
Radoux, D.; De Groote, D. (Fleurus, Belgium): The Total Cytokine Concept: The Influence of Soluble Receptors in the Cytokine Measurement.....	251

*Gene Transfer of Cytokines*

Mullen, C. A. (Bethesda, Md., USA): Development of Live Tumor Vaccines Using Retroviral Vectors for Transfer of Suicide Genes and Cytokines.....	260
Rosenthal, F. M.; Cronin, K.; Guarini, R.; Gansbacher, B. (New York, N. Y., USA): Generation of a Cellular Antitumor Immune Response by Retrovirally Mediated Cytokine Gene Transfer .....	269
Hock, H.; Dorsch, M.; Blankenstein, T.; Diamantstein, T. (Berlin, FRG): Tumor-Cell-Targeted Interleukin-7 Gene Transfer Reveals T-Cell-Dependent Antitumor Activity in vivo.....	277
Richter, G.; Platzer, C.; Blankenstein, T.; Diamantstein, T. (Berlin, FRG): Detection of Cytokines Induced by and Involved in the Antitumor Response Provoked by Tumor Cell-Derived Interleukin-4 .....	281

*Biological Function of Cytokines and Adhesion Molecules*

Gilleece, M. H. (Manchester, UK), et al.: Phase I Dose Toxicity Clinical Evaluation of Interleukin-4 .....	286
de Waal Malefyt, R.; de Vries, J. E. (Palo Alto, Calif., USA): Biological Properties of Human Interleukin-10 .....	294
Kekow, J.; Gross, W. L. (Lübeck, FRG): Transforming Growth Factor $\beta$ – Multiple Actions in Immune Function and Oncology .....	301
Holler, E. (München, FRG), et al.: Involvement of Cytokines in Graft-versus-Host Disease and Graft-versus-Leukemia Activity .....	318
Garofalo, A.; Dossi, R.; Giavazzi, R. (Bergamo, Italy): Cytokine-Induced Adhesion Molecules and Tumor Spread .....	330
Fenchel, K.; Bergmann, L.; Jahn, B.; Mitrou, P. S. (Frankfurt a. M., FRG): Up-Regulation of Adhesion Molecules by Immunotherapy as a Mechanism of Cytotoxicity in Renal Cell Cancer, Malignant Melanoma, and Acute Myelocytic Leukemia .....	336

*Miscellaneous*

Gerhartz, H. H.; Schmetzer, H.; Mayer, F. (Munich, FRG): Immunological Detection and Surveillance of Residual Acute Myeloid Leukemia during Remission .....	347
Ziegler, I.; Schott, K. (München); Schwuléra, U. (Dreieich, FRG): Regulation of H4bi- opterin Synthesis in Human Mononuclear Cells during Immune Response.....	360
Löw-Friedrich, I., et al. (Frankfurt a. M., FRG): Cytokines Directly Affect Contractility and Stress Protein Formation of Cardiac Myocytes.....	368

*Immunotherapy in Cancer: Concepts and Prospects*

Whiteside, T. L.; Herberman, R. B. (Pittsburgh, Pa., USA): Current Concepts and Future Prospects for Immunotherapeutic Approaches in Cancer Treatment.....	374
Subject Index.....	388

## Interferon- $\alpha$ in the Treatment of B-Cell Chronic Lymphocytic Leukemia

W. Knauf<sup>a</sup>, I. Langenmayer<sup>b</sup>, C. Nerl<sup>c</sup>, D. Adorf<sup>c</sup>, H. Dietzfelbinger<sup>d</sup>,  
P. Maubach<sup>e</sup>, H.W.L. Ziegler-Heibrock<sup>f</sup>, B. Emmerich<sup>b</sup>, E. Thiel<sup>a</sup>

<sup>a</sup>Abteilung für Hämatologie und Onkologie, Klinikum Steglitz, Freie Universität Berlin;

<sup>b</sup>Abteilung für Hämatologie, Klinikum Innenstadt, Ludwig-Maximilians-Universität München;

<sup>c</sup>Städtisches Krankenhaus, München-Schwabing;

<sup>d</sup>Abteilung für Hämatologie, Klinikum rechts der Isar, Technische Universität München;

<sup>e</sup>I. Medizinische Klinik Ingolstadt;

<sup>f</sup>Institut für Immunologie, Ludwig-Maximilians-Universität München, BRD

### *Introduction*

The majority of previously untreated patients with early phase B-cell chronic lymphocytic leukemia (B-CLL) 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 2 years after establishment of diagnosis. Diffuse bone marrow involvement [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. Treatment with chlorambucil during the early phase of the disease revealed no benefit with respect to survival, but led to an increased risk for secondary malignancies [1]. Therefore, early stage B-CLL usually is not treated until progression has occurred.

In pilot studies, interferon- $\alpha$  (IFN- $\alpha$ ) was shown to have antileukemic activity in early stage B-CLL [5–8] whereas only marginal or no beneficial effects were reported in advanced stage disease [9, 10]. Here, we report on our own experiences obtained from a pilot study with IFN- $\alpha$  in early stage B-CLL. Furthermore, we present first results of a still ongoing randomized

multicenter trial. Encouraged by the results of our pilot study, this trial was activated to examine the possible benefit of an IFN- $\alpha$  treatment in early stage disease at high risk for progression. We will also discuss future concepts dealing with IFN- $\alpha$  in the treatment of B-CLL.

### *IFN- $\alpha$ in a Pilot Study on B-CLL*

#### *Patient Characteristics*

Prompted by the obvious efficacy of IFN- $\alpha$  in hairy cell leukemia [11], a pilot study in B-CLL was initiated [7, 12]. Nine patients with previously untreated early stage B-CLL (4 females, 5 males) were included in this phase II trial. Median age was 48 years (range 42–58 years). They all had Binet stage A disease [13], according to Rai stages varying from 0 to II [14]. Median time from first diagnosis was 16 months (range 2–65 months). Four patients had a lymphocyte doubling time (LDT) < 12 months. A diffuse bone marrow involvement was found in another 2 patients. Overall, the tumor load was considered to be low, since the total circulating lymphocyte count in each patient did not exceed 50,000 l/ $\mu$ l at the time of recruitment for the study.

#### *Treatment*

Treatment consisted of  $5 \times 10^6$  IU IFN- $\alpha$  subcutaneously (Intron A<sup>®</sup>, supplied by Essex-Pharma, Munich, FRG) 3 times weekly. Duration of treatment has been in the range of 15–36 months. Treatment was overall well tolerated. In 6 patients toxic side effects included flu-like symptoms, which did not exceed WHO grade II. While in 2 patients depression was observed, another 2 patients did not experience any toxic side effects.

#### *Results*

All patients responded to IFN- $\alpha$  with a decrease of their lymphocyte count. However, the lymphocyte count increased again despite continued IFN- $\alpha$  treatment in 1 patient 3 weeks after initiation of therapy. Splenomegaly resolved in 1 patient, and this particular patient turned from Rai stage II to stage I disease. A rise of immunoglobulin levels was observed in 3 patients, and in 4 patients HLA-DR expression on monocytes was doubled. Four patients achieved a partial remission according to the remission criteria proposed by Cheson et al. [15], whereas another 4 patients had stable disease.

#### *Conclusions*

This pilot study showed the antileukemic efficacy of IFN- $\alpha$  in early stage B-CLL. The high rate of responding patients (8 out of 9) was in



Table 1. Pilot studies on IFN- $\alpha$  in B-CLL

Author	Patients	CR	PR	Ref.
Foon et al.	18	0	2	9
O'Connell et al.	4	0	1	16
Pangalis and Griva	10	1	4	6
Talpaz et al.	10	0	3	10
Rozman et al.	10	0	8	8
Ziegler-Heitbrock et al.	9	0	8	7

accordance with some previous reports [6, 8], but in striking contrast to other findings [9]. However, that latter report discussed data obtained in a trial on patients with advanced stage and in some cases pretreated but refractory B-CLL. One may therefore speculate that a low tumor load and lack of prior cytotoxic therapy as in our patients could be a prerequisite condition for the effectiveness of IFN- $\alpha$ . (A summary of published remission rates in B-CLL treated with IFN- $\alpha$  is listed in table 1.)

Of major interest was the finding that patients with a LDT < 12 months and with a diffuse bone marrow involvement also responded to treatment. Beside high levels of serum thymidine kinase [4], a short LDT [2] as well as a diffuse bone marrow involvement [3] were identified as risk factors for progression in early stage B-CLL.

Thus, in consequence of the results of this pilot study, a phase III trial on IFN- $\alpha$  in early stage B-CLL at high risk for progression was initiated.

### *IFN- $\alpha$ in Early Stage B-CLL – Preliminary Results of a Phase III Trial*

#### Materials and Methods

##### *Inclusion Criteria and Study Design*

Patients who were not older than 75 years and having a morphologically and immunologically proven, previously untreated B-CLL in Binet stage A were included in this trial. All the patients had to give their written informed consent. The lymphocyte count had to be < 100,000 / $\mu$ l. Patients were stratified by risk factors. A diffuse bone marrow infiltration and a LDT < 12 months and /or serum levels of thymidine kinase > 5 U/l qualified for the high-risk group. Patients in the high-risk group were randomized into an arm A with IFN- $\alpha$

therapy, and an arm B without treatment. Patients with a nodular bone marrow infiltration, and all those with a diffuse infiltration but without an additional risk factor, were allocated to the low-risk group (arm C, no treatment). The aims of the study are freedom from progression and long-time survival.

#### *Patient Characteristics*

At the time of this analysis (April 15, 1992), 13 patients were evaluable in arm A, 13 patients in arm B, and another 28 patients in arm C. Median age of the three study arms was 60 years. No severe concomitant diseases were evident. Median serum levels of the thymidine kinase were 7 U/l in arm A and 8.3 U/l in arm B, but 3.8 U/l in arm C ( $p < 0.01$ ). Median LDT was 10 months in arm A, 24.5 months in arm B (no significant difference), and 42 months in arm C ( $p < 0.05$ ).

#### *Treatment*

High-risk patients randomized into arm A were treated with IFN- $\alpha$  (Intron A<sup>®</sup>) subcutaneously. The planned dosage per week was  $3 \times 5 \times 10^6$  IU IFN- $\alpha$ . Dose modifications for individual reasons like toxic side effects were allowed. Dose escalation up to  $3 \times 8 \times 10^6$  IU IFN- $\alpha$  was proposed in case of increasing lymphocyte counts during IFN treatment.

#### *Definitions*

Complete remission (CR) was defined as the complete disappearance of peripheral signs of CLL, i.e. lymphocytosis, lymphadenopathy, and hepatosplenomegaly. Partial remission (PR) was defined as the 50% or more reduction of the tumor load. Beside an upstaging to Binet B or Binet C disease, progression of disease was defined as the increase of the total lymphocyte count  $>100,000$  l/ $\mu$ l, or occurrence of new enlarged lymph nodes, or increase of prior enlarged lymph nodes, liver, or spleen.

## Results

#### *Status of Disease*

Five out of the 13 high-risk patients with IFN- $\alpha$  treatment (arm A) achieved a PR with time to reach remission varying from 1 to 5 months. Two patients had stable disease. The remaining 6 patients had progressive disease, and 2 of them had to be treated with conventional chemotherapy. It has to be noted, however, that for individual reasons only 45% of the patients in arm A received the 100% dosage of IFN- $\alpha$  according to the study protocol, i.e.  $3 \times 5 \times 10^6$  IU/week. In arm B (high risk, no treatment) 7 out of 13 patients had stable disease, whereas the disease was progressive in the remaining 6 patients. Four of the latter ones had to be treated with conventional chemotherapy. In contrast to the high-risk patients, the vast majority (23 out of 28 patients) of the low-risk patients had stable disease. Even though 5 patients experienced disease progression, none of

Table 2. Results

Arm A: n = 13	treatment with IFN- $\alpha$ , 'high-risk' <sup>1</sup> PR 5 NC 2 PD 6, with 2 in need for chemotherapy
Arm B: n = 13	no treatment, 'high risk' PR 0 NC 7 PD 6, with 4 in need for chemotherapy
Arm C: n = 28	no treatment, 'low risk' PR 0 NC 23 PD 5, with 0 in need for chemotherapy

PR = partial remission; NC = no change; PD = progressive disease.

<sup>1</sup> Only 45% of the patients were treated with the 100% dosage of IFN- $\alpha$  ( $3 \times 5 \times 10^6$  IU sc) as outlined in the protocol.

them was in need for chemotherapy. Time until progression differed significantly ( $p < 0.05$ ) between the high-risk and the low-risk patients. No influence of IFN- $\alpha$  became evident so far, while median time to progression was 12 months in arm A, and 13 months in arm B. The median was not yet reached in arm C within an observation time of 30 months. The results are listed in table 2.

### *Toxic Side Effects*

IFN- $\alpha$  was well tolerated in the majority of patients. Flu-like symptoms, alopecia, and weight loss did not exceed WHO grade II toxicity. A slight increase of serum levels of GOT and creatinine, respectively, was observed only in 1 patient (WHO grade I toxicity). Nevertheless, 3 patients were excluded from further IFN- $\alpha$  treatment due to toxic side effects. Two of them experienced depression (WHO grade II). One patient suffered from diarrhea and nausea to be classified as WHO grade III toxicity. This particular patient had to definitely discontinue IFN- $\alpha$  therapy despite a dosage reduction from  $3 \times 3 \times 10^6$  FU IFN- $\alpha$ /week to  $3 \times 1 \times 10^6$  IU/week, and despite concomitant treatment with antiemetic drugs. The toxic side effects are listed in table 3.

Table 3. Toxic side effects

Side effects	WHO grade			
	I	II	III	IV
Fever	2	1		
Myalgia	5			
Headache	1			
Alopecia	4			
Weight loss	2			
Diarrhea		1	1	
Nausea	2		1	
Dizziness	1	2		
Depression	1	2		
SGOT	1			
Creatinine	1			

Only 1 patient with WHO > II toxicities; 3 patients off treatment due to toxicities.

### Discussion

The preliminary results of this randomized trial on IFN- $\alpha$  in early stage B-CLL seem to confirm the concept of stratification by risk factors. Five out of 28 patients at low risk for progression had progressive disease, whereas 12 out of 26 patients at high risk (13 patients in arm A, another 13 patients in arm B) had progressive disease. Moreover, a significant difference in time until progression became evident. In the two high-risk groups, median time to progression was 12 and 13 months, respectively. In the low-risk group, however, the median was not yet reached within an observation period of 30 months. Therefore, the occurrence of a diffuse bone marrow infiltration together with a LDT < 12 months and/or levels of serum thymidine kinase > 5 U/l define in fact a condition of high risk for progression in early stage B-CLL.

Antileukemic effects of IFN- $\alpha$  were evident in some patients. Five out of 13 patients in our study achieved a PR. Foon et al. [9] reported on 2 patients out of 12 achieving a PR, and O'Connell et al. [16] found 1 PR in 4 patients. Somewhat better results were obtained by Pangalis et al. [6] who reported on 5 out of 10 patients achieving a remission (1 CR and 4 PR). In that particular study, the 4 patients who attained a PR had Binet stage A dis-

ease and had not received prior chemotherapy. A high rate of responding patients was reported by Rozman et al. [8]. All the 10 patients examined in their study had a transient reduction of the number of circulating lymphocytes. Moreover, an increase of the granulocyte count was detected in 8 patients. Interestingly, all the patients in the study of Rozman et al. had Binet stage A disease without prior treatment, according to Rai stages O–I.

While some efficacy of IFN- $\alpha$  in early stage B-CLL is obvious, little is known until today about the mechanisms of action. Efficacy of IFN- $\alpha$  may depend on the number of receptors on the target cells. While low numbers of receptors were found in advanced stage B-CLL, high numbers detected in early stage could be prerequisite for the antileukemic effects of IFN- $\alpha$  [17]. Moreover, induction of HLA-DR expression with activation of monocytes [7], recruitment of NK cells [16], and a relative increase of the T<sub>4</sub>-positive lymphocyte subset [16] during IFN- $\alpha$  treatment were reported. These latter findings may also be related to the responsiveness of early stage B-CLL to IFN- $\alpha$ .

IFN- $\alpha$  may interact with other cytokines. Tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) was found to act as an autocrine growth factor in B-CLL [18, 19], and high serum levels of TNF- $\alpha$  are thought to be a characteristic feature in early stage disease [20]. The disruption of the TNF- $\alpha$  dependent proliferation in B-cell malignancies by IFN- $\alpha$  was postulated to represent the mechanism by which IFN- $\alpha$  could counteract cell proliferation [21]. However, IFN- $\alpha$  does not seem to have an influence on the production of TNF- $\alpha$  in B-CLL cells, and furthermore, it enhances TNF- $\alpha$  release in hairy cell leukemia [22]. Thus, efficacy of IFN- $\alpha$  seems to be mediated by other pathways.

The prognostic impact of the response to IFN- $\alpha$  treatment in early stage B-CLL remains undefined, since no studies on the long-time follow-up of the responding patients were published so far. A larger number of patients and a follow-up for several years in our study may contribute to elucidate that point.

### *Future Concepts*

So far, efficacy of IFN- $\alpha$  in B-CLL was shown in a number of pilot studies (see table 1). A consistent observation was that the effectiveness of IFN- $\alpha$  was higher in early stage than in advanced stage disease. Induction of remission in case of a low tumor load is therefore possible, but the ben-

efit with respect to survival and freedom from progression remains to be defined.

Maintenance of remission is another goal in the treatment of B-CLL. IFN- $\alpha$  was shown to prolong the duration of remission in multiple myeloma after prior 'inductive' chemotherapy [23]. In analogy, IFN- $\alpha$  could provide the chance of maintained remission in early as well as in advanced stages of B-CLL after conventional chemotherapy. Montserrat et al. [24] published first results of a pilot study, in which the tumor load of 11 patients with early stage B-CLL was reduced by intermittent chlorambucil. Then, IFN- $\alpha$  was administered, and the quality of remission was improved in 5 patients. Additional studies on IFN- $\alpha$  after prior chemotherapy in advanced stage B-CLL are urgently warranted.

IFN- $\alpha$  is currently examined in combination with 5-fluorouracil (5-FU) in a number of trials on solid tumors of the gastrointestinal tract. The rationale of these trials is to modify the cytotoxicity of 5-FU by IFN- $\alpha$  [25]. Modulation of cytotoxicity could be an approach also in B-cell malignancies. Pini and Foa [26] reported on 2 patients with B-CLL having received chlorambucil in combination with IFN- $\alpha$ . The progressive disease in both patients could not be further controlled by chlorambucil alone. But, the additional application of IFN- $\alpha$  led to a reduction of circulating lymphocytes followed by a stable disease. This preliminary observation should initiate pilot studies to assess the feasibility and efficacy of combined treatments with IFN- $\alpha$  and cytotoxic agents.

A number of cytokines seem to be involved in the regulation of cell growth in B-CLL. Interleukin-4 (IL-4) shows antiproliferative activity [27], while, for example, TNF- $\alpha$  and interleukin-2 (IL-2) are known to stimulate proliferation [18, 19, 28]. Therefore, studies on the combination of IFN- $\alpha$  with IL-4 are needed and might be helpful for understanding the cytokine network in B-CLL.

In summary, IFN- $\alpha$  provides some antileukemic activity in B-CLL. However, its modes of action and most effective modalities of treatment still remain to be clarified.

### *References*

- 1 French Cooperative Group on Chronic Lymphocytic Leukemia: Effects of chlorambucil and therapeutic decision in initial forms of chronic lymphocytic leukemia (stage A): Results of a randomized clinical trial on 612 patients. *Blood* 1991;75:1414-1421.

- 2 Rozman C, Hernandez-Nieto L, Montserrat E, Bruges R: Prognostic significance of bone marrow patterns in chronic lymphocytic leukaemia. *Br J Haematol* 1981;47:529–537.
- 3 Montserrat E, Sanchez-Bisono J, Vinolas N, Rozman C: Lymphocyte doubling time in chronic lymphocytic leukaemia: Analysis of its prognostic significance. *Br J Haematol* 1986;62:567–575.
- 4 Källander CFR, Simonsson B, Hagberg H, Gronowitz JS: Serum deoxythymidine kinase gives prognostic information in chronic lymphocytic leukemia. *Cancer* 1984;54:2450–2455.
- 5 Thiel E, Schlag R, Hill W, Kettner G, Flieger D, Ziegler HWL: B-CLL in early phase responds to recombinant alpha-2b-interferon therapy as determined in a pilot study. *Blut* 1987;55:243A.
- 6 Pangalis GA, Griva E: Recombinant alpha-2b-interferon therapy in untreated, stages A and B chronic lymphocytic leukemia. *Cancer* 1988;61:869–872.
- 7 Ziegler-Heitbrock HWL, Schlag R, Flieger D, Thiel E: Favorable response of early stage B-CLL patients to treatment with IFN-alpha-2. *Blood* 1989;73:1426–1430.
- 8 Rozman C, Montserrat E, Vinolas N, Urbano-Ispizua A, Ribera JM, Gallart T, Compernelle C: Recombinant alpha-2-interferon in the treatment of B chronic lymphocytic leukemia in early stages. *Blood* 1988;71:1295–1298.
- 9 Foon KA, Bottino GC, Abrams PG, Fer MF, Longo DL, Schoenberger CS, Oldham RK: Phase II trial of recombinant leukocyte A interferon in patients with advanced chronic lymphocytic leukemia. *Am J Med* 1985;78:216–220.
- 10 Talpaz M, Rosenblum M, Kurzrock R, Reuben J, Kantarjian H, Gutterman J: Clinical and laboratory changes induced by alpha-interferon in chronic lymphocytic leukemia – A pilot study. *Am J Hematol* 1987;23:341–350.
- 11 Quesada JR, Reuben J, Manning JT, Hersh EM, Gutterman JE: Alpha-interferon for induction of remission in hairy cell leukemia. *N Engl J Med* 1984;310:15–18.
- 12 Schlag R, Flieger D, Ziegler-Heitbrock HWL, Hill W, Emmerich B, Thiel E: Interferon-alpha-2b in the treatment of chronic lymphocytic leukaemia of the B-cell type. *Dtsch Med Wochenschr* 1990;115:1088–1095.
- 13 Binet JL, Catovsky D, Dighiero CG, Montserrat E, Rai KR, Sawitsky A: Chronic lymphocytic leukaemia: Proposals for a revised prognostic system. *Br J Haematol* 1981;48:365–367.
- 14 Rai KR, Sawitsky A, Cronkite EP, Chanana AD, Levy RN, Pasternack BS: Clinical staging of chronic lymphocytic leukemia. *Blood* 1975;46:219–234.
- 15 Cheson BD, Bennett JM, Rai KR, Grever MR, Kay NE, Schiffer CA, Oken MM, Keating MJ, Boldt DH, Kempin SJ, Foon KA: Guidelines for clinical protocols for chronic lymphocytic leukemia. Recommendations of the National Cancer Institute-sponsored working group. *Am J Hematol* 1988;29:152–163.
- 16 O'Connell MJ, Colgan JP, Oken MM, Ritts RE, Kay NE, Itri LM: Clinical trial of recombinant leukocyte A interferon as initial therapy for favorable histology non-Hodgkin's lymphoma and chronic lymphocytic leukemia. An Eastern Cooperative Oncology Group pilot study. *J Clin Oncol* 1986;4:128–136.
- 17 Dadmarz R, Cawley JC: Heterogeneity of CLL: High CD23 antigen and  $\alpha$ -IFN receptor expression are features of favourable disease and of cell activation. *Br J Haematol* 1988;68:279–282.

- 18 Cordingley FT, Bianchi A, Hoffbrand AV, Reittie JE, Heslop HE, Vyakarnam A, Turner M, Meager A, Brenner MK: Tumor necrosis factor as an autocrine tumour growth factor for chronic B-cell malignancies. *Lancet* 1988;i:969-971.
- 19 Digel W, Stefanie M, Schöniger W, Buck C, Raghavachar A, Frickhofen N, Heimpel H, Porszolt F: Tumor necrosis factor induces proliferation of neoplastic B cells from chronic lymphocytic leukemia. *Blood* 1989;73:1242-1246.
- 20 Foa R, Massaia M, Cardona S, Tos AG, Bianchi A, Attisano C, Guarini A, Francia di Celle P, Fierro MT: Production of tumor necrosis factor-alpha by B-cell chronic lymphocytic leukemia cells: A possible regulatory role of TNF in the progression of the disease. *Blood* 1990;76:393-400.
- 21 Heslop HE, Bianchi ACM, Cordingley FT, Turner M, de Mel WCP, Hoffbrand AV, Brenner MK: Effects of interferon-alpha on autocrine growth factor loops in B lymphoproliferative disorders. *J Exp Med* 1990;172:1729-1734.
- 22 Jansen JH, Wientjens GJHM, Willemze R, Kluin-Nelemans JC: Production of tumor necrosis factor-alpha by normal and malignant B lymphocytes in response to interferon-alpha, interferon-gamma and interleukin-4. *Leukemia* 1992;6:116-119.
- 23 Mandelli F, Avvisati G, Amadori S, Boccadoro M, Gernone A, Lauta VM, Marmont F, Petrucci MT, Tribalto M, Vegna ML, Dammacco F, Pileri A: Maintenance treatment with alpha-2b-recombinant interferon significantly improves response and survival duration in multiple myeloma patients responding to conventional induction chemotherapy. Results of an Italian randomized study. *N Engl J Med* 1990;322:1430-1434.
- 24 Montserrat E, Villamor N, Urbano-Ispizua, Ribera JM, Lozano M, Vives-Corrons, Rozman C: Treatment of early stage-B chronic lymphocytic leukemia with alpha-2b-interferon after chlorambucil reduction of the tumoral mass. *Ann Hematol* 1991;63:15-19.
- 25 Kreuser E-D, Wadler S, Thiel E: Interactions between cytokines and cytotoxic drugs: Putative molecular mechanisms in experimental hematology and oncology. *Semin Oncol* 1992;19(suppl 4):1-7.
- 26 Pini M, Foa R: Combined use of alpha-2b-interferon and chlorambucil in the management of previously treated B-cell chronic lymphocytic leukemia. *Leuk Lymphoma* 1991(suppl 1):143-148.
- 27 Karray S, Defrance T, Merle-Beral H, Banchereau J, Debre P, Galanaud P: Interleukin-4 counteracts the interleukin-2 induced proliferation of monoclonal B cells. *J Exp Med* 1988;168:85-94.
- 28 Moberts R, Hoogerbrugge H, van Agthoven T, Löwenberg B, Touw I: Proliferative response of highly purified B chronic lymphocytic leukemia cells in serum-free culture to interleukin-2 and tumor necrosis factors alpha and beta. *Leukemia Res* 1989; 13:973-980.

Prof. Dr. E. Thiel  
Abteilung für Hämatologie und Onkologie  
Klinikum Steglitz der Freien Universität  
Hindenburgdamm 30  
D-12203 Berlin (FRG)