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Management of CLL Patients after Chlorambucil Therapy. Special Value of a Second RAI Staging

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Abstract—*In studying the prognosis in* 155 *patients with chronic lymphocytic leukemia (CLL), a significant difference was found twice between two groups of patients with regard to the median survival duration. The staging classification as proposed by Rai* et al. *was used before and after* 6 months *of chlorambucil administration. The second staging allowed us to define two types of response, sensitivity and resistance to chlorambucil. The median survival times (MST for stages* 0–I *and* II–III–IV *were over* 100 *and* 32 months *respectively, calculated from the date of diagnosis. After chlorambucil test, the MST was* 88 months *in responders to therapy and* 30 months *in non-responders. When considering MST according to the second Rai staging the results were similar with* 104 months *in stages* 0–I *and* 24 months *in stages* II–III–IV. *This notion outlines the prognostic signification of the Rai classification and resistance to chlorambucil appears to be the best criterion of bad prognosis in CLL. In addition* 12 *patients were splenectomized during their evolution. Among the 'resistant' patients only two with splenic nodular infiltration became sensitive when receiving a second chlorambucil test. In view of these results it may be concluded that in resistant forms, splenectomy should be scheduled earlier in the treatment planning. Moreover the presence of fibrosis and nodular infiltration in spleen seemed to be an element of favorable prognosis, thus sensitivity to further treatment.*

INTRODUCTION

CLL is a malignant proliferation and a progressive accumulation of small and most often immunologically incompetent lymphocytes [1] usually of B-cell lineage. It may have a quite variable clinical course. CLL seems to be likely benign disease in some patients, who may survive for 10–20 years, specially patients over 60 years old.

Various symptoms may influence the prognosis in B-CLL particularly anaemia, thrombocytopenia and splenomegaly [2]. Recently Rai [3] proposed a clinical staging based on Dameshek's concept: stage 0, bone marrow and blood lymphocytosis only; stage I, lymphocytosis with enlarged lymph nodes; stage II, lymphocytosis with enlarged spleen or liver or both; stage III, lymphocytosis with anaemia and stage IV, lymphocytosis with thrombocytopenia. The classification was generally agreed as an indicator of prognosis for survival. Stage 0 is considered as a so-called benign disease and the general rule is that no benefit can be gained by treatment. Stage I has been considered as a severe disease; chemotherapy has hardly altered the clinical course and survival. Stages III and IV are associated with poor prognosis. In a recent prospective study using a statistical method. Degos *et al.* [4] have shown some agreement with Rai classification in the definition of parameters relative to poor prognosis. These authors suggested that CLL should be classified according to the scale in three clinical features: lymph node proliferation, lymphoid infiltration and cytopenia. Prognosis was essentially related to cytopenia whatever the mechanism involved. Stage II remains as an intermediate prognostic form. Dighiero *et al.* [5] recently identified a pure splenic form of CLL of favorable prognosis according to survival duration. This identifi-

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cation was made on the basis of clinical, cytological and immunological criteria.

The Rai staging system allowed the testing of different therapies in CLL patients defined by stage. Most trials are likely to involve the poor-risk patients with stages II, III and IV in order to improve their survival. The latter were treated either with a combined chemotherapy regimen using vincristin, cyclophosphamid and prednisone (COP) or with total body irradiation (TBI). On the other hand, chlorambucil was commonly used in the benign form.

A retrospective study of 155 patients treated in the Centre Hospitalier de Grenoble is reported. Except for stage 0, all patients were treated with a homogeneous chemotherapy regimen using high intermittent doses of chlorambucil. All studied patients were classified according to the Rai staging system twice, i.e., at clinical examination and 6 months after chlorambucil treatment. The patients treated before 1975, submitted to a retrospective classification were restaged like the others. The purpose of this paper is to demonstrate that second step classification is the best criterion for a prognosis in B-CLL. The second staging performed after 'chlorambucil test' permitted us to define responders and non-responders to chlorambucil. It allowed us to schedule another therapeutic program concerning only non-responders, who had a really bad prognosis (MST: 30 months), compared to a good prognosis (88 months).

Discussion remains open regarding the most effective treatment in the CLL patients with a bad prognosis, i.e., irradiation, splenectomy and chemotherapy.

MATERIALS AND METHODS

A retrospective study was undertaken on 155 patients with CLL (B-cell), at the Hematology Department during the period May 1967–June 1978. Twenty patients were excluded from this study because the follow-up information was inadequate. Our series includes 86 men and 69 women (sex ratio 1:24); mean age was 67 years.

(A) *Diagnostic criteria*

In all patients, the diagnosis was made on the basis of peripheral lymphocytosis over 6000/mm^3 combined with bone marrow lymphocytic infiltration over 30%. The study of immunological markers allowed us to assert the monoclonal nature of the B lymphocytes: EA rosettes, EAC rosettes, cell-surface immunoglobulins [6–8].

(B) *Classification*

Patients were staged according to the classification of Rai *et al.* [3] on the basis of clinical and haematological data. They all entered a first classification before treatment. Then 97 out of 135 patients were submitted to a second classification after a so-called 'chlorambucil test' as proposed by Ezdinly and Stutzman [9], which necessitated a 6-month therapeutic period. Patients treated before 1975 were staged retrospectively at first presentation and after 6 months chlorambucil treatment. Indeed, we are convinced that the effectiveness of chemotherapy is evaluated in terms of regression of the initial staging.

(C) *Treatment*

The therapeutic approach used in this study was quite homogeneous for all patients, except for stage 0. However, among patients in stage 0, seven were treated because of massive lymphocytosis. Therapy consisted of high doses of chlorambucil, combined to prednisone in the first course. Chlorambucil test was performed as follows: an induction treatment combining chlorambucil (12 mg/day) with prednisone (0.5 mg/kg/day) for 3 or 4 weeks; the same daily dosage of the same drugs was given as a maintenance therapy 10 days a month during 5 months.

After chlorambucil test, twelve stage IV patients who presented splenomegaly, were splenectomized [10, 11]. Among these 12 patients, eight were subsequently submitted to a second chlorambucil test.

(D) *Evaluation of response to treatment*

Sensitivity is estimated in terms of disease regression (except for stage 0 patients having a disappearing lymphocytosis). Complete remission (CR) was defined by the resolution of all measurable disease which corresponded to the greatest sensitivity to chlorambucil, i.e., regression to stage 0 with lymphocytosis $<3000/mm^3$. The criteria for the complete remission included hemoglobin above 12 g/100 ml; platelet count above 100,000/mm^3, no disease symptoms and less than 30% lymphocytes in bone marrow aspirate. Resistance is characterized by progression or stability of the disease.

Patients were classified as sensitive when responding to chlorambucil and as resistant when non-responding.

(E) *Statistical methods*

Actuarial survival is estimated by the method of unique information at a fixed date [12]. Every estimated actuarial survival, at regular intervals is accompanied by its confidence intervals (95%). Exponential fitting [13] is a simple mathematical model allowing us to examine the information concerning a group of homogeneous patients. The survival (S) vs time (t) is given by the equation $S = e^{-\lambda t}$ where λ is the death rate characterizing the group itself. Its variance, $t\lambda^2$ of course, is estimated, allowing us to know the confidence zone (95%) of the obtained fitting. The frequency of different parameters was studied by the means of a third statistical method which is the log-likelihood ratio test, i.e., G-test [14].

RESULTS

(A) *Study of survival according to the first staging* (*Fig.* 1)

After staging, patients are allocated to groups as follows: in stage 0, 45 patients (38 of them being untreated): in stage I: 14; stage II: 33; stage III: 15 and stage IV: 28.

The statistical study of 5 exponential survival curves according to the stage showed a highly significant difference between stages 0–I patients and stages II–IV patients ($P = 2.84 \times 10^{-8}$). Median survival durations are respectively over 100 months and 32 months.

(B) *Study of survival after chlorambucil test* (*Fig.* 2)

Ninety-seven evaluable patients were treated for 6 months with chlorambucil and prednisone. A second staging still according to

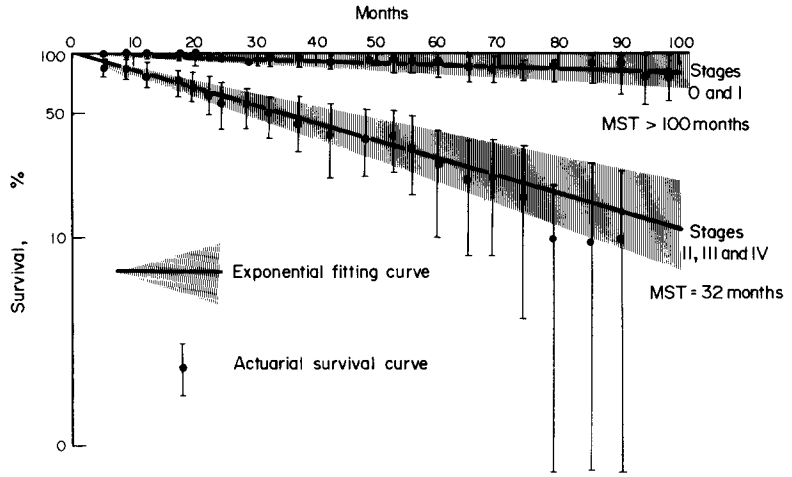

Fig. 1. *Actuarial survival and exponential fitting curves calculated from diagnosis after the first Rai staging* (135 *patients*) *MST: Median Survival Time.*

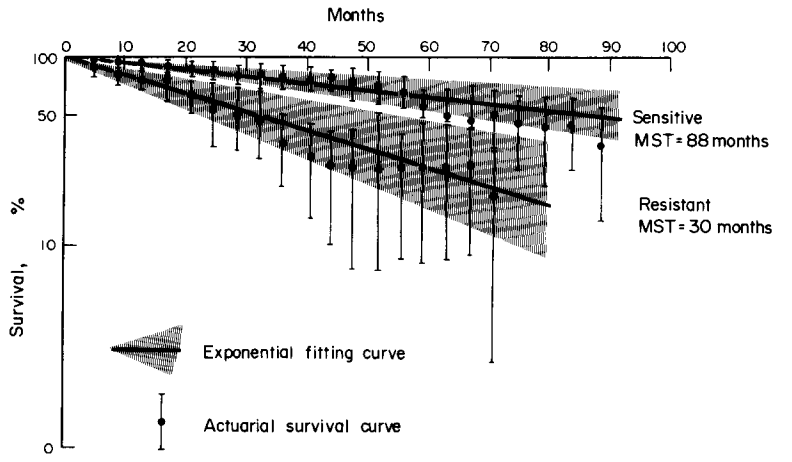

Fig. 2. *Actuarial survival and exponential fitting curves according to the response to the first chlorambucil test* (97 *patients*). *MST: Median Survival Time.*

Rai *et al.* [3] was performed, which allowed us to define sensitivity and resistance to treatment.

Sixty-two were sensitive to the test (64% of total patients) and 35 were resistant (25 stable and 10 progressive). Two populations of patients (sensitive and resistant) were determined by a statistical study made after chlorambucil test. The survival curves of both populations are of a highly significant difference ($P=2.91\times10^{-3}$). Median survival durations are 88 months and 30 months respectively for sensitive and resistant patients.

The difference between the two populations was confirmed by the analysis of the median survival time (MST), estimated in the same way as for the first staging. Indeed, at the time of the second Rai staging we found a significant difference concerning the MST between patients in stages 0–I = (104 months) and patients in stages II–III–IV (24 months). This notion emphasized the prognostic signification of the Rai classification.

of 28 in stage IV were sensitive, 9 of which regressed to stage 0). In addition (Table 2) we have used another statistical method which led to the same conclusions. In the sensitive group, patients in C.R. with disappearing lymphocytosis (46) were differentiated from patients with persistant lymphocytosis (16). This method also demonstrated that among the 35 patients resistant to chlorambucil, 25 showed a double resistance, that is lymphocytic and splenic resistance.

(C) *Effect of splenectomy*

Because of disease's progression during evolution, a late splenectomy was performed in twelve patients; among them 8 received afterwards a second chlorambucil test. All patients were in stage IV at first staging. They have been divided into two groups of patients by means of response to the first chlorambucil-test. Group A (6 patients) consisted of patients who were resistant to the test and remained in

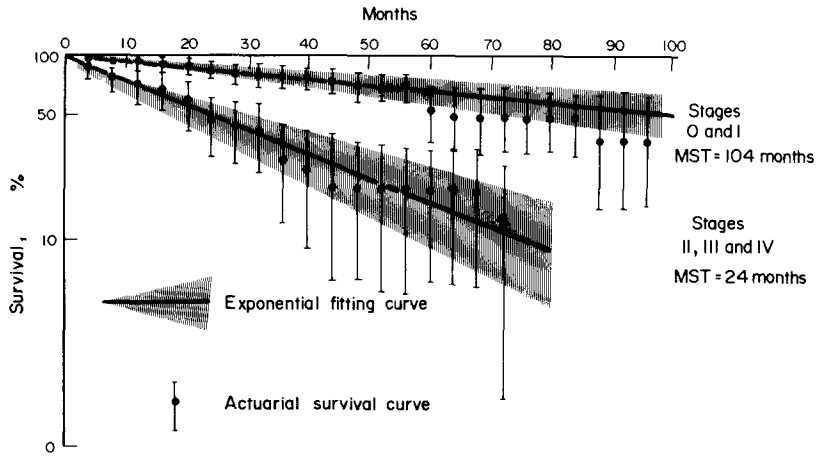

Fig. 3. Actuarial survival and exponential fitting curves calculated from treatment after second Rai staging (97 patients). MST: Median Survival Time.

The study of sensitivity to chlorambucil showed that (Table 1):

(1) 18 patients out of 21 in stages 0 and I were considered as sensitive (i.e., 86%); and among them 12 patients with stage I disease regressed to stage 0.

(2) 44 patients out of 76 in stages II, III and IV were sensitive (i.e., 60%). Among them, 34 were reclassified as stage 0.

These findings show that stage IV does not seem to be at the first staging, an initial factor of poor prognosis since the sensitivity to chlorambucil is comparable to the one obtained in patients in stages II and III (15 patients out

stage IV. Group B (6 patients) consisted of patients who initially responded to chlorambucil (sensitive patients) then became resistant to it during the evolution of the disease's progression to stage IV, including splenomegaly.

We recorded four deaths in the splenectomized patients, immediately after surgery (two in each group).

(a) *Response to splenectomy.* In group A, all patients responded to splenectomy with regression of their disease: we then obtained two stages 0; one stage I; and one stage III. In

Table 1. *Results of two stagings according to the Rai classification at diagnosis and after* 6 months *chlorambucil*

At diagnosis		After chlorambucil	
Stage	Number of patients		
0	7 (38 untreated)	S=6 (86%)	
		R=1 (14%)	
1	14	S=12 (86%)	12 Stage 0 1 Stage I
		R=2 (14%)	1 Stage IV
II	33	S=20 (61%)	4 Stage I 16 Stage 0
		R=13 (39%)	8 Stage II 5 Stage IV
III	15	S=9 (60%)	9 Stage 0 3 Stage III
		R=6 (40%)	3 Stage IV
IV	28	S=15 (54%)	9 Stage 0 2 Stage I 2 Stage II
		R=13 (46%)	2 Stage III 13 Stage IV
Total of patients	97	S=62 (64%)	
		R=35 (36%)	

R: resistant to chlorambucil, i.e., progression or stability of the disease.
S: sensitive to chlorambucil, i.e., regression of the disease.

Table 2. *Patients' distribution according to the response to chlorambucil. Demonstration of a significant difference between sensitive and resistant patients by statistical method (G-test)*

	Response to chlorambucil	Disease's progression No. of patients	Disease's stability No. of patients	Disease's regression No. of patients	Statistical test	
Sensitivity	Disappearing lymphocytosis	0	6	40	*G*	*G*
	Persistent lymphocytosis	0	0	16	=	=
Resistance	Lymphocytic resistance	2	3	0	72, 72	79, 28
	Splenic resistance	2	3	0	*P* ≃	*P* ≃
	Double resistance	6	19	0	0	0

group B there were two responders to splenectomy (one stage 0 and one stage III) and two non-responders remaining in the same stage.

(b) *Effect of the second chlorambucil test.* In group B, responders to splenectomy were sensitive to chlorambucil and non-responders were resistant. In group A, two patients were resistant to chlorambucil and two were sensitive to it. The latter showed a nodular infiltration of the spleen, indeed histologically confirmed, whereas diffuse lymphocytic infiltration was found in the other cases.

DISCUSSION

Taking account of the therapeutic homogeneity, this retrospective study allows us to

define and to once again determine criteria of CLL prognosis. The 'therapeutic test' allows us to perform two stagings according to the Rai classification before and after 6 months administration of chlorambucil, in an attempt to assess and to increase its validity according to the prognosis of CLL.

The best prognostic criterion seems to be the response to chlorambucil, which in turn permits us to define resistance or sensitivity.

On the basis of the study of the median survival time calculated for patients classified as previously mentioned, we found a high statistical difference between two populations twice.

The staging at diagnosis gives, therefore, a first estimation of prognosis. When it is performed a second time to evaluate sensitivity to chlorambucil, it represents the greatest prognostic criterion. We can compare our first findings concerning the survival according to the first staging to the results of other authors on median survival time from the date of diagnosis. Reviews about CLL have shown MSTs from diagnosis ranging from 1.7 to 9 yr [2] and some have attempted to correlate survival with symptoms [15], leucocytosis, anemia and /or thrombocytopenia [4, 16], the pattern of leucocyte count elevation during the disease and the degree of bone marrow lymphocytic infiltration [17, 18]. In order to validate the proposed method of staging as a prognostic indicator, Rai *et al.* [3] applied their staging criteria to two other series reported in the literature [18, 19]. It will be observed that in each of the 3 series studied by Rai there were essentially three rather than five groups which differed with respect to the median survival time (in months): stage 0 (150), stage I (101), stage II (71) and stage III and IV (19). In our study we found 2 groups with a highly significant difference as regards to the survival, stages 0 and I with a survival above 100 months and stages II, III and IV (32 months).

We believe that stage II can be part of the second group, which includes patients who the first time were sensistive to chlorambucil but became resistant afterwards, during evolution, thus increasing the bad prognosis. In addition, after using a second staging we obtained nearly the same significant difference between two groups as defined in reference to sensitivity or resistance to chlorambucil: MST was 88 months and 30 months respectively.

Moreover, this difference was confirmed when comparing the MST of patients in stages 0–I (104 months) and patients in stages II, III, IV (24 months). This notion outlines the prognostic significance of the Rai classification, which is magnified when it is performed before and after a therapeutic test including chlorambucil. We may say that resistance to chlorambucil is one of the best criteria of bad prognosis of CLL. We may compare our findings concerning median survival after chlorambucil to the results of Johnson [20]. Correlating the response to total body irradiation (TBI) and survival, this author defined two types of responders, the MST was 102 months in type 1 responders and 46 months in types 2–3 responders respectively. In a further study [21] the same author has shown that a higher complete remission rate was obtained, when using TBI and chemotherapy, and might exert a favorable influence on survival.

In an attempt to improve the duration of survival after primary or secondary resistance to chlorambucil, we performed a splenectomy in 12 patients [10, 11]. It is of great interest to make a second chorambucil test after splenectomy and analyse the results of patients resistant to it.

The latter were all sensitive to splenectomy and this corresponds to a regression of their disease. When receiving a second chlorambucil test, only patients presenting a splenic nodular infiltration became sensitive.

As for these patients, we think that splenectomy must be included in the treatment and should be scheduled earlier. The prognosis, consequently sensitivity to further treatment, seemed to be correlated with fibrosis and nodular infiltration of the spleen.

In conclusion, the CLL patients having a resistance to chlorambucil (resistant forms) have the worst prognosis. They are defined by a massive and homogeneous lymphocytic infiltration of blood or spleen after 6 months chlorambucil administration without regression. For this reason, it is of utmost importance to find better therapeutic approaches in order to prolong duration of survival: total body irradiation [20, 21]; leukapheresis alone or combined with another chemotherapy [2]; and other chemotherapy.

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