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REVIEW ARTICLE

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# Cytokines in the pathophysiology and treatment of chronic B-cell malignancies

## A review

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**Abstract** Chronic B-cell malignancies are characterized by accumulation of transformed B cells of low proliferative index in lymphatic and extralymphatic tissues. Cytokines do not appear to play a role in the primary step of transformation. However, proliferation as well as inhibition of apoptosis of malignant B cells can readily be explained by cytokine effects. Clinical trials of interferons (IFN) and interleukin-2 alone or in combination have been performed in patients with hairy cell leukemia (HCL), CLL, and low- and intermediate-grade non-Hodgkin's lymphoma. While IFN alpha became standard therapy of HCL, responses in other entities were variable, ranging from 0 to 70% in selected populations. Combination of IFN and cytotoxic chemotherapy in general revealed no additional benefit as compared to chemotherapy alone. Perspectives for future clinical testing of cytokines in low-grade B-cell lymphomas are discussed.

**Key words** CLL · Hairy cell leukemia · Low-grade lymphoma · Cytokines

## Introduction

Low-grade B-cell lymphomas represent a challenging problem in basic and clinical hematology. Following a clinically indolent course, so far, low-grade lymphomas are incurable with standard chemotherapy regimens. Hairy cell leukemia (HCL) was the first disease in which cytokine therapy with interferon (IFN) became clinical standard. Administration of cytokines with or without additional cytotoxic chemotherapy has been extensively tested in chronic lymphocytic leukemia (CLL) and follicular lymphomas. The following review is aimed first at summarizing and discussing preclinical data on the influence of cytokines on the growth, survival, and differentiation of malignant B cells. Second, the rationale for and results of clinical application of cytokines in low-grade B-cell malignancies are presented.

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## Pathophysiology of low-grade B-cell neoplasia

The approach to understanding the pathophysiology of low-grade lymphomas is to characterize alterations as compared with normal B-lymphocyte development: Malignant B cells exhibit a lack of differentiation, which can be explained by genotypic transformation. Potentially causative mechanisms are structural chromosomal aberrations affecting genes involved in cell cycle control. For example, about 75% of mantle-cell lymphomas have t(11;14) translocations rearranging the bcl-1/PRAD1/cyclin D1 gene, which is reported to regulate G1/S transition in the cell cycle [8, 69]. Lymphomas with t(14;19) translocations show an up-regulation of the bcl-3 gene, which encodes a specific inhibitor of the transcription factor NF-kappa B [71]. Rearrangements of the bcl-6/LAZ 3 gene on chromosome 3q27 encoding a member of the zinc-finger family of transcription factors also are found in some follicular lymphomas [6, 36]. These and other mutations might deregulate B-cell development. In addition, they might provide a growth advantage for the transformed clone. In contrast, deregulation of cytokine expression does not appear to play a role in the primary step of lymphomagenesis. It appears unlikely that up-regulated autocrine or paracrine production of ubiquitous cytokines such as tumor necrosis factor (TNF) alpha or interleukin (IL)-6 alone has the potential to transform B cells.

The second pathophysiological mechanism of low-grade lymphoma is proliferation and expansion of the

to stimuli provided by cytokines. Several in vitro studies described autocrine secretion of proinflammatory cytokines such as TNF alpha [20, 30, 55] and IL-6 [7, 55], as well as secretion of B-cell growth factor [23] by malignant B cells. However, using the in situ hybridization technique, IL-6 message was detectable only on environmental macrophages and endothelial cells, suggesting a paracrine rather than an autocrine secretion [17]. Additional paracrine signals might be provided by T lymphocytes, which were found to be present in comparable numbers in CLL patients and healthy controls [31]. Furthermore, T cells from CLL patients behaved largely normally regarding inducibility of Th1 and Th2 cytokine secretion patterns (Decker T, Flohr T, Trautmann P, Huber C, Peschel C: Blood *in press*). In vitro, T-cell cytokines such as IL-2 [11, 42], IL-4 [5], and IL-10 [18] were observed to enhance proliferation and to induce CD23 expression [29, 59, 66] on CLL- or HCL-B cells. Finally, the lack of spontaneous in vitro proliferation of low-grade malignant B cells underscores the requirement of growth stimulation as provided by cytokines and direct cell-cell interaction with T lymphocytes or environmental cells.

Further, low-grade lymphomas are characterized by accumulation of malignant B cells in lymphoid and extralymphatic tissues. This can be explained largely by inhibition of programmed cell death (apoptosis) of lymphoma cells, resulting from both gene mutations and cytokine effects. Apoptosis is controlled by intracellular inducers, such as Fas/APO-1, p53 or c-myc, and by suppressors such as bcl-2 and related genes (for review see [70]). In concordance, bcl-2 protein and Fas antigen were found to be inversely expressed in normal lymph node and peripheral blood lymphocytes [72]. Translocations t(14; 18) resulting in overexpression of the bcl-2 gene under control of the lg heavy-chain promotor [4, 13, 68] are detected in 80–90% of follicular lymphomas. Furthermore, inhibition of apoptosis of malignant B cells is described for IL-4 [14, 48], IFN gamma [10], and IFN alpha [49] in vitro. Thus, concerted effects of genetic deregulation of B-cell development, as well as growth- and survival-promoting signals provided by cytokines form a model for the pathophysiology of chronic B-cell malignancies.

Another pathophysiological mechanism involving cytokines especially in CLL and HCL might cause pancytopenia, which plays an important role in the morbidity and mortality of these diseases. High levels of TNF are measured in serum and bone marrow from HCL patients, and TNF mRNA is detectable in HCL-B cells. Supernatants from HCL cell cultures inhibit growth of normal bone marrow cells. Anti-TNF antibody enhances hematopoiesis of HCL and CLL bone marrow cells in vitro [21, 35, 41]. The adherent bone marrow cell fraction from CLL patients produces increased amounts of transforming growth factor (TGF) beta, while G-CSF and GM-CSF levels are normal. Their supernatants support only 25% of normal blast colony-forming culture growth, and this inhibition is abrogated by anti-TGF beta antibody [34].

In conclusion, there is abundant preclinical evidence for a direct or indirect influence of a variety of cytokines on the pathophysiology of low-grade B-cell lymphomas. These data provide a rationale for clinical study of modulation of the cytokine network in these diseases.

## Clinical results of cytokine therapy in chronic B-cell malignancies

### Hairy cell leukemia

Since the first reports of effective treatment of HCL with IFN alpha appeared [54, 56, 65], these results

**Table 1** Summary of clinical results of cytokine therapy in chronic B-cell malignancies (*CLL* chronic lymphocytic leukemia, *HCL* hairy cell leukemia, *IFN* interferon, *MU* million units, *tiw* thrice a week, *cct* combination chemotherapy)

| Disease | Stage | Regimen | Response | References |
|---|---|---|---|---|
| HCL | Untreated | IFN alpha 0.2–2 MU | 50–80% hematological responses (CR 10.15%) superior to splenectomy, chemotherapy | [47, 62] [45, 60] [24, 63] |
| CLL | Untreated, early | IFN alpha 1–5 MU tiw | 90–100% transient reduction of lymphocytes, survival benefit unclear | [58, 73] [9, 50] [39, 43] |
| Follicular lymphoma | Relapsed | IFN alpha 1–50 MU/m$^2$ | 15–50% responses, med. duration 8 months | [22, 25] |
| Follicular lymphoma | Relapsed | IL-2 1.5–20 MU/m$^2$ | 0–50% responses, duration 1–17 months, TRM 5% | [2, 67] [16, 40] [26] |
| Follicular lymphoma | Advanced | IFN alpha + alkylating agent | 50–70% responses, no benefit of IFN regarding response rate or duration | [12, 53] [46] |
| Follicular lymphoma | Advanced | IFN alpha + anthracycline-based cct | 70–86% responses, survival benefit of IFN group in one trial [64] | [3, 61] [64] |

have been confirmed in numerous studies. Recently, clinical research has focused on three main topics: the efficacy of IFN treatment in comparison to standard therapies, the optimal dosage of IFN alpha, and, finally, the durability and maintenance of IFN response.

A randomized trial of 20 untreated HCL patients compared splenectomy with IFN alpha treatment. A total of three responses with a median time to treatment failure of less than 1 month were observed in ten patients undergoing splenectomy, whereas all ten patients treated with IFN responded. A decrease in bone marrow infiltration was observed in seven of ten patients, and median time to treatment failure exceeded 18 months in the IFN group [62]. Another study compared the outcome of 128 HCL patients receiving recombinant human (rh) IFN alpha 2b with that of 71 historical controls treated with chlorambucil. Hematological responses were noted in 73% of the IFN group versus 18% of patients treated with chlorambucil. Fatal infections occurred in 1.6% versus 23%, and mortality of the entire group at 12 months was 3.1% versus 28%. Finally, IFN treatment was calculated to be 2.8 times less expensive, especially due to reduction of in-hospital days for therapy of infections [46].

Following treatments of 22 HCL patients with a dose of 0.2 million units (MU)/$m^2$ rh IFN alpha 2b three times a week (tiw) for 6–12 months, an overall response rate of 54% with only 18% complete (CR) and partial responses (PR) was observed. These results were inferior to those obtained with the standard dose [45]. However, in a randomized trial accruing 138 patients a dose of 0.2 MU/$m^2$ natural IFN alpha administered daily for 28 days, then tiw, was equally effective as a dose of 2 MU/$m^2$ regarding neutrophil and platelet recovery [60]. In a study of rh IFN alpha 2c a dose of 2 MU was administered to 18 HCL patients for a median of 35 weeks. Another 21 HCL patients were treated with optimal biological doses, as assessed by maximum neopterin induction in vivo. These doses ranged from 0.2 to 0.6 MU/$m^2$ given daily for 3 months, then every alternate or every third day for a median of 31 weeks. Both regimens were shown to be equally effective [24].

Duration of IFN alpha response preferentially depended upon response quality. Median response duration of patients achieving CR was 37.5 months as compared with 23 months in patients with PR and 3.5 months in patients with minor responses [74]. The majority of another cohort of 69 HCL patients treated with rh IFN alpha 2b had to be retreated for failure of initial therapy. However, 16 patients remained alive without further treatment requirements [27]. Feasability of long-term therapy with rh IFN alpha 2a was demonstrated in 32 patients treated for a median of 5 years. Interestingly, 16 patients exhibiting a minor response after 18 months of therapy developed partial responses subsequently [63].

Due to the efficacy of IFN alpha, no other cytokines have been extensively tested in HCL. In summary, IFN alpha treatment of HCL was shown to be clinically and economically more effective than splenectomy or chlorambucil therapy. Even lower doses of IFN alpha appear to be as effective as the standard regimen, resulting in a reduction of side effects and costs of cytokine therapy. Long-term remissions without further treatment requirements are achieved in only about 20% of patients. Accordingly, a high relapse rate is observed after an interval depending on quality of initial response. However, effective retreatment with IFN alpha as well as feasibility of long-term IFN alpha therapy have been convincingly demonstrated in HCL. It remains to be seen whether IFN alpha will be replaced as standard treatment of HCL by newer chemotherapeutic agents such as deoxycoformycin [33] or cladribine [51]. Preliminary results of an ongoing trial comparing deoxycoformycin with IFN alpha as first-line therapy of HCL revealed significantly more remissions in the group receiving deoxycoformycin [28]. However, data on long-term follow-up are still awaited. In any case, clinical testing of additional cytokines in HCL is largely precluded by the presence of two effective new therapies.

## Chronic lymphocytic leukemia

Clinical trials of cytokine therapy in CLL also are largely restricted to IFN alpha. A group of ten untreated CLL patients (7 Rai stage 0, 3 stage I) were treated with rh IFN alpha 2c at a dose of 2 MU/$m^2$ tiw for a minimum of 14 weeks. A decrease of total leukocyte and lymphocyte counts was observed in all patients. However, 2–6 months after IFN therapy, eight of the ten patients exhibited pretreatment leukocyte counts again [58]. Treatment of nine early-stage CLL patients with 5 MU rh IFN alpha 2b tiw also resulted in decreased lymphocyte counts in all, and in partial responses or increments of plasma IgG levels in some patients [73]. Similar results were obtained with lower doses of rh IFN alpha 2b [9, 50], rh IFN alpha 2a [39, 43], and natural IFN alpha [52]. However, in an ongoing prospective trial performed by the AIO, so far no advantage of IFN treatment of CLL has so far been observed (B. Emmerich, personal communication). Administration of IFN alpha 2b following pretreatment with chlorambucil to 11 patients with early CLL led to two CR and six Rai stage-0 diseases. Responses achieved with chlorambucil alone were improved by IFN therapy in only five of 11 patients [44]. In summary, IFN treatment of CLL does not seem to be more effective than standard cytotoxic chemotherapies. However, the poor results of standard treatments regarding survival should encourage study of other potentially effective cytokines, as will

cytokine therapies are patients who cannot participate in trials of allogeneic bone marrow transplantation or high-dose therapy with autologous stem cell support.

## Cytokine therapy of low-grade non-Hodgkin's lymphoma

In an early study, 45 heavily pretreated non-Hodgkin's lymphoma (NHL) patients received rh IFN alpha at a dose of 50 MU/m$^2$ tiw for 3 months or longer. Of 24 evaluable low-grade NHL patients, 13 achieved responses (9 PR, 4 CR) with a median response duration of 8 months. Only three of 13 evaluable intermediate and high-grade NHL patients responded [22]. The overall CR rate for IFN alpha monotherapy in low-grade lymphomas is approximately 10% [25].

In a phase-II study of IL-2 at doses of 1.5–3 MU/m$^2$ for 5 days every alternate week, 17 patients with CLL or lymphoma were included. Only 12 of 17 patients were evaluable for response, showing three PR and one minor response, lasting from 1 to more than 17 months [2]. With a higher dose of 18 MU/m$^2$/d IL-2 as continuous infusion therapy, five of ten relapsing low-grade lymphoma patients responded for a median duration of 4 months, whereas no effect was seen in four patients with Hodgkin's disease and seven patients with diffuse large-cell lymphoma [67]. In contrast, another phase-II trial of high-dose IL-2 plus LAK cells obtained no response in 15 lymphoma patients accrued [40]. A trial of 49 refractory lymphoma patients randomized them between IL-2 alone and IL-2 in combination with IFN beta. Overall response was low, only 7/49, and no difference was seen between the two treatment arms [16]. Of 24 patients with low-grade lymphomas treated at a dose level of 20 MU/m$^2$ IL-2 for three courses, one achieved a CR, six an MR, and seven stable disease [26]. In general, toxicity of IL-2 therapy was severe, with treatment-related mortality of about 5%. One larger trial studied IFN alpha therapy in a group of 88 patients with IgM monoclonal gammopathy, including 38 patients with Waldenström's macroglobulinemia. Whereas patients with a low monoclonal component were mainly unresponsive, 12 patients with Waldenström's disease had a reduction of their paraprotein of more than 50% of baseline values. Another six patients had a reduction between 25 and 50%. Furthermore, disappearance of hyperviscosity symptoms and improvement of anemia have been observed [57].

Several trials assessed the efficacy of IFN alpha in combination with cytotoxic chemotherapy in low-grade lymphoma. In a study of 124 patients with stage-III or -IV follicular lymphomas, they were randomized to chlorambucil versus chlorambucil plus rh IFN alpha 2b treatment. Responders were again randomized between "watch and wait" or IFN maintenance therapy for 12 months. Response rates were similar (71% versus 55%), and no survival difference was observed at a median follow-up of 2.5 years [53]. Similar results with response rates of approximately 60% in both groups and no advantage of IFN maintenance were obtained in further trials with chlorambucil and rh IFN alpha 2b [12] and cyclophosphamide and rh IFN alpha 2b [47]. A trial enrolling 291 stage-III and -IV low-grade NHL patients compared rh IFN alpha 2a plus an anthracycline-containing chemotherapy regimen (COPA) with chemotherapy alone. The initial report [61] demonstrated prolonged time to treatment failure and prolonged duration of response as well as a survival benefit for the IFN group. However, after 5 years follow-up there was no longer a survival difference between the two treatment arms [3]. A French study randomly assigned 242 patients with advanced follicular lymphomas to either 12 aggressive anthracyline-containing chemotherapy courses (CHVP) within 12 months or chemotherapy plus additional rh IFN alpha 2b for 18 months. Response rates were 69% with CHVP versus 85% with CHVP plus IFN alpha, and median event-free survival was 19 versus 34 months. Only in this trial a significant difference in overall survival (69% versus 86%) was observed between the treatment arms at 3 years' median follow-up [64].

In summary, cytokine monotherapy with IFN alpha or IL-2 produces durable responses in a subset of about 15% of refractory lymphomas. From present phase-II trials, neither an advantage of a specific cytokine nor a dose-response relationship can be deduced. On the other hand, the significantly higher toxicity of IL-2 favors IFN therapy. However, based on these data, cytokine monotherapy cannot be viewed as a standard salvage regimen in refractory lymphoma, and its use should be restricted to clinical trials. Regarding combination of cytotoxic chemotherapy with IFN alpha, so far, only one randomized trial [64] has demonstrated a survival benefit of additional cytokine therapy in low-grade lymphoma. As toxicity and costs are enhanced, longer follow-up and confirmatory trials are needed to draw definite conclusions.

## Future developments

Based on preclinical data, cytokine action on malignant B lymphocytes can be either directly antiproliferative or indirect, via regulation of growth signals or induction of apoptosis. Direct inhibition of in vitro B-cell proliferation is reported for IL-4 [38] and IL-10 [19]. The proliferative response of CLL-B cells to IL-2, TNF alpha, IFN alpha, and BCGF is inhibited by addition of IL-4 and is prevented by pretreatment with IL-4 [38]. Growth stimulation of monoclonal B cells from low- and intermediate-grade non-Hodgkin's lymphoma and from CLL by anti-μ antibody and IL-2 is also suppressed by IL-4 [15, 32]. A decrease of high-affinity IL-2R following IL-4 treatment is observed

[32]. Growth of CLL-B cells induced by TNF alpha and beta is inhibited by IL-6, while anti-IL-6 and anti-IL-6R antibodies potentiate B-cell proliferation. However, constitutive IL-6 production of monocytes and B cells from CLL patients was found to be low [1]. In CLL-B cells exclusively, IL-10 induced apoptosis via down-regulation of bcl-2 and decreased cell viability in all samples observed. Apoptosis was prevented by anti-IL-10 antibody, IL-2, IL-4, IFN gamma, and anti-CD40 antibody. No induction of apoptosis by IL-10 was observed in B cells from lymphoma or HCL patients [19]. Exogenous TGF beta completely inhibits CLL-B-cell proliferation induced by anti-μ antibody, whereas anti-TGF beta antibody increases proliferation of malignant B cells in a dose-dependent and specific manner [37].

However, these data cannot be readily extrapolated into the in vivo situation. First, representative in vitro models of low-grade lymphomas are lacking. Second, all cytokines mentioned above exhibit pleiotropic effects on the clonal target cell itself and on surrounding host tissues. For example, IL-10 was reported to promote proliferation [18] as well as to induce apoptosis [19] of anti-CD40-activated CLL-B cells in vitro. Bivalent effects were similarly found for IL-4 [14, 15, 32, 38, 48]. Therefore, clinical effects of cytokine administration are not predictable from preclinical data. On the other hand, there is no evidence for induction of irreversible disease progression from present clinical experience with interferons, interleukins, and hematopoietic growth factors. In consequence, further clinical cytokine trials involving new agents in context with preclinical investigation are urgently required. This might produce more important insights to allow for innovative therapeutic interventions beyond standard pharmacological testing of cytokines.

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## References

1. Aderka D, Maor Y, Novick D, Engelmann H, Kahn Y, Levo Y, Wallach D, Revel M (1993) Interleukin-6 inhibits the proliferation of B-chronic lymphocytic leukemia cells that is induced by tumor necrosis factor-alpha or -beta. Blood 81:2076–2084
2. Allison MA, Jones SE, McGuffey P (1989) Phase-II trial of outpatient interleukin-2 in malignant lymphoma, chronic lymphocytic leukemia, and selected solid tumors. J Clin Oncol 7:75–80
3. Andersen JW, Smalley RV (1993) Interferon alfa plus chemotherapy for non-Hodgkin's lymphoma: five-year follow-up. N Engl J Med 329:1821–1822
4. Bakhshi A, Jensen JP, Goldman P, Wright JJ, McBride OW, Epstein AL, Korsmeyer SJ (1985) Cloning of the chromosomal breakpoint of t(14;18) human lymphomas: clustering around JH on chromosome 14 and near a transcriptionally active locus on chromosome 18. Cell 41:889–901
5. Barut BA, Cochran MK, O'Hara C, Anderson KC (1990) Response patterns of hairy cell leukemia to B-cell mitogens and growth factors. Blood 76:2091–2097
6. Bastard C, Deweindt C, Kerckaert JP, Lenormand B, Rossi A, Pezzella F, Fruchart C, Duval C, Monconduit M, Tilly H (1994) LAZ3 rearrangements in non-Hodgkin's lymphoma: correlation with histology, immunophenotype, karyotype, and clinical outcome in 217 patients. Blood 83:2423–2427
7. Biondi A, Rossi V, Bassan R, Barbui T, Bettoni S, Sironi M, Mantovani A, Rambaldi A (1989) Constitutive expression of the interleukin-6 gene in chronic lymphocytic leukemia. Blood 73:1279–1284
8. Bosch F, Jares P, Campo E, Lopez Guillermo A, Piris MA, Villamor N, Tassies D, Jaffe ES, Montserrat E, Rozman C et al (1994) PRAD-1/cyclin D1 gene overexpression in chronic lymphoproliferative disorders: a highly specific marker of mantle cell lymphoma. Blood 84:2726–2732
9. Boussiotis VA, Pangalis GA (1991) Interferon alfa-2b therapy in untreated early stage, B-chronic lymphocytic leukaemia patients: one-year follow-up. Br J Haematol 79 [Suppl 1]:30–33
10. Buschle M, Campana D, Carding SR, Richard C, Hoffbrand AV, Brenner MK (1993) Interferon gamma inhibits apoptotic cell death in B cell chronic lymphocytic leukemia. J Exp Med 177:213–218
11. Carlsson M, Totterman TH, Rosen A, Nilsson K (1989) Interleukin-2 and a T cell hybridoma (MP6)-derived B cell-stimulatory factor act synergistically to induce proliferation and differentiation of human B-chronic lymphocytic leukemia cells [see comments]. Leukemia 3:593–601
12. Chisesi T, Congiu M, Contu A, Coser P, Moretti L, Porcellini A, Rancan L, Salvagno L, Santini G, Vinante O (1991) Randomized study of chlorambucil (CB) compared to interferon (alfa-2b) combined with CB in low-grade non-Hodgkin's lymphoma: an interim report of a randomized study. Non-Hodgkin's Lymphoma Cooperative Study Group. Eur J Cancer 27 [Suppl 4] :S31–33
13. Cleary ML, Sklar J (1985) Nucleotide sequence of a t(14;18) chromosomal breakpoint in follicular lymphoma and demonstration of a breakpoint-cluster region near a transcriptionally active locus on chromosome 18. Proc Natl Acad Sci USA 82:7439–7443
14. Dancescu M, Rubio Trujillo M, Biron G, Bron D, Delespesse G, Sarfati M (1992) Interleukin 4 protects chronic lymphocytic leukemic B cells from death by apoptosis and upregulates Bcl-2 expression. J Exp Med 176:1319–1326
15. Defrance T, Fluckiger AC, Rossi JF, Magaud JP, Sotto JJ, Banchereau J (1992) Antiproliferative effects of interleukin-4 on freshly isolated non-Hodgkin malignant B-lymphoma cells. Blood 79:990–996
16. Duggan DB, Santarelli MT, Zamkoff K, Lichtman S, Ellerton J, Cooper R, Poiesz B, Anderson JR, Bloomfield CD, Peterson BA, et al (1992) A phase-II study of recombinant interleukin-2 with or without recombinant interferon-beta in non-Hodgkin's lymphoma. A study of the Cancer and Leukemia Group B. J Immunother 12:115–122
17. Emilie D, Leger Ravet MB, Devergne O, Raphael M, Peuchmaur M, Coumbaras J, Crevon MC, Galanaud P (1993) Intratumoral production of IL-6 in B cell chronic lymphocytic leukemia and B lymphomas. Leuk Lymphoma 11:411–417
18. Fluckiger AC, Garrone P, Durand I, Galizzi JP, Banchereau J (1993) Interleukin 10 (IL-10) upregulates functional high-affinity IL-2 receptors on normal and leukemic B lymphocytes. J Exp Med 178:1473–1481
19. Fluckiger AC, Durand I, Banchereau J (1994) Interleukin 10 induces apoptotic cell death of B-chronic lymphocytic leukemia cells. J Exp Med 179:91–99
20. Foa R, Massaia M, Cardona S, Tos AG, Bianchi A, Attisano C, Guarini A, di Celle PF, Fierro MT (1990) Production of tumor necrosis factor-alpha by B-cell chronic lymphocytic leukemia cells: a possible regulatory role of TNF in the progression of the

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