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Downstaging Rai stage III B-chronic lymphocytic leukemia patients with the administration of recombinant human erythropoietin

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Background and Objectives. To investigate the effectiveness of recombinant human erythropoietin (r-HuEPO) on disease-related anemia in patients with B-chronic lymphocytic leukemia (B-CLL) and to explore whether improvement of anemia could delay the initiation of cytotoxic therapy.

Design and Methods. Twenty five B-CLL patients (12 males and 13 females; median age 70 years) with disease-related anemia were treated with r-HuEPO. Patients were either on no treatment or on a standard regimen, and had at least Rai stage III disease, with a hematocrit (Hct) <32%. Eleven were newly diagnosed, whereas 14 developed anemia during follow-up. Treatment induction lasted for a maximum of 3 months, during which patients were receiving 150 IU/kg of r-HuEPO s.c. t.i.w. with an escalation to 300 IU/kg t.i.w. if response was slow after one month. Responding patients were placed on maintenance r-HuEPO with 150 IU/kg s.c. once weekly, continuously. Complete response (CR) was defined as an increase of Hct to 38% or more and partial response (PR) as an increase of >6% from pretreatment level.

Results. CR was observed in 18/25 (72%) and PR in 2/25 (8%) of the patients. Six patients were *downstaged* to stage Rai 0, 9 to Rai I and 4 to Rai II. Response was sustained with maintenance therapy. At a median follow-up of 32 months only 4 of the responders required antileukemic treatment. The median survival of responders has not been reached, and 3-year survival is 84%.

Interpretation and Conclusions. r-HuEPO was efficient in *downstaging* Rai stage III B-CLL patients, and delayed the initiation of antileukemic therapy. Whether this effect can be translated into better survival rates remains to be clarified in randomized trials.

Key words: CLL, anemia, erythropoietin, Rai stage III.

Anemia occurring in patients with untreated B-chronic lymphocytic leukemia (B-CLL) may be due to extensive bone marrow infiltration, autoimmune hemolysis, hypersplenism, deficiency of hematopoietic co-factors or blood loss. In these cases anemia can be corrected by proper therapeutic manipulations. The so-called *anemia of chronic disease* also occurs frequently in B-CLL patients. This type of anemia is caused by the release of specific cytokines such as interleukin (IL)-1α, IL-1β, tumor necrosis factor-α, transforming growth factor-β and IL-6. These cytokines inhibit erythropoietin (EPO) production and diminish the responsiveness of erythroid progenitors to EPO.[1-7] Furthermore direct suppression of erythropoiesis and impaired iron availability also contribute to the anemia of chronic disease.[4-6]

In B-CLL patients, hemoglobin < 11 g/dL and hematocrit (Hct) level < 33% designates Rai stage III disease[8] while hemoglobin <10 g/dL Binet stage C[9] independently of lymphadenopathy or organomegaly. According to the NCI criteria, B-CLL patients with a hemoglobin level <10 g/dL are candidates for chemotherapy.[10] If anemia is corrected, patients will be downstaged, and this might affect treatment decisions. So far an increase of Hct in these patients has been achieved either by blood transfusions or by the administration of chemotherapy. However, it has recently been reported that disease-related anemia could be improved by the administration of recombinant human erythropoietin (r-HuEPO) which sustains the viability of colony-forming-unit-erythroid (CFU-Es).[11-15]

In this study, we examined whether the *downstaging* of B-CLL patients by improvement of disease-related anemia could postpone the initiation of cytotoxic therapy and eventually offer a survival benefit.

Design and Methods

Patients

Between September 1994 and January 1998, 32 B-CLL patients were consecutively diagnosed in our Unit as having Rai stage III or IV disease. Twenty-five of them, who were included in this study, met the following criteria: no treatment or standard regimen for the treatment of CLL for at least 1 month prior to study entry; performance status 0, 1 or 2; life expectancy of at least 6 months. Patients had to be clinically stable for at least 1 month preceeding entry, with a Hct <32% on two occasions two weeks apart. Anemia was disease-related, as documented by negative direct Coombs' test, corrected reticulocytes <3% and no evidence of untreated iron, folate or B_{12} deficiency. Other less important exclusion criteria have been reported elsewhere.[11,15] Patients gave informed consent after they had fully understood the details of the study. The patients' characteristics are shown in Table 1. Lymphadenopathy was characterized as limited or generalized when one or ≥2 nodal sites were involved, respectively. Nodal sites were defined according to Binet's system.[9] The term bulky was used for patients with at least one lymph node with its greater diameter ≥7 cm. Eleven patients were anemic at diagnosis and 14 developed anemia during regular follow-ups over a median of 53.5 months (17-120). Important individual clinical characteristics of the patients at presentation and prior to r-HuEPO administration are shown in Table 2. Nine patients had received prior treatment which had, however, been discontinued for at least 3 months prior to study entry. Thus, anemia could not be attributed to previous treatment. One patient was receiving chlorambucil during the study period.

Table 1. Patients' characteristics.

Male/female	12/13
Median age, years (range)	70 (50-81)
Rai stage	
III§	24
IV	1
Lymphadenopathy (no. of patients)	
Limited	10
Generalized	9
Splenomegaly [patients (cm below left costal margin)]	7 (3-8)
Hepatomegaly [patients (cm below right costal margin)]	2 (3 and 3)
Hematocrit level [%, (range)]	29.5 (22-32)
Hemoglobin level [g/dL (range)]	9.4 (5.8-9.9)
Reticulocyte count [$\times 10^9$/L (range)]	36 (25.6-48.4)
Lymphocyte count [$\times 10^9$/L (range)]	34.2 (9-210)
Performance status (EGOG scale, no. of patients))	
1:	8
2:	17
Bone marrow pattern of infiltration (no. of patients)	
Non diffuse	12
Diffuse	13
Mean estimate of non-lymphoid marrow cellularity [% (range)]	20 (<5-50)
Prior or concurrent treatment status (no. of patients)	
None	15
Concurrent	1
Prior	9
Prior or concurrent regimens (no. of patients)	
Chlorambucil	8*
Prednisone	1
Multiple	1°

*§All patients had Binet stage C disease; *plus prednisone in one patient; °including CHOP, fludarabine, chlorambucil, and prednisone.*

Treatment Protocol

The treatment protocol included an induction and a maintenance phase.[11,15] During the induction phase, all patients received r-HuEPO 150 IU/kg subcutaneously (s.c.) t.i.w. If response was slow (Hct rise <6%) after one month, then the dose of r-HuEPO was escalated by increments of 50 IU/kg every two weeks, up to a maximum dose of 300 IU/kg t.i.w. The induction phase lasted for a maximum period of 3 months. Following the induction phase, all responding patients were switched to maintenance therapy, with 150 IU/kg r-HuEPO s.c. weekly. When response was sustained for 3 months with this maintenance policy, the interval between doses was increased from 1 week to 10 days. Ferrous sulfate was given orally at a dose of 150 mg b.i.d. during the induction phase. Blood counts were evaluated every two weeks during the induction phase and monthly thereafter. In case of disease progression during r-HuEPO induction or maintenance, cytotoxic therapy was initiated.

Response criteria

A rise of Hct to levels above 38% was considered as a complete response (CR), whereas an increase of >6% from pretreatment levels, to a level of less than 38%, was considered as a partial response (PR).

Pretreatment erythropoietin levels

In all patients, but one, serum erythropoietin levels prior to study entry were determined by radioimmunoassay according to the manufacturer's instructions (INCSTAR Corporation, Stillwater, Minn USA). The range of serum EPO levels of healthy donors in our laboratory were 4.9-52.7 mU/mL. For Hct values ≤ 38%, the predicted EPO level is given by the following equation: log EPO=4.746-(0.093×Hct).[16]

Table 2. Clinical and laboratory parameters at presentation, prior to and post-r-HuEpo administration.

Pt.	Age/Sex	Rai stage	Prior treatment	Response	Time to response (wks)	Rai stage (at 3 mos)	Duration of response (mos)	OS from time of rHuEPO initiation (mos)	DP/need of CT post r-HuEPO	PS A/D
1	68/M	III	None	CR	4	I	64+	65+	No/No	A
2	70/F	0/III*	None	CR	12°	0	30	33	No/No	D[&]
3	87/M	III	None	CR	8	0	46+	48+	No/No	A
4	74/M	III	CHOP, Fludarabine, Chlorambucil, Prednisone[§]	CR	10	0	36.5+	39+	No/No	A
5	65/M	III	Prednisone, Chlorambucil	CR	6	II	33.5+	35+	No/No	A
6	50/F	I/III*	None	CR	12°	I	32+	35+	Yes/Yes+	A
7	68/F	III	Chlorambucil	CR	4	I	36+	37+	Yes/Yes+	A
8	74/F	I/III*	None	CR	9	I	34+	36+	No/No	A
9	68/F	IV	None	PR	10	IV[§§]	30.5+	33+	Yes/Yes+	A
10	75/F	III	None	CR	9	I	29+	31+	No/No	A
11	79/M	I/III	None	CR	6	0	27.5+	29+	No/No	A
12	68/F	0/III*	None	CR	4	0	28+	29+	No/No	A
13	71/M	III	None	CR	8	II	28+	30+	No/No	A
14	68/M	II/III*	Chlorambucil	PR	9	II	28+	30+	Yes/Yes+	A
15	75/F	0/III*	None	CR	4	0	30+	31+	No/No	A
16	68/M	I/III*	Prednisone	NR	NA	III	NA	0	NA/Yes++	A
17	75/F	I/III*	Chlorambucil (concurrent)	CR	5	I	31+	32+	No/No	A
18	68/F	I/III*	None	NR	NA	III	NA	34+	NA/Yes++	A
19	72/M	III	Chlorambucil	NR	NA	III	NA	24	NA/Yes++	D**
20	72/F	0/III*	Chlorambucil	CR	4	I	30+	31+	Yes/Yes[¶]	A
21	42/F	II/III*	Chlorambucil	NR	NA	III	NA	30	NA/Yes++	D[&]
22	61/F	0/III	Chlorambucil	CR	5	I	28+	29+	No/No	A
23	71/M	III	None	NR	NA	III	NA	24	NA/Yes++	A
24	76/M	0/III*	None	CR	5	II	24	25	No/No	D[&]
25	63/M	III	None	CR	4	I	31+	32+	No/No	A

**At presentation/prior to r-HuEPO administration; CR= complete response; PR= partial response; NR= no response; OS = overall survival; DP = disease progression; CT = chemotherapy; PS= present status; A= alive; D= dead; NA = not applicable, ° = dose escalation was necessary; + = due to bulky disease; [§§] = due to persisting platelets <100×10⁹/L; ++= due to persisting stage III disease, [¶] = due to autoimmune hemolysis; ** = died of disease; [&] = died of infection, [§] = given without success during a six-month period in another institution prior to his presentation in our Unit.*

Bone marrow findings

Bone marrow smears plus biopsy sections were studied in all patients at the time of diagnosis and/or prior to r-HuEPO administration. The pattern of bone marrow infiltration on histologic sections was also determined.[17-19] In 6 patients randomly selected among the complete responders, an additional bone marrow evaluation was performed at the completion of the induction phase.

Statistical analysis

Identification of patients' pretreatment characteristics that were correlated with the probability of response was based on the χ^2 test with continuity correction (categorical variables) or the Mann-Whitney U-test (continuous variables). *p* values of 0.05 or less were considered statistically significant.

Results

Response

The response of individual patients is shown in Table 2. A complete response was achieved in 18/25 patients (72%) and a partial one in 2/25 (8%), for an overall response rate of 80%. Five patients did not respond. Among 14 previously untreated patients, a complete response was achieved in 12 (86%) and a partial response in 1 (7%), for an overall response rate of 93%. The difference in response rates between untreated and previously treated patients was of borderline statistical significance, as shown in Table 3 (p=0.07).

Among 20 responders, 18 have a sustained response at a median of 30.8+ months (27.5+ to 64+), while 2 have died of infection at 24 and 30 months of r-HuEPO initiation, while still responding. Dose escalation of r-HuEPO up to 300 IU/kg t.i.w., was necessary in 7 non-responding patients after the completion of one month of therapy; in two of them a subsequent complete response was achieved. The median time to response was 6 weeks (4-12) (Table 2). The median pretreatment Hct level was 29.5% (22% - 32%; Table 1). The median Hct level of responders after the completion of 3 months of r-HuEPO was 45% (36-51%).

Correlation of response with clinical, hematologic and bone marrow findings

Among tested factors, the presence of generalized lymphadenopathy and splenomegaly had a negative effect on response to r-HuEPO (p=0.005 and p=0.02, respectively). Furthermore, the response rate of patients with inadequately elevated serum EPO levels was inferior to that of patients with adequate levels for the degree of anemia (p=0.03). In contrast, the pattern of bone marrow infiltration did not affect the probability of response (Table 3).

Among responders who were not receiving chemotherapy, two patients had a significant regression of palpable lymphadenopathy and another two had a decrease of lymphocyte counts from 30.4×10^9/L to 6.8×10^9/L (patient #5) and from 51×10^9/L to 35×10^9/L (patient #12). In the 6 patients in whom a bone marrow aspiration plus biopsy was performed at completion of the induction phase, it was evident that a considerable increase (>20%) of the red cell precursors was present as compared to pre-r-HuEPO bone marrow findings. The percentage of lymphocytic infiltration was not substantially changed.

Impact of anemia correction on disease stage

After completion of 3 months of r-HuEPO administration, the responding patients were *downstaged* so that among 19 patients with stage III disease 6 changed to Rai stage 0, 9 to Rai stage I, and 4 to Rai stage II, whereas in one patient anemia was corrected but thrombocytopenia persisted (Tables 2 and 4).

Follow-up

The response obtained during the induction phase was sustained by maintenance r-HuEPO administration. During the follow-up of the 20 responding patients, anti-leukemic therapy became necessary in 4 in whom disease progression occurred (Table 2). Of the 4 patients whose disease progressed, two developed bulky lymphadenopathy (patients #6 and #7) and spleen size increased in another two (patients #9 and #14). Corticosteroids were also given to another patient who developed autoimmune hemolysis. Thus, 15/20 responding patients (11/13 previously untreated and 4/7 previously treated) remained free of antileukemic therapy for a median of 31+ months (25-65+). The median overall survival of responders after r-HuEPO administration has not been reached yet, with 2-, and 3-year survival rates of 100% and 84%. These figures were 92% and 77% versus 100% and 100% for untreated and previously treated patients, respectively. In the whole series of 25 patients the median overall survival has also not been reached, and the 2- and 3-year survival rates were 96% and 78%.

Table 3. Treatment of B-CLL with r-HuEPO. Prognostic factors for response.

Patients' characteristics	*Response rate* #	%	p^a	p^b
Age				
≤65 years	4/5	80	1.0	0.35
>65 years	16/20	80		
Sex				
male	9/12	75	0.92	Na
female	11/13	85		
Lymphadenopathy				
no	6/6	100	0.41	Na
yes	14/19	74		
Generalized lymphadenopathy				
no	16/16	100	0.005	Na
yes	4/9	44		
Bulky lymphadenopathy				
no	17/22	77	0.87	Na
yes	3/3	100		
Splenomegaly				
no	17/18	94	0.02	Na
yes	3/7	43		
Absolute lymphocyte count				
≤30×10^9/L	9/9	100	0.18	0.25
>30×10^9/L	11/16	69		
Pattern of BM infiltration				
non-diffuse	10/12	83	1.0	Na
diffuse	10/13	77		
Non-lymphoid BM cellularity				
≤10%	5/8	63	0.34	0.45
>10%	15/17	88		
Treatment				
no	13/14	93	0.07	Na
yes	7/11	64		
sEPO levels (O/P)				
≤1	18/19	95	0.03	Na
>1	2/5	40		
sEPO levels				
<200 mU/mL	19/20	95	0.007	0.04
≥200 mU/mL	1/4	25		

[a]Comparisons made by χ^2 test with continuity correction; [b]comparisons made by Mann-Whitney test (continuous variables); Na: not applicable; sEPO=serum EPO; (O/P)= ratio of the observed EPO levels to those predicted by hematocrit.[25]

Discussion

The median survival of Rai stage III patients is approximately 3 years, although series of patients with longer survival times have been reported.[8,9,20–22] It appears that autoimmune hemolytic anemia does not compromise survival beyond that predicted by other prognostic factors. In contrast, survival is clearly affected by the presence of Coombs'-negative anemia.[23]

Disease-related anemia in B-CLL patients may be due to extensive bone marrow (BM) infiltration by lymphocytes or may have the features of the anemia of chronic disease, in which endogenous EPO regulation by soluble factors plays a major role.[1–7,24,25] Based on previous observations it appears that the extent of BM disease in B-CLL patients is not necessarily by itself the cause of anemia, since diffuse BM infiltration may not be complicated by anemia.[17-19,26] The results obtained in this series (Table 4) of anemic B-CLL patients who were given r-HuEPO confirm previous observations indicating that this type of anemia, irrespectively of its severity, can be reversed in the vast majority of cases.[11,12,15] This finding applies to other malignancies as well.[13,27-33]

In recent years, efforts have been made to improve the treatment programs for B-CLL patients in order to obtain better response rates and increase survival. For this purpose, new drugs have been used such as fludarabine and 2-chlorodeoxyadenosine, without offering an overall survival advantage over chlorambucil.[34,35] Given the fact that a subset of patients with early Rai stage or stable (smoldering) B-CLL may not be treated at all and enjoy a long life, with a median survival similar to that of the general population,[36,37] it is tempting to think that, if disease-related anemia of Rai stage III B-CLL patients could be corrected, these patients would be *downstaged*, treatment initiation could be postponed and they might obtain the survival benefit of their *new* stage.

In the present study, we have shown that 80% of Rai stage III B-CLL patients, who fulfilled the criteria to enter the study, were *downstaged* by r-HuEPO. Treatment with chemotherapy was avoided or postponed in the vast majority of them. This was achieved by the use of r-HuEPO s.c. for a median period of 6 weeks (range 4-12) followed by maintenance r-HuEPO administration weekly or every ten days. Based on these as well as previous observations,[15] it appears that maintenance r-HuEPO administration is necessary in order to sustain response, as cessation of treatment with r-HuEPO is followed by secondary anemia.[38]

Among the 20 patients who responded to r-HuEPO, 15 remained without antileukemic therapy for a median period of 31+ months (25+–65+ months), enjoying an excellent quality of life and having no side effects. During this period disease progression was observed in 4/20 responding patients and autoimmune hemolytic anemia in one. The probability of response was negatively affected by elevated pretreatment serum EPO levels, generalized lymphadenopathy and splenomegaly, but it was independent of the extent of BM infiltration by lymphocytes, indicating that the existing BM erythrocyte precursor reserves could not be adequately appreciated.

Table 4. Rai stage prior to and at the completion of the induction phase of r-HuEPO administration.

Rai Stage	*r-HuEPO administration*			
	Prior		*After 3 months*	
	# of patients	*%*	*# of patients*	*%*
0	–	–	6	24
I	–	–	9	36
II	–	–	4	16
III	24	96	5	20
IV	1	4	1*	4

*– = none, * = but without anemia.*

With only two deaths recorded so far, the median survival of the responding patients has not been reached yet with a 3-year survival of 84%. This figure compares favorably with any other study of Rai stage III patients who are, by definition, treated with cytotoxic therapy. The fact that all of our patients had stage C(III) and none A(III) or B(III), that more than half of them had been already followed-up for a median of 4 years from the diagnosis and that many of them were in relapse after previous treatment, further strengthens our results.

However, it is not clear whether r-HuEPO is able to induce a true *downstaging* of B-CLL, since response to r-HuEPO might simply indicate selection of a subset of Rai stage III patients with less aggressive disease. Nonetheless, whatever the true effect of r-HuEPO administration in Rai stage III B-CLL patients is, our data demonstrate that the correction of anemia may delay the initiation of cytotoxic chemotherapy, improve quality of life[12,15] with minimal side effects and offer a survival length comparable to that achieved by chemotherapy. The present study does not prove that r-HuEPO exerts a real biological effect on the course of B-CLL. The regression of lymphadenopathy and/or decline of lymphocyte counts in 4/20 responders suggests a real effect of r-HuEPO on B-CLL, but does not provide sufficient evidence to make such a statement. In support of our observations, recently published studies have suggested a favorable effect of r-HuEPO on the course of various malignancies, both *in vivo* and *in vitro*.[39-41] An alternative explanation for our findings could be based on the hypothesis that response to r-HuEPO may simply indicate selection of a subset of Rai stage III patients with less

aggressive disease. If we accept that *downstaging* of B-CLL with r-HuEPO is just an *artificial* phenomenon, then anemia may not be suitable to be used for B-CLL staging. Thus, there is a need to develop staging systems based on parameters directly related to the tumor burden and the biology of the disease.[42,43] The ideal approach in order to investigate whether r-HuEPO affects the natural history of B-CLL[44] would be to design a randomized trial comparing immediate chemotherapy with r-HuEPO administration followed by chemotherapy given upon disease progression and/or r-HuEPO failure in Rai stage III patients.

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GAP was primarily responsible for this work from conception to submitted manuscript, and should be considered as the principal author. All authors qualified for authorship according to the World Association of Medical Editors (WAME) criteria, and have taken specific responsibilities, as described below: GAP, MPS, MKA: collection of data; GAP, MPS, MKA, TPV, MCK, KK, PT, GAV, FNK: management of clinical data covering a long follow-up period; TPV: statistical analysis. All authors contibuted to the writing of the paper. The authors are listed according to a criterion of decreasing individual contribution to the work.

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Disclosures

Conflict of interest: none.

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Peer Review Outcomes

Manuscript processing

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What is already known on this topic

Patients with CLL may have anemia for a variety of reasons, a fact which is not taken into account in clinical staging systems.

What this study adds

r-HuEPO may be effective in a proportion of patients with CLL and, as a result, the need for therapy might be delayed.

Potential implications for clinical practice

Rai stage III B-CLL patients, who have no other indication for treatment initiation except of anemia, can be safely treated with r-HuEPO monotherapy, with a response rate of 80%: this implies a change of stage. This strategy can postpone the initiation of cytotoxic treatment for prolonged periods of time in most responders, and offer a survival that compares favorably with reported series of Rai stage III patients treated with chemotherapy.

Emili Montserrat, Associate Editor