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PROGNOSTIC FEATURES AND THERAPEUTICAL APPROACHES IN B-CELL CHRONIC LYMPHOCYTIC LEUKEMIA: AN UPDATE

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ABSTRACT

In the past few decades important progress has been made in the understanding of chronic lymphocytic leukemia (CLL). Indeed, systematic studies of natural history and prognostic factors have made it possible to predict the outcome of disease. Although clinical stage (i.e. Rai and Binet stages) is the strongest predictor of survival, additional prognostic parameters, including patterns of bone marrow (BM) infiltration, lymphocyte doubling time (LDT), immunophenotype and cytogenetics, have now been identified. Furthermore, criteria of *smoldering* CLL (i.e. stage A, low lymphocyte count, non-diffuse BM histology, relatively high hemoglobin level, LDT > 12 months) allow identification of a subgroup of patients with indolent course and good prognosis for whom treatment should be delayed, unless progression occurs. Recent meta-analysis of clinical trials has demonstrated no survival advantage for immediate versus referred treatment in low clinical stages. The same considerations apply when comparing combination versus single-drug regimens.

Purine analogues like fludarabine, 2'-chlorodeoxyadenosine and 2'-deoxycoformicin are active in CLL. Data on these drugs come from uncontrolled clinical trials; randomized studies are in progress. In addition, some issues concerning the relationship between response and survival, cross-resistance between purine analogues and eradication of the CLL clone, remain still unresolved. There are also increasing data on bone marrow transplants in CLL, although the high treatment-related mortality suggests that this procedure may have some benefit only in selected refractory young CLL patients with adverse features.

This review will focus on recent progress in the prognosis and therapy of CLL. Issues that remain controversial will be a matter of discussion.

Key words: B-CLL, prognostic features, therapeutical approaches

In the past 20 years important progress has been made in the understanding of chronic lymphoproliferative disorders with leukemic expression. Indeed immunological, cytogenetic and molecular biology methodologies have provided insight into the nature of lymphoid neoplasms. As far as B-cell chronic lymphocytic leukemia (CLL) is concerned, studies regarding its natural history and prognostic factors, which were started in the late sixties, have made it possible to predict the outcome of patients with different degrees of disease.[1-6] Clinical stage, bone marrow (BM) histology, peripheral lymphocyte count, lymphocyte doubling time (LDT), number of prolymphocytes in peripheral blood and cytogenetic abnormalities, are considered reliable prognostic factors.[7-8] However, all these studies were carried out in series that included mostly elderly patients with a median age over 60 years. Whether prognostic factors, identified in the overall CLL population, also apply to younger patients, who generally account for 10% of cases, has been a matter of debate.[7]

Therapeutic approaches to CLL should take

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into account patient classification, when to treat, and the potential role of new drugs. Patient classification is important because disease outcome is heterogeneous,[7-8] and therefore patient prognosis must be carefully assessed to determine the need for treatment.[9]

More recently, therapeutic results of purine analogues such as fludarabine and 2-chlorodeoxyadenosine have shown that a significant number of B-cell CLL patients may obtain a complete remission documented at the molecular level. Long-term follow-up is required to establish whether these agents improve overall survival; if this is ascertained, it could represent the first step towards achieving a cure.[10-12]

With this background it seems appropriate to review the prognostic and therapeutic advances made in B-CLL, which has long been considered the *cinderella* of leukemias.[13]

Clinical stages

The Rai staging system

As recently suggested by Rozman,[13] the modern CLL era started with the paper by Rai et al.[14] in which a five-stage staging system was proposed. The initially described five-stage system correlated with survival: stage 0, lymphocytosis only (median survival over 15 years); stage I, lymphocytosis plus lymphadenopathy (median survival 9 years); stage II, lymphocytosis plus spleen and/or liver enlargement (median survival 5 years); stage III, lymphocytosis and hemoglobin level < 11 g/dL (median survival 2 years); stage IV, lymphocytosis and platelet count $< 100\times10^9$/L (median survival 2 years). The Rai system has recently been simplified. The original five stages has been reduced into three groups: stage 0 (low risk), stages I and II (intermediate risk), and stages III and IV (high risk), with median survivals of > 10 years, 7 years, and 1.5 years, respectively[15] (Table 1).

Table 1. Modified Rai staging system for CLL.

Rai stage	*Three-stage system*	*Clinical features*	*Median survival (yrs)*
0	Low-risk	only lymphocytosis in blood and marrow	> 10
I II	Intermediate-risk	Lymphocytosis + lymphadenopathy + splenomegaly ±hepatomegaly	7
III IV	High-risk	Lymphocytosis + anemia + thrombocytopenia	1.5

The Binet et al. staging system

In 1981, Binet et al.[16] proposed a staging system based on multivariate analysis. According to the number of involved lymphoid areas and the presence or absence of anemia and thrombocytopenia, three prognostic groups were distinguished: stage A, < 3 node-involved areas (median survival 12.5 years); stage B ≥ 3 node-involved areas (median survival 5 years); stage C, anemia and/or thrombocytopenia (median survival 2 years) (Table 2).

The integrated International Workshop on CLL staging system

The *International Working Group on CLL (IWCLL)*[17] defined substages of the Binet system in order to integrate the Rai stages: e.g. A (0), A (I), A (II), B (II), C (III), C (IV). Unfortunately, most investigators found the integration cumbersome and used either the Binet or Rai system, but not both.

Table 2. Binet staging system.

Stage	*Clinical features*	*Median survival (yrs)*
A	No anemia, no thrombocytopenia and less than three involved lymphoid areas*	12
B	No anemia, no thrombocytopenia and three or more involved lymphoid areas	5
C	Anemia (Hb < 10 g/dL) and/or platelet count < 100 x 10^9/L	2

*Lymphoid areas considered are: cervical, axillary and inguinal, spleen and liver.

Several studies support the usefulness of the integrated IWCLL system. In a large series by the French Cooperative Group for CLL Study,[18] the 5-year survival rate of 127 patients in stage A (0) was 89% compared with 77% for 182 patients in stage A (I-III) ($p = 0.005$). In a study based on a small number of patients followed at a single institution, a survival rate of 80% was found at 8 years for patients in stage A (0), compared to 42% for those in stage A (I-II) ($p < 0.001$).[19] Finally, in the series from Montserrat et al., although no statistical significance was reached, survival of 159 patients in stage A (0) was different from that of patients in stage A (I-II) (median not reached versus 103 months; p = NS).[7]

On the basis of these results subclassification of early and intermediate Binet stages according to Rai criteria is recommended.

Other staging systems

Other staging systems which correlate with survival have been proposed. Mandelli et al.[20] evaluated clinical and biological data from 1777 cases of the GIMEMA group and identified four risk groups based on the incidence of four negative prognostic variables: hemoglobin concentration lower than 11 g/dL, peripheral blood lymphocytosis over 60×10^9/L, more than 3 involved lymphoid areas and hepatomegaly. Stage I (benign lymphocytosis) includes patients without risk variables; stage II (low risk) contains patients with one of the four variables; stage III (intermediate risk) has patients with two of the four variables, and stage IV (high risk) is for patients with at least three of the four variables. The median survival for stage I and stage II groups had not been reached (78% and 60% alive at 84 months, respectively), while it was 59 months for stage III patients and 32 months for stage IV patients.

Jaksic and Vitale[21] suggested that the tumor burden of CLL could be used to predict outcome and they defined a useful score to estimate total tumor mass (TTM). The TTM score is the sum of 1) the square root of the blood lymphocyte count per microliter; 2) the diameter of the largest palpable lymph node; 3) below costal margin spleen enlargement. Patients with a high TTM at presentation (i.e. > 9.0) had an expected median survival of 39 months, compared with 101 months for those with a lower TTM.

Lee et al.[22] analyzed a large series of CLL patients at the M.D. Anderson Hospital in Houston and demonstrated that serum lactate dehydrogenase (LDH) level (above 325 units/dL), uric acid (>7 mg/dL), alkaline phosphatase (> 80 units/dL), age (> 60 years) and the presence of adenomegalies were useful for identification of different risk groups. Patients with a serum LDH < 325 units/dL and with none or only one of the above mentioned criteria were considered to be in the low-risk group. Patients with an LDH level < 325 units/dL or with two or three of these factor, or with an LDH > 325 units/dL and one additional unfavorable factor were considered to be in the intermediate risk group; finally, patients with an LDH level > 325 units/dL and two unfavorable factors or with all four of them were considered to be in the high risk group. The median survival times were approximately 10 years, 6 years and 2 years, respectively, for the low, intermediate and high risk groups.

All these systems are useful for identifying patients with different outcomes; however, they do not offer additional information with respect to the ones proposed by Rai, Binet and the integrated International Workshop on CLL classifications.

Other prognostic parameters

Although clinical stage remains the strongest predictor of survival in patients with CLL, the heterogeneity, even within clinical stages, has led to a search for laboratory and clinical prognostic factors to improve on currently available staging systems.

A large number of factors have been reported to correlate with disease progression and survival. For the purposes of the present review, we analyzed the prognostic variables on which a general consensus has been reached (Table 3).

Age and sex

Older age has consistently been shown to confer a poor prognosis in CLL.[1,20,22,23] In contrast, the assessment of prognosis in younger CLL patients is more controversial. Some stud-

Table 3. Factors affecting prognosis in CLL.

Related to:		
Tumor burden	*Intrinsic malignancy*	*Host and tumor-host relationship*
• Anemia	• Large and atypical lymphocytes in blood	• Advanced age
• Thrombocytopenia	• Hypogammaglobulinemia	• Male sex
• High lymphocyte count	• Complex and multiple cytogenetic abnormalities	• Poor performance status
• Bulky disease	• Immunophenotype (e.g. SmIg^{++},CD23^{-}, FMC7^{+}, myelomonocytic antigen, low CD44 expression)	• Inversion of CD4/CD8 ratio
• Diffuse bone marrow histology	• Rapid lymphocyte doubling time	
• Increased serum LDH level	• Increased cells in S phase	
• Increased serum uric acid level		
• Increased serum alkaline phosphatase level		
• Increased soluble CD 25 receptors		
• Increased serum β2 microglobulin level		

Reviewed in ref. #7 and 8.

ies suggest that younger patients with CLL have a poorer prognosis and rather unpredictable survival.[24] However, on the basis of other reports, it seems that the survival of younger CLL patients is not necessarily worse than that of older ones.[25] Moreover, well-known prognostic factors also apply to the general population of CLL patients regardless of age.[26-28] As far as the sex is concerned, most studies suggest that females with CLL survive longer than males, even if matched for other known prognostic factors such as clinical stage.[22,23,29] The reasons for this difference are not clear.

Peripheral blood lymphocyte count and lymphocyte doubling time

In the past some authors found that a high lymphocyte count was indicative of poor prognosis.[2,3,5] In more recent analyses, lymphocyte count has been found to be an important predictor of survival independently of clinical stage. Although lymphocyte count affects prognosis by working as a continuous variable, a lymphocyte cut-off value of 40-50$\times 10^9$/L is generally used to segregate patients into low- and high-risk groups. Moreover, two independent studies confirmed lymphocytosis as an useful parameter for subclassifying low and intermediate CLL stages in both the Rai and International Workshop on CLL staging systems.[30,31]

In 1966 Galton[2] demonstrated that the pattern of increase in blood lymphocyte count in CLL patients not receiving cytotoxic therapy, predicts the clinical course of the disease.

Further studies two decades later showed that lymphocyte doubling time (LDT) (the period of time needed to double the blood lymphocyte count) is an independent prognostic variable. Indeed patients with a long LDT (more than 12 months) fare better than those with a short LDT (less than 12 months).[32-35] Although not directly available at diagnosis, LDT is easy to calculate by extrapolation shortly after diagnosis.

Interestingly, even if only patients with stage A disease are considered, LDT retains its prognostic power.[19,36] LDT has been considered representative of disease progression, although the correlation between LDT and clinical stage progression is far from absolute ($r = 0.11$). However, when analyzed as a time-dependent variable, LDT significantly affected the rate of clinical stage progression, which was faster among patients who doubled their initial lymphocyte count than among those who did not (Figure 1).

Finally, LDT may reflect the *in vitro* mitogenic activity of lymphocytes after polyclonal lymphocyte stimulation,[37] as well as the percentage of lymphocytes in S-phase determined by cytofluorimetry.[38] In this context the recently reported correlation between LDT and the proliferative rate, as measured by the proliferating cell nuclear antigen, is of interest.[39]

Lymphocyte morphology

The heterogeneity of peripheral blood lymphocytes in CLL has been previously recognized. Although some morphological variants have been described,[40] results are controversial with respect to prognosis.[41-43] Nonetheless, there is general consensus that an increase in large, immature-appearing lymphocytes (prolymphocytes) is associated with a short life expectancy. Two separate studies demonstrated that an increase in the relative (i.e. >5-15%) or absolute (i.e. 5-15×10^9/L) number of peripheral blood prolymphocytes is an independent prognostic parameter.[44,45]

Pattern of bone marrow involvement

The bone marrow in CLL has traditionally been considered to be diffusely infiltrated by mature-appearing lymphocytes; however, a substantial number of patients exhibit a non-diffuse (i.e. nodular, interstitial, mixed) pattern of involvement. The pattern of bone marrow infiltration separates CLL patients into two different prognostic groups.[46-50] Patients with diffuse infiltration have a median survival ranging between 2 and 4 years, while this value is between 8 and 10 years for those with a non-diffuse pattern .[7]

The pattern of BM infiltration correlates with clinical stage and therefore predominates in advanced cases. Furthermore, patients in early clinical stages may be subclassified into two different prognostic subgroups on the basis of BM histology.[51] In this context, it is of interest to point out that patients in early clinical stages with diffuse BM histology tend to progress quickly toward a more advanced clinical stage.[52]

The BM histologic pattern is useful not only in the diagnosis and assessment of prognosis of CLL patients, but it may provide important information for evaluating response to therapy: nodular or focal lymphoid infiltration is compatible with a complete response.[53]

Finally, recent literature data suggest a close association between a diffuse pattern of BM infiltration and myelomonocytic antigen expression (i.e. CD13, CD33) in B-cell CLL.[54,55] This observation is of interest in view of the structural relationship of CD33 to the family of neural cell adhesion molecules.[56]

Cytogenetics

An increasing body of data supports the prognostic importance of cytogenetics in CLL.[57-59] Chromosomal abnormalities occur in approximately 50% of CLL cases, with trisomy 12 and structural abnormalities of chromosomes 13, 14, 11 and 6 being the commonest findings.[59] Despite the controversial results in a previous report,[57] it is now well established than an extra chromosome 12 indicates poor prognosis.

In the first IWCLL study the number of

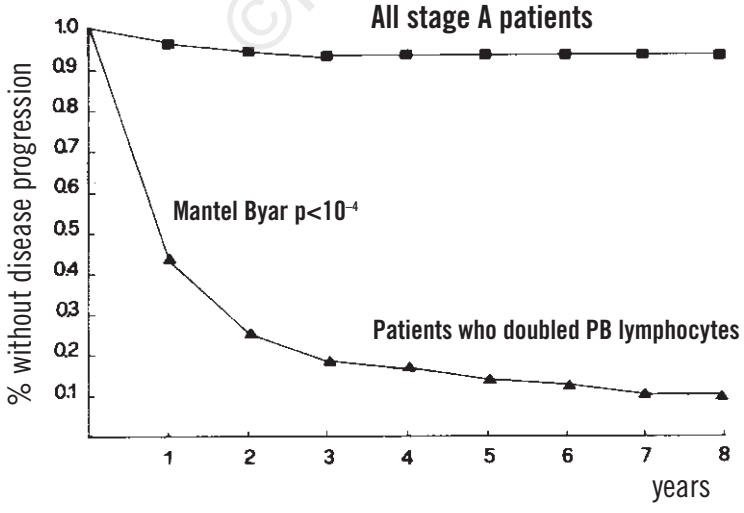


Figure 1. Clinical stage progression rate for patients who doubled their initial lymphocyte count and for those who did not.

patients with a single chromosomal abnormality was large enough to allow significant separation of the survival curves for patients with trisomy 12 (median 5.6 years) and other alterations (median 8.6 years) with respect to those with normal karyotypes (median 14 years).[59] Very similar survival curves were found in an updated and expanded report.[60] It is noteworthy that a high percentage of cells in metaphase with chromosomal abnormalities was the only other parameter associated with shorter survival besides advanced age, male sex and Binet stage.[59,60]

Recently, several studies have shown that individuals with trisomy 12 can be identified by fluorescence *in situ* hybridization (FISH) even when the abnormality is concealed in preparations for conventional cytogenetic analysis.[61-63] Since FISH is a powerful tool for the detection of numerical chromosome abnormalities in both dividing and non-dividing cells, it is likely that systematic application of this technique on large numbers of patients might allow an evaluation of the real incidence of trisomy 12 in CLL.

Immunophenotype

Malignant cells in CLL exhibit a typical coexpression of pan B-cell antigens such as CD19 and CD20 along with CD5, CD23 and weak SmIg expression.[64] Several studies attempted a correlation between surface Ig expression and survival. Baldini et al.[65] evaluated 76 patients and concluded that ones with SIgM had a worse prognosis. These results contrast with those reported by Hamblin et al.[66] who identified a subset of patients expressing SIgMκ that were more likely to be in stage A at presentation and had a significantly longer survival.

The prognostic impact of other immunological markers was recently evaluated. Geisler et al.[67] noted a shorter survival for patients whose cells expressed FMC7 but not CD23. Orfao et al.[68] were unable to identify a relationship between immunophenotype and survival in 62 previously untreated CLL patients.

More recently, a number of CLL variants have been described. As far as CD11c expression is concerned, Wormsley et al.[67] reported that 26 out of 199 cases morphologically diagnosed as CLL, in addition to CD5 expressed the CD11c antigen, considered to be particular to hairy cells. It is well known, however, that CD11c may be expressed on otherwise typical B-cell CLL and that the frequency depends on the monoclonal antibody utilized.[69-74] Finally, De Rossi et al.[74,75] extensively studied the role of adhesion molecules in the behavior of B-CLL. What emerges from these studies is the heterogeneity of adhesion molecule expression and the prognostic role of CD44 in terms of a significant shorter survival for patients with low CD44 expression (Figure 2). These data prompt speculation that this molecule may play a role in the disease progression.

Prognosis of patients with early CLL

Prognostic assessment of CLL patients diagnosed at an early stage (Binet stage A, Rai stage 0) is complex. Indeed staging systems have some limitations, the most important of which being their inability to distinguish between patients with early disease that will remain stable for many years and require no therapy, and those who will develop progressive disease needing treatment.

Some investigators have attempted to address this issue by analyzing the effects of a rapidly increasing lymphocyte count and diffuse BM histology in early CLL stages. Han et al.[76] reported on a retrospective group of 20 patients with Rai stage 0 who had a normal karyotype and stable disease for 6.5 to 24 years. This form of CLL has been defined as *benign monoclonal lymphocytosis*. Female sex, low level of lymphocytes in the blood, normal karyotype and phenotype were the most frequent features of stable CLL.

In a series from Chisesi et al.[77] patients with *indolent* stage A (no general symptoms, hemoglobin level >10 g/dL, platelet count > 100×10^9/L, no disease progression at 24 months) had a better survival expectancy than those with *active* stage A.

Tura et al.[78] and Oscier et al.[79] analyzed their series of Rai stage 0 patients in order to identify factors affecting disease progression to more advanced clinical stages. Parameters correlating with an increased risk of disease progression included LDT in the former study, and the ini-

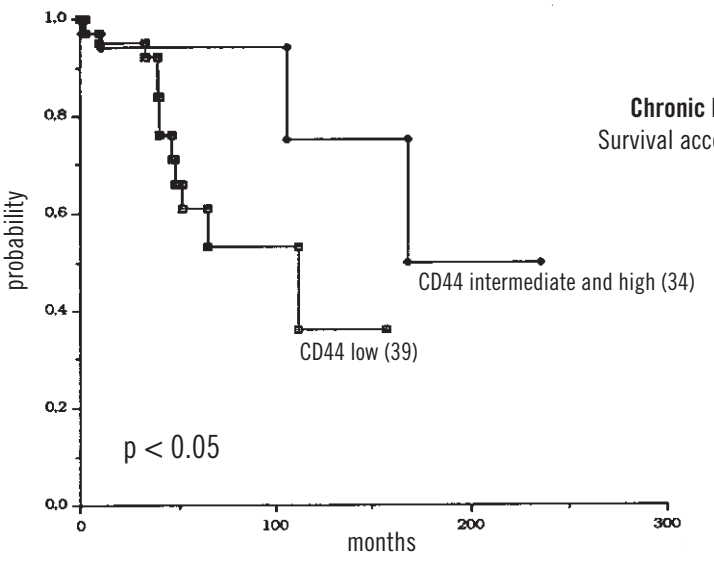


Figure 2. Survival rates of B-CLL patients as related to CD44 expression on leukemic cells.

tial lymphocyte count, surface immunoglobulin μδκ phenotype, and some complex karyotype abnormalities in the latter.

In 1988 Montserrat et al.[80] first proposed criteria for identifying patients with *smoldering* CLL (namely, stage A, non-diffuse BM histology, hemoglobin level > 13 g/dL, lymphocyte count $< 30 \times 10^9$/L, LDT > 12 months).

The need for a better understanding of the natural history of stage A CLL patients was considered at a recent International Workshop on CLL meeting[81] (Table 4). Analysis of large series followed up at a single institution[13] or entered into randomized clinical trials[12] allowed the identification of stage A patients in whom disease may progress and survival is likely to be shorter. Clinical and laboratory indicators of such events were: high lymphocyte count, short LDT, diffuse BM histology, relatively low hemoglobin concentration, and A (I-II) sub-stage.

Although all systems are able to identify patients with a low probability of progression and long survival, about 15-20% of patients with smoldering CLL progress, and current criteria are unable to identify them.[49] It is not clear whether these patients might gain some benefit from being treated before progression to a more advanced stage.

Problems and potential solutions for staging and prognosis

Each of the currently used staging systems receptors) and patient condition (age, performance status) without providing information about the biology of the disease. On the other hand, the Binet system does not include patients with Rai stage 0 (lymphocytosis only), whereas the Rai system does not account for the occasional patients with splenomegaly without lymphadenopathy, a subgroup displaying very good prognosis.[82] Finally, none of the systems readily permits the integration of new prognostic factors (e.g. LDT, BM) and this may be responsible, at least in part, for the considerable heterogeneity within clinical stages. In early

Table 4. Smoldering CLL.

Montserrat et al. criteria[36]
Stage A
Non-diffuse bone marrow histology
Hemoglobin ≥ 13 g/dL
Blood lymphocytes ≤ 30 x 10^9/L
Lymphocyte doubling time > 12 months
French Cooperative Group on CLL criteria[18]
A-1
Stage A
Hemoglobin ≥ 12 g/dL
Blood lymphocytes ≤ 30 x 10^9/L
A-2
Stage A
Hemoglobin ≥ 12 g/dL
Blood lymphocytes ≤ 30 x 10^9/L
Lymphocytes in bone marrow aspirate < 80%
Number of enlarged lymphoid areas < 2

stage disease the absolute lymphocyte count and the LDT may distinguish a subgroup of patients with a normal life expectancy from those with a worse prognosis.[18,19] The additional prognostic value of cytogenetics and bone marrow histologic pattern needs to be examined further. In addition, these procedures are expensive and uncomfortable for the patients.

Treatment of CLL

Although B-cell CLL has been treated heterogeneously in the past, the mainstay of its treatment has been chlorambucil (CLB). Recently both the NCI and the IWCLL[83,84] defined criteria for evaluating clinical-hematological response to treatment; however, criteria for evaluating true clonal complete remission (CR) have yet to be established.

Radiotherapy

Radiation treatment of CLL dates back quite a few decades.[85] Methods of irradiation vary: 32P total body irradiation, extracorporeal irradiation, localized radiotherapy, thymic irradiation.[86-90] However, the results of these treatments are biased by the inclusion of patients who are heterogeneous with respect to clinical-hematological features.

Splenic irradiation (SR) has been used instead of splenectomy when large splenomegaly was evident.[91-96] In the CLL MRC protocol 2, stage B and C patients with splenomegaly more than 5 cm below the costal margin, were randomized to receive SR (100 cGy weekly up to a total of 1000 cGy) or CLB. The results did not show significant differences in terms of survival.[91,92]

Roncadin et al.[96] achieved 78% hematologic response with an overall median survival of 40 months in 38 patients treated with SR. Chisesi et al.[93] obtained 44% CR and 38% PR in 52 patients. Median duration of response was 4 months. De Rossi et al.[94] treated 22 patients in Rai II stage with SR, achieving 14 PR; however, 12 out of these 14 responding patients required chemotherapy with CLB+PDN, because of progressive disease 6 to 36 months after SR.

SR can induce a short-lived reduction of PB lymphocytosis, splenic and node involvement. Lymphocytic compartments undergo continuous replacement, and the spleen is a focal point of such activity; therefore SR can destroy transiting lymphocytes as well as the intrasplenic lymphocytic compartment, thus inducing a tumor mass reduction.

Splenectomy

The main and infrequent indications for splenectomy are autoimmune hemolytic anemia, thrombocytopenia or hypersplenism resistant to corticosteroids and cytotoxic therapy. Furthermore, splenectomy may be used in patients with painful splenomegaly. Although the results of some reports are encouraging,[97-99] the role of splenectomy in the management of CLL patients has not been assessed thus far. The majority of studies, based mainly on retrospective patient series, did not demonstrate a real advantage in terms of overall survival.

Single-agent chemotherapy

CLB, an aromatic derivate of nitrogen mustard, is the most commonly used drug in CLL. CLB has been utilized in different modalities: alone, with prednisone (PDN), continuously, intermittently at high doses until maximum response, and as maintenance therapy. Responses were heterogeneous and sometimes difficult to interpret because of the heterogeneity of patient populations and the different response criteria utilized.[92,101-108] However, these studies do provide some definitive conclusions about the use of CLB and PDN: 1) results, in terms of overall survival, are not affected by the schedule of CLB administration (continuous vs intermittent);[109] 2) high doses of CLB (15 mg) given daily until response induce higher remission rates.[110] CLB plus PDN, because of low side effects, oral administration and relatively acceptable response rates, remains the best treatment for patients over 60 when a conservative therapy approach is required. However, an important issue that must be addressed is that of resistance to CLB. Before defining a patient as refractory to CLB, it should be determined whether the drug was administered at an adequate dosage (0.2-0.3 mg/kg/day) for a significant period of time (some weeks). In this con-

text the criteria recently proposed by De Rossi et al.[111] for defining CLL patients who are truly resistant to CLB are of interest (Table 5).

As far as cyclophosphamide (CF) is concerned, this drug has mainly been utilized in cases of CLB failure.[104,106,107,112,113] It should be stressed that in terms of response the results are similar to those reported with CLB, although in long-term treatment more serious side effects have been observed (cystitis, pancytopenia).[107]

Corticosteroids

While it is well known that corticosteroids possess lymphocytolytic activity, prednisone by itself has a limited antileukemic effect in CLL.[114] Nevertheless, it is useful when dealing with autoimmune hematological complications. The limits of corticosteroid treatment in B-CLL are related to the metabolic and/or cardiovascular complications that sometimes appear in long-term therapy, especially in the elderly.

Combination chemotherapy

Numerous multidrug regimens have been used in B-CLL, mainly in advanced stages and in patients with lymphoma-like presentation (*bulky* tumor), or in CLB refractory cases. Multidrug regimens employed in B-CLL include M2 (melphalan, cyclophosphamide, BCNU, prednisone), CAP (cyclophosphamide, doxorubicin, prednisone), POACH (cyclophosphamide, doxorubicin, vincristine, prednisone, cytarabine), DHAP (dexamethasone, high-dose cytarabine, cisplatin), ACP (cytarabine, cyclophosphamide, prednisone), CMP (cyclophosphamide, melphalan, prednisone), EC (epirubicin and chlorambucil), COP (cyclophosphamide, vincristine, prednisone), VAD (vincristine, doxorubicin, dexamethasone), CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone).[115-123]

COP (CF, VCR, PDN) is the combination that has been utilized the most in B-CLL treatment. The Spanish Group,[124] in a randomized trial comparing the COP regimen to CHL+PDN in stage C patients, showed no significant differences in terms of response rate (49% vs 31%) or overall survival between the two regimens. COP results were also similar to those obtained with CLB in two additional randomized trials.[125,126]

Table 5. Definition of resistance to CLB plus PDN.

1. After at least 4 weeks at maximum dosage *(CLB 0.2 mg/kg/day; PDN 1.5 mg/kg/day)*
   a) No significant changes (< 20%) in PB lymphocytosis.
   b) No significant changes (< 20%) in enlargement of spleen, liver, nodes, others.
2. After at least 8 weeks at maximum tolerated doses, if WBC $< 1\times10^{10}$/L and lymphoma-like involvement.
   a) No significant changes (< 20%) in enlargement of spleen, liver, nodes, others.

The addition of doxorubicin to COP protocols has yielded controversial results. Responses and 5-year survival rates reported by the French Cooperative Group on CLL (CLL-80 trial), who compared a CHOP regimen with low-dose doxorubicin (25 mg/m^2) to COP in stage C patients, were consistently in favor of the former treatment.[123,127] However, the superiority of CHOP over CLB was not confirmed in stage B patients.[128] In keeping with these results are those of Jaksic and Brugiatelli[129,130] and those of Hansen et al.[131] Interestingly, in the former study high-dose CLB gave significantly better results in terms of response rate and actuarial survival than low-dose doxorubicin CHOP.[129,130]

Cytosine arabinoside (ARA-C) has also been added to COP-based regimens.[111,112] De Rossi et al.[111] reported the results of a combination regimen based on ARA-C, cyclophosphamide and PDN in patients with advanced disease resistant to CHL+PDN. They obtained 47% PR with a median duration of 20 months. Keating et al.[132] reported 2 CR and 6 PR in 31 previously treated patients receiving a schedule that included CF, doxorubicin, ARA-C, VCR and PDN.

Fludarabine

Fludarabine (9-D-arabinofuranosyl-2-fluoroadenine monophosphate) is a fluorinated analogue of ara-adenine and, together with 2 chlorodeoxyadenosine, is the most recent chemotherapeutic approach to B-CLL (Table 6). It is usually used at a dosage of 25-30 mg/m^2 i.v. for 5 days every 28 days, for 4-6 cycles.[134, 135] It is also

possible to administer a loading dose (20 mg/m^2) on the first day, followed by continuous infusion on days 2 and 3 at a dosage of 30 mg/m^2 per day.[136]

The first results on fludarabine therapy reported by Grever and Keating were impressive.[134,135] O'Brien et al.[137] in a large series of 264 patients reported an overall response (OR) of 79% and a CR of 63% in previously untreated patients, versus 52% OR and 37% CR in pretreated and/or refractory ones. Obviously, the percentage of responses correlates significantly with Rai stages: median survival was 18 months for pretreated patients, while it was not reached for the untreated group. These results were confirmed in recent studies by Keating[138] and De Rossi et al.[139]

The most important side effects of fludarabine therapy are myelosuppression and infections. As a consequence of the decrease in CD4-positive cells a certain number of opportunistic infections have been described (*Listeria monocytogenes*, *interstitial pneumonitis*, etc.).[137-139]

Keating et al.[138] in 337 courses of therapy reported 25 episodes of pneumonia, 28 of fever of unknown origin (FUO), 4 septicemias and 6 minor infectious episodes. De Rossi et al.[139] in 22 previously treated patients who received fludarabine as second-line therapy observed 9 pneumonias, 3 abscesses, 11 severe mucositis and 10 herpes virus infections; the cumulative incidence of infections was higher in advanced stage patients than in early stage ones. Significant adverse non-hematological events associated with the use of fludarabine have been reported. Tumor lysis syndrome responding well to conventional treatment and not recurring in subsequent courses when fludarabine was administered with allopurinol and forced diuresis was described.[140] Three reports of severe autoimmune anemia, possibly associated with fludarabine treatment, have appeared in the literature;[141,142] however, 2 of the 3 patients had a prior history of hemolytic anemia.

A severe progressive syndrome of CNS demyelination was reported in patients receiving high dose fludarabine (> 96 mg/m^2/day for 5 days).[143] In CLL, at currently recommended doses (25-30 mg/m^2/day for 5 days), 15% of patients experienced some form of neurotoxicity which was generally mild and reversible.[144]

An important problem with fludarabine treatment is certainly the duration of response: median time to disease progression was 30 and 22 months in untreated and previously treated patients, respectively.[137] Indeed patients obtaining a clinically defined complete remission exhibited a lower relapse rate than those with nodular partial responses. Since CR can be obtained in CLL patients treated with fludarabine,[10,145] techniques for detecting minimal residual disease should be utilized to predict the duration of remission.[145] When cytotoxic response was assessed using dual parameter flow cytometry, the 2-year outcomes of patients without persisting malignancy were significantly higher than those of patients with residual disease.[10] Therapeutic efforts should now be directed toward programming protocols effective in maintaining the high response rate induced by fludarabine. This goal will probably be achieved through other approaches such as interferons during maintenance.[146,147]

Table 6. Purine analogues in chronic lymphocytic leukemia.

Study	*N. pts*	*Previously treated*	*CR (%)*	*PR (%)*
Fludarabine				
Grever et al.[134]	32	+	3	9
Keating et al.[138]	75	+	13 (16)*	28
O'Brien et al.[137]	69	+	12 (26)*	14
Keating et al.[138]	36	–	36 (39)*	8
O'Brien et al.[137]	95	–	30 (32)*	19
Sorensen et al.[133]	637	+	4	27
Puccio et al.[136]	42	+	0	52
De Rossi et al.[139]	22	+	4.5	36
Zinzani et al.[140]	35	+	2.8	45.7
Spriano et al.[146]	21	+	4.7	33.3
2'-chlorodeoxyadenosine				
Saven et al.[151]	90	+	4	40
Juliusson et al.[148]	18	+	39	28
O'Brien et al.[153]	28	+**	0	7
2'-deoxycoformycin				
Grever et al.[144]	25	+	4	10
Dillman et al.[146]	39	26	3	23
Ho et al.[147]	26	26	0	27

** Number in parentheses represents nodular CR; **Patients previously treated with fludarabine.*

Finally, a recent multicentric study by the French Cooperative Group on CLL is trying to address the value of fludarabine over anthracycline-based protocols (CAP, CHOP).[148]

Preliminary results suggest that fludarabine induces a higher response rate in stage B patients than polychemotherapy regimens containing anthracyclines. However, these results are no longer observed in stage C patients, and the effect of fludarabine in terms of survival needs to be demonstrated.[148] We are looking forward soon to hearing the results of ongoing phase III studies comparing fludarabine with CLB. These studies will probably redefine the standard initial therapy for CLL.

Deoxycoformycin

2-deoxycoformycin (DF) or pentostatin, a potent inibitor of the enzyme adenosine deaminase, has been shown to have anti-tumor activity in a variety of lymphoproliferative diseases.[149]

Grever et al.[150] treated seven refractory CLL patients and obtained 2 good responses with a 4 mg/m^2 IV push weekly for at least 5 weeks. A different schedule of administration used by the same author gave similar results in a series of 25 patients.[151]

Dillman et al.[152] employing a schedule of 4 mg/m^2 IV push weekly for three weeks and then every other week, reported an OR of 26% in previously treated and untreated patients. With the same schedule Ho et al.[153] showed 27% PR in 26 refractory patients.

Although less myelosuppressive than other purine analogs, DF is highly lymphocytotoxic, especially for T cells, and therefore the degree of immunosuppression could be responsible for severe opportunistic infections.

The role of DF in B-CLL treatment should be examined better in randomized trials.

2-chlorodeoxyadenosine

2-chlorodeoxyadenosine (2-CdA) is a halogenated purine nucleoside that does not inhibit ADA, but is an ADA-resistant purine substrate analogue. Administration of 2-CdA to patients with CLL causes a rapid accumulation of CdA nucleotides in the leukemic cells due to the high levels of deoxycytidine kinase in lymphoid cells.[154] 2-CdA is equally active against resting and proliferating cells and is a potent inducer of apoptotic death in CLL, a feature that correlates with disease status.[155]

The treatment results with 2-CdA in B-CLL are noteworthy. Piro et al.[156] and Saven et al.[157] treated 94 refractory B-CLL using a continuous infusion for 7 days at 4-week intervals (0.1 mg/kg/day) and reported 4% CR and 41% PR. Recently, Juliusson and Liliemark[154] obtained 39% CR and a cumulative response rate of 67% in 18 previously treated patients. Interestingly, six out of 7 CR patients are still in CR at 14 months. It has been reported that 2-CdA may be useful in patients resistant to fludarabine.[158] However, O'Brien et al. recently concluded that patients who are refractory to fludarabine and have an advanced Rai stage are unlikely to benefit from treatment with 2-CdA.[159]

Therapy with biological agents

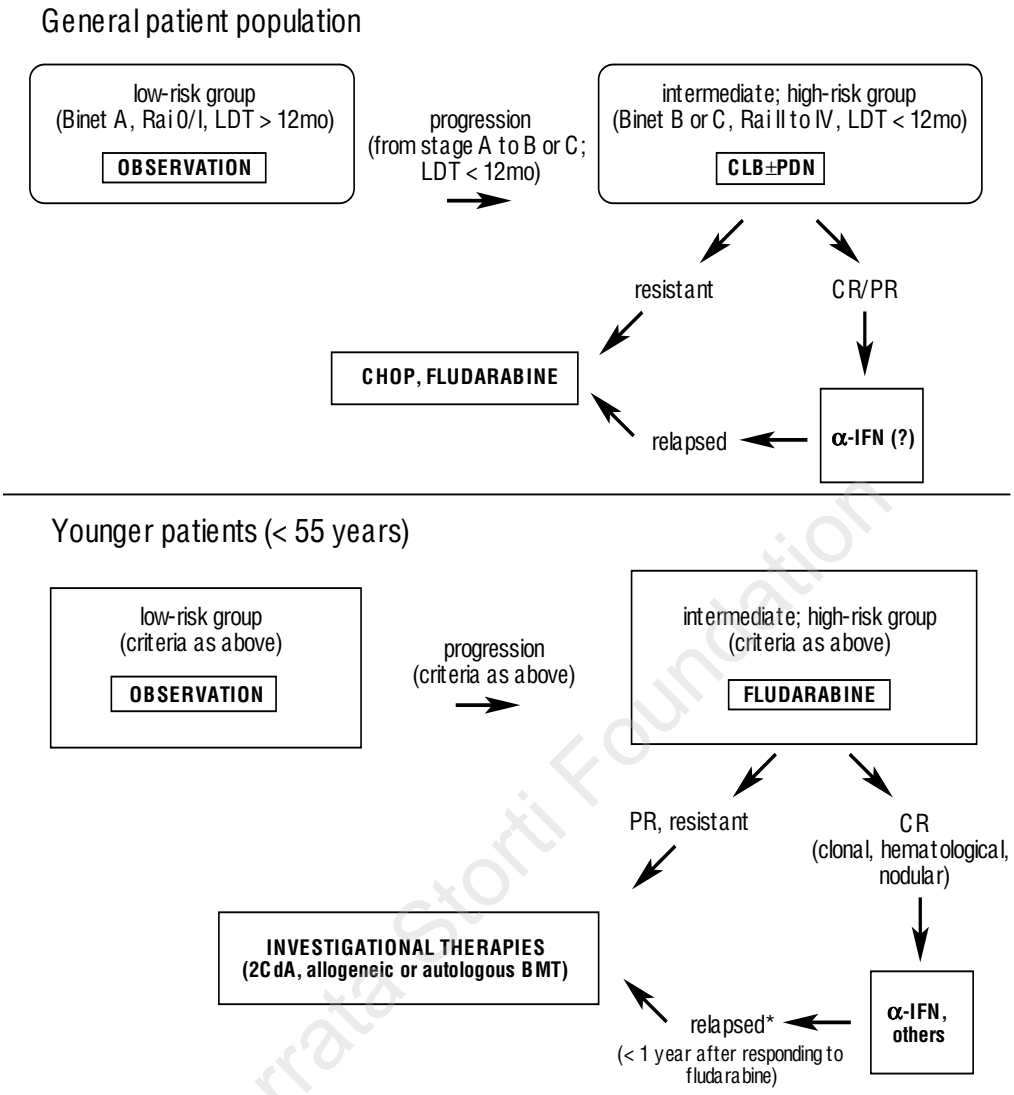
Biological agents have not been successful in treating CLL. Pangalis et al.,[160] Rozman et al.,[161] Molica et al.[162] and Morabito et al.[163] used α-IFN in untreated, low-stage patients with significant responses, thus providing evidence of the general efficacy of α-IFN on B-CLL clones.

IFN could be interesting as a maintenance option in B-CLL, after response and maximum cytoreduction,[164] or in association with CLB in previously CLB-resistant patients. Some recent reports have indeed shown that α-IFN can induce a second response to CLB.[165-167] Ongoing trials are now testing the association α-IFN/fludarabine in induction and/or maintenance therapy.

Although cells from approximately 50% of cases express receptors for it, interleukin-2 has limited clinical activity in CLL and considerable toxicity.[168] Monoclonal antibodies directed against CD5 or anti-idiotype antibodies have achieved only transient reduction in circulating lymphocytes. Some activity has been reported with the CAMPTH monoclonal antibodies.[169]

Preliminary data suggest activity for immunotoxins, including anti-CD19 conjugated to intact ricin.[170]

Bone marrow transplantation



CLB: chlorambucil; PDN: prednisone; IFN: interferon; CR: complete remission; PR: partial remission; BMT: bone marrow transplantation.
*Patients who relapse a year or more after responding to fludarabine may be successfully retreated.[144]

Figure 3. CLL: decisional tree.

The age of B-CLL patients represents a drawback to the employment of bone marrow transplantation (BMT) procedures;[171] however, about 10% of patients are under 50 years old. The life expectancy in this group is unpleasant and therefore intensive therapy aimed at curing the disease is the future goal of B-CLL treatment.

Rabinowe et al.[172] used allogeneic BMT (T cell depleted) in 8 patients and obtained 7 CR documented at the molecular level, with a median follow-up (after BMT) of 12 months. The same group utilized monoclonal antibody-purged autologous BMT in 12 patients and achieved 10 CR. The preparative regimen was identical for all patients and consisted of CF and TBI. The European Group for BMT[173] reported a 70% CR rate, with 46% surviving at 3 years, and a leukemia-free survival of 44% at 3 years in 54 patients (21-57 years) treated for the most part with CF, TBI and allogenic BMT.

Finally, Khouri et al.,[174] using autologous bone-marrow depleted of B cells by an anti-CD19 monoclonal antibody, treated five patients and obtained 5 CR, three of whom are surviving disease free, although the follow-up was less than 12 months.

Conclusive remarks

B-CLL is a heterogeneous disease which includes benign cases whose survival does not differ from that of the age-matched population, as well as very aggressive cases whose behavior and survival are not different from those of non responsive acute leukemias. Between these two extremes are many cases that are heterogeneous with respect to prognosis.

The mean age of B-CLL patients is over 60 yrs; however, about 10-15% of them are under 50. Therefore the decision of when to treat as well as the modality and intensity to employ are related to:

a. patient age;
b. patient performance status;
c. prognostic factors;

(a + b) = life expectancy.

It is well known that patients in the initial stages do not need treatment, because many of them who fulfill the criteria for *benign monoclonal B-cell lymphocytosis*[76] or *smoldering* CLL[36] enjoy a survival similar to that of the age-matched healthy population. Moreover, recent meta-analysis of clinical trials on CLL showed no advantage for immediate versus deferred treatment in low-stage disease.[175]

In intermediate and advanced stages, the choice of treatment should take into account age, performance status and therefore the life expectancy of the patients. In older patients (60-65 yrs and over) treatment with CLB+PDN yields good results with a survival and quality of life that are impossible to obtain with other aggressive therapies, which frequently compromise weak metabolic and cardiovascular balances. In contrast, younger patients in intermediate advanced stages, whose life expectancy is very low, should be considered candidates for therapy aimed at curing the disease rather than maintaining a steady state (Figure 3).

The new drugs (fludarabine, 2CdA, interferons, etc.) used in induction and/or maintenance therapy could help clinicians to reach the therapeutical goal, which is very similar to the one we now have for acute leukemias and lymphomas: to eradicate the disease.[134-160, 168]

On the other hand, allogeneic BMT is still a personalized therapy in B-CLL. Less than 10% of patients are candidates for this procedure and among them only those with a matched donor may really be transplanted. Autologous BMT could be one of the most interesting therapeutic approaches to B-CLL in the future. Specific conditioning regimens and purging systems (MoAbs and anti-idiotype antibodies) make it possible to obtain maximal cytoreduction.

In conclusion, B-CLL is a hematological entity encompassing different clinical conditions that require different and proportionate therapeutical approaches (Figure 3).

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