B-cell chronic lymphocytic leukemia: Recent progress in biology, diagnosis, and therapy

E. Montserrat, F. Bosch & C. Rozman
Postgraduate School of Hematology Farreras Valentí, Department of Medicine, University of Barcelona, Hospital Clinic, Barcelona, Spain

Summary

B-cell chronic lymphocytic leukemia (CLL) is a highly common form of leukemia characterized by the accumulation of long-lived, functionally inactive, mature appearing neoplastic B lymphocytes. In addition, immune disturbances such as hypogammaglobulinemia and autoimmune phenomena (particularly, autoimmune hemolytic anemia) are frequently found in CLL patients [1-2]. The etiology of CLL is unknown. In contrast with other leukemias, there is no relationship between CLL and exposure to radiation or other cytotoxic agents. A genetic basis is highly likely since there are differences in the incidence of CLL in different countries (e.g., CLL accounts for 30%-40% of all the leukemias in Western countries as compared to 5%-10% in Asian countries) and the risk of contracting CLL is higher among persons with first-degree relatives with the disease [3].

Because the incidence of CLL increases with age and the longer life expectancy of the general population, the age of patients at diagnosis is increasing. The median age at diagnosis is now about 70 years, with only one-third of the patients being less than 60 years of age. In the majority of the series, males predominate over females in a proportion of 1.5/1. The prognosis of patients with CLL is variable. However, clinical stages and other prognostic factors allow the individual risk of each patient to be assessed very accurately, which is useful for making treatment decisions.

In the past two decades, significant progress has been made in CLL [4-10]. This review summarizes recent advances in the biology, diagnosis, and therapy of CLL.

Key words: B-cell chronic lymphocytic leukemia, CLL biology, CLL diagnosis, CLL therapy

Biology

The neoplastic B cell in B-CLL

The neoplastic B lymphocytes from CLL have been characterized by using a number of monoclonal antibodies against antigens present on the neoplastic cells; these cells express pan-B-cell-associated antigens such as CD19, CD20, CD21, CD23, CD24, the receptors for mouse erythrocytes, and have surface immunoglobulins (usually IgM and/or IgD) in small amounts and a single light Ig chain (kappa or lambda). CLLs also express the CD25 antigen (a pan T-cell marker) and receptors for IL-2R (C25) and myelomonocytic antigens. Altogether, this antigenic profile is similar to that of the cells present in the mantle zone of lymphoid tissue from where the neoplastic B lymphocytes of CLL seem to arise. A small proportion of blood lymphocytes also exhibit the same immunophenotype.

On the other hand, the majority of the neoplastic lymphocytes are in Go phase of the cell cycle and respond poorly to stimuli such as lipopolysaccharide, EBV proteins, and anti-IgM antibody. They also exhibit a restricted expression of V_H and V_L genes and produce polyreactive, low-affinity autoantibodies. On this basis, neoplastic B-CLL B lymphocytes have been defined as 'antiself B cells' [10]. Although patients with CLL frequently present autoimmune phenomena, particularly directed against hemopoietic cells, in most instances this phenomenon is due to abnormalities of normal, non-neoplastic B lymphocytes rather than to neoplastic B-CLL cells [11, 12].

Cytogenetics

Clonal chromosomal abnormalities are observed in approximately 50% of patients [13-18]. The most frequent abnormalities are trisomy 12, structural changes of the long arm of chromosome 13 (13q14), abnormalities of chromosome 14 (14q+), deletions of chromosome 6, and deletions of chromosome 11 [12-14]. Chromosomal abnormalities prevail in the advanced phases of the disease and in most instances are acquired events [14, 19]. Trisomy 12 is associated with atypical morphology, advanced disease, and poor prognosis and is better detected by fluorescence in situ hybridization (FISH) [16, 17]. In turn, del(6)(q21q23) has been associated with an increased proportion of prolymphocytes in peripheral blood [18]. Abnormalities of the chromosome 14 (14q+) are frequent in prolymphocytic leukemia [14]. Karyotypic evolution, usually associated with disease progression, occurs in 14%-40% of the patients with CLL [14, 20]; deletions of 11q have been reported to be particularly frequent in patients undergoing disease progression [21].
Genes

Up to now, studies aimed at identifying genes associated with CLL have given no conclusive data. Reports suggesting the involvement of bcl-1 and bcl-2 genes in 5%–15% of the patients have not been confirmed and bcl-3 has been only occasionally involved [22–24]. Multi-drug-resistant genes (mdr-1, mdr-3) have been found to be variably expressed depending on the techniques used for their detection, prior therapy, and the phase of the disease [25–28]. Although bcl-2 is rarely, if ever, translocated, it is constantly overexpressed. Mechanisms accounting for bcl-2 overexpression are under scrutiny. Elevated transcription is a probable candidate mechanism since the bcl-2 gene appears to be hypomethylated in CLL cells [29]. Microenvironment signals seem to play an important role in the biology of CLL cells, as removal of these cells from their in vivo microenvironment (e.g., bone marrow) causes a rapid down-regulation of bcl-2. In turn, the bax gene is downregulated, and there is increasing evidence that the bcl-2/bax ratio may play an essential role in CLL homeostasis [30, 31]. The MDM-2 gene has been found to be overexpressed in about half of the patients with CLL, particularly in the more advanced phases of the disease; this gene, however, is neither amplified nor rearranged [32].

Up to one-third of the patients with CLL present a homozygous deletion of a genomic region telomeric to the retinoblastoma (Rb1) gene. Different loci have been analyzed (e.g., D13S25, D13S218, D13S133) [33, 34]. In a recent study, loss of heterozygosity (LHO) of D13S218 was demonstrated in 24% of the patients with CLL, whereas LHO of D13S133 was only found in 4% of the cases; Rb protein levels were not correlated with LHO of D13S218 and clinical stage [34]. In addition, Cyclin D2 (CCND2) is overexpressed in about 85% of the cases [35]. In a study, the A-myb gene was found to be strongly expressed in 5/20 (25%) cases of CLL [36]. Recently, in a small subset of patients with CLL (2/29, 7%) a replication error phenotype (RER+) has been identified [37].

In cases of disease progression, overexpression of the c-myc oncogene, deletions of the Rb1 gene, mutations of the p53 tumor-suppressor, and somatic mutations of D and/or JH segments of the Ig gene have been reported [38, 39]. Also, in one case of CLL evolving into Richter’s syndrome a drastic reduction in the expression of A-myb was observed [36].

Cytokines

Cytokines are involved in CLL pathogenesis [40–45]. For example, TNF-α, IFN-α, IFN-γ, IL-2, IL-4, IL-10, IL-13, IL-15, and basic fibroblast growth factor (bFGF) enhance survival of neoplastic B-cell lymphocytes by acting as growth factors (e.g., TNF-α, IL-2, IL-15), by inhibiting apoptosis (e.g., IFN-α, IFN-γ, IL-4,bFGF) or both mechanisms (e.g., IL-13); these effects take place by a number of different and complex pathways (e.g., IL-4 inhibits TNF-α-induced proliferation and also protects cells from IL-5-induced apoptosis) [40, 41], which are far from being completely elucidated.

Autoimmunity

Hypogammaglobulinemia and autoimmune complications in CLL are usually considered to be due to abnormalities of non-neoplastic B cells, although in some instances neoplastic CD5+ B cells as well as abnormalities in T-cell subsets (e.g., inversion of the CD4+/CD8+ ratio) and in NK function might also be involved [11, 12].

Diagnosis

Criteria to diagnose CLL have been published [46, 47] (Table I). Although different absolute lymphocyte counts have been proposed as the threshold for defining the disease, CLL can be diagnosed whenever there is an absolute increase in the number of lymphocytes in blood and their morphology and immunophenotype are consistent with the diagnosis. Usually, neoplastic B lymphocytes from CLL are small and mature-appearing. Bone marrow is infiltrated by the same lymphoid cells present in peripheral blood. The typical phenotype of the neoplastic B lymphocytes in CLL is SmIg+/-, CD5+, CD19+, CD20+, CD23+, FMC7−, CD22+/− [48].

On the basis of the proportion of atypical lymphoid cells in peripheral blood, CLL has been divided into different morphologic variants (Table I) [49]. This subclassification should be reanalyzed in light of the recent identification of lymphomas (e.g., splenic lymphoma with villous lymphocytes, mantle-cell lymphoma) that can mimic CLL morphologically and immunophenotypically [50–53]. As already mentioned, CLL cases with trisomy 12 are associated with atypical morphology as demonstrated in different studies [16, 17], and deletions of chromosome 6 have been correlated with the presence of prolymphocytes in peripheral blood in a group of small lymphocytic lymphomas [18].

Table I. Chronic lymphocytic leukemia diagnostic criteria.

| 1. Absolute lymphocytosis in peripheral blood |
| > 5 x 10⁹/l (NCI/Working Group) |
| > 10 x 10⁹/l (International Workshop on CLL) |

| 2. The majority of lymphocytes should be small and mature in appearance |
| Morphologic subtypes (FAB Group) |
| 2.1 Typical or classic CLL (<10% atypical lymphocytes) |
| 2.2 Mixed CLL/PL (prolymphocytes in blood between 11 and 54%) |
| 2.3 Atypical CLL: variable proportion of atypical lymphocytes |

| 3. Characteristic immunophenotype |
| Smlg+/-, CD5+, CD19+, CD20+, CD23+, FMC7−, CD22+/− |

| 4. Bone marrow infiltration |
| > 30% lymphocytes in bone marrow aspirate, or consistent pattern in bone marrow biopsy |

Refs. [46–48].
Although atypical CLL cases do exist, these should not be accepted without carefully ruling out other chronic lymphoproliferative disorders with leukemic expression. In this regard, the analysis of the immunophenotype of the leukemic cells as well as their cytogenetic and molecular biology features may be of help in the diagnosis of difficult cases (Table 2), as it can be in the histological study of lymph nodes or spleen.

In practice, it might be useful to distinguish a 'morphologically atypical' CLL (i.e., with atypical lymphocytes but a typical immunophenotype) and an 'immunophenotypically atypical CLL' (i.e., with typical morphology but atypical cell markers such as strong SmIg, CD5-, FMCh+, CD1lc+, etc). In this context, prolymphocytic leukemia should be considered as a separate entity rather than an atypical form of CLL.

**Therapy**

*When to treat*

Owing to their age, patients with CLL may also have other chronic diseases, which may preclude intensive treatment approaches. In younger patients, on the other hand, age by itself should not be considered as criterion for treatment.

The median survival of patients with CLL has increased from about 5 years in the early seventies to about 10 years; this is basically a result of the larger proportion of patients currently diagnosed when asymptomatic, in an early phase of the disease. Since survival of patients with CLL is highly variable, treatment decisions must be made taking into consideration the individual risk of each patient and whether symptoms related to the disease are present.

Clinical stages [54–56] are the most important prognostic factors (Tables 3 and 4). The major limitation of clinical stages is that the mechanisms through which cytopenias appear (e.g., bone marrow failure because of bone marrow infiltration by lymphocytes, autoimmune cytopenias, hypersplenism) are not considered separately.

In other words, criteria to define clinical stages do not necessarily reflect the tumor burden. Besides clinical stages, there are other important prognostic parameters such as the degree of bone marrow infiltration [57–59], blood lymphocyte levels [60], blood lymphocyte doubling time [61], lymphocyte morphology [62], and cytogenetic abnormalities [14]. Some of these parameters may add discriminant power to clinical stages. For example, patients in early stage with heavy bone marrow infiltration or rapidly increasing blood lymphocyte counts are likely to have progressive disease, whereas those with nonmassive bone marrow involvement and low, stable blood lymphocyte levels of the disease tend to have an indolent and nonprogressive (smoldering) disease [63]. A similar discriminant power has been claimed for thymidine-kinase, LDH, CD23, ICAM-1, and β-2-microglobulin serum levels [64–67], although the prognostic value of these markers should be studied further. It is possible that in the future a clinicobiological system (i.e., a system combining clinical and biological parameters) can replace the current staging systems based on clinical and routine analytical data.

The situations that justify therapy in CLL are the following: presence of general symptoms (i.e., weight loss, fever, night sweats), increasing anemia or throm-

### Table 2  
**Mature B-cell lymphoid malignancies: immunophenotype, cytogenetic, and molecular features.**

<table>
<thead>
<tr>
<th>SmIg</th>
<th>CD5</th>
<th>CD43</th>
<th>CD22</th>
<th>CD23</th>
<th>CD25</th>
<th>FMCh</th>
<th>CD103</th>
<th>CD1lc</th>
<th>CD10</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLL</td>
<td>-/+</td>
<td>+</td>
<td>+</td>
<td>-/+</td>
<td>+</td>
<td>+/-</td>
<td>-/+</td>
<td>-/+</td>
<td>-/+</td>
</tr>
<tr>
<td>Lymph</td>
<td>++</td>
<td>-/+</td>
<td>+/-</td>
<td>+/-</td>
<td>+</td>
<td>-/+</td>
<td>+</td>
<td>+</td>
<td>+/-</td>
</tr>
<tr>
<td>PL</td>
<td>++</td>
<td>-/+</td>
<td>+/-</td>
<td>-/+</td>
<td>-/+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+/+</td>
</tr>
<tr>
<td>HCL</td>
<td>++</td>
<td>-/+</td>
<td>+/-</td>
<td>+/-</td>
<td>+/-</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+/+</td>
</tr>
<tr>
<td>SLVL</td>
<td>++</td>
<td>-/+</td>
<td>+/-</td>
<td>+/-</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+/+</td>
</tr>
<tr>
<td>MZL</td>
<td>++</td>
<td>-/+</td>
<td>+/-</td>
<td>+/-</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+/+</td>
</tr>
<tr>
<td>MCL</td>
<td>++</td>
<td>+</td>
<td>+</td>
<td>-/+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+/+</td>
</tr>
<tr>
<td>FL</td>
<td>++</td>
<td>-/+</td>
<td>+/-</td>
<td>-/+</td>
<td>-/+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+/+</td>
</tr>
</tbody>
</table>

All express pan B-cell markers (e.g., CD19, CD20) and HLA-DR class II antigens. Owing to their age, patients with CLL may also have other chronic diseases, which may preclude intensive treatment approaches. In younger patients, on the other hand, age by itself should not be considered as criterion for treatment.

**Table 3. Chronic lymphocytic leukemia Rai staging system**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
<th>Median survival (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>lymphocytosis alone</td>
<td>14.5</td>
</tr>
<tr>
<td>I</td>
<td>lymphocytosis</td>
<td>7.5</td>
</tr>
<tr>
<td>II</td>
<td>lymphocytosis lymphadenopathy</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>lymphocytosis spleen and/or liver enlargement</td>
<td>2.5</td>
</tr>
<tr>
<td>IV</td>
<td>lymphocytosis anemia (Hb &lt; 11 g/dl)</td>
<td></td>
</tr>
<tr>
<td>V</td>
<td>lymphocytosis platelet &lt; 100 x 10^9/l</td>
<td></td>
</tr>
</tbody>
</table>

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bocytopenia due to bone marrow failure, bulky lymphadenopathy, extensive splenomegaly causing compressive problems or hypersplenism, hypogammaglobulinemia with repeated infections, autoimmune cytopenias, rapidly increasing blood lymphocyte counts in peripheral blood, and diffuse bone marrow involvement. Although all these situations require treatment, chemotherapy is not necessarily the most appropriate treatment in all of the cases, as discussed below.

How to treat

Patients with low-risk disease
Treatment of patients in early stage (Binet A, Rai O) has resulted in a delay in the rate of disease progression but no survival benefit [68–73]. In fact, early treatment has been shown to have a detrimental effect on survival in some studies [70]. Therefore, patients with early and stable disease should be observed at three- to six-month intervals and should be treated only in case of disease progression.

Patients with intermediate- and high-risk disease
A proportion of patients in intermediate-risk stage (Rai I,II, Binet B) have an indolent disease; these patients may be followed with no therapy as are those with low-risk disease. Nevertheless, the majority of patients with intermediate stages of the disease and virtually all patients with advanced stage (Rai III, IV, Binet C) due to bone marrow infiltration eventually require therapy. Over the last two decades, chlorambucil (e.g., 0.4–0.8 mg/kg orally every two weeks) has been the treatment of choice [68]. The combination of chlorambucil plus prednisone does not appear to be superior to chlorambucil alone [71, 72]. In a series of studies from the same group, high-dose chlorambucil (10–15 mg daily until complete remission or toxicity) has given excellent results. In one of these trials, response rates obtained with high-dose chlorambucil (89.5%) were significantly superior to those achieved with a modified CHOP regimen (75%) (P < 0.001), and survival was also significantly longer (median, 68 months vs. 47 months; P < 0.005) in patients treated with high-dose chlorambucil [74, 75]. These studies, besides showing a dose-response relationship for chlorambucil in CLL, have opened the door to further trials using this approach in CLL treatment.

Patients treated with combination chemotherapy regimens achieve higher response rates than those treated with chlorambucil at standard doses, but this does not translate into longer survival [68, 72, 76–80]. Nevertheless, frontline treatment with combination chemotherapy (e.g., CHOP) may be indicated in tumor forms of the disease with compressive problems, a setting in which a rapid response is desirable; to that purpose, local radiotherapy may also be useful [33]. For patients failing frontline therapy, particularly fludarabine (e.g., 25 mg/m² i.v. daily for five days every four weeks) and 2-CDA (e.g., 0.10 mg/kg i.v. daily for seven days every four weeks), are considered the treatment of choice, with response rates of 40%–60% [68, 81–83]. The number of previous treatments, prior response to therapy, patient age, general status, serum albumin, and β₂-microglobulin levels correlate with the response to fludarabine in previously treated patients [68, 81–83]. At present, front- line therapy with fludarabine or other purine analogs should only be considered if forming part of clinical trials. The role of purine analogs in CLL therapy is further discussed below.

Patients with cytopenias due to immune mechanism
These patients – i.e., stage C (III,IV) immune – should be treated initially with corticosteroids (e.g., 40–60 mg/day) with cytotoxic agents added only in case of no response after two to four weeks of treatment. In patients with autoimmune hemolytic anemia not responding to or difficult to control with corticosteroids plus cytotoxic agents, high-dose immunoglobulin or cyclosporine may be tried. A proportion of these patients, however, eventually require splenectomy or low-dose spleen radiation [84]. Pure red-cell aplasia (PRCA) may occasionally be associated with CLL; good treatment results have been reported with cyclosporine [85].

Patients with hypersplenism
In such cases, splenectomy or low-dose radiotherapy of the spleen may be of benefit.

Therapy of systemic complications
Hypogammaglobulinemia is frequent in CLL (40%–50% of patients) and is the major cause of infections, which are the first cause of death and a significant cause of morbidity. In a placebo-controlled randomized study, 400 mg per kg of immunoglobulin given intravenously at intervals of three weeks for one year was found to be effective [86]. Cost-benefit considerations, however, make the routine use of immunoglobulin in all patients with hypogammaglobulinemia questionable [87]. Lower doses of immunoglobulin (e.g., 18 g every three weeks, 10 g every three weeks, 250 mg/kg every four weeks) might be as effective as higher doses [88–90]. The role of oral antibiotics as prophylaxis has not been investigated. Vaccines are considered to produce a suboptimal response because of the impairment of the immune system. As in

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**Table 4. Chronic lymphocytic leukemia Binet staging system.**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
<th>Median survival (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>No anemia, no thrombocytopenia</td>
<td>14</td>
</tr>
<tr>
<td>B</td>
<td>Less than 3 lymphoid areas enlarged</td>
<td>5</td>
</tr>
<tr>
<td>C</td>
<td>Anemia (Hb &lt; 10 g/dl) and/or platelets &lt; 10 x 10⁹/l</td>
<td>2.5</td>
</tr>
</tbody>
</table>

* Lymphoid areas considered are cervical, axillary, and inguinal lymphadenopathies (whether uni- or bilateral), spleen, and liver. Reproduced from ref. [9] with permission.
other settings, recombinant hemopoietic growth factors may overcome neutropenia related to treatment [91]. Finally, erythropoietin may be useful to treat anemia unresponsive to other measures [92].

**Disease transformation**

In 3%-10% of patients, CLL evolves into a large-cell lymphoma (Richter’s syndrome). The appearance of progressive lymphadenopathy or splenomegaly, fever, night sweats, and increased LDH levels should raise the possibility of disease transformation. Although the prognosis of such an event is usually poor (median survival, less than six months), patients responding to combination chemotherapy regimens may have longer survival [93].

**New treatment approaches**

**Purine analogs**

Deoxycorticovycin (Pentostatin), fludarabine (Fludara), and 2-chlorodeoxyadenosine (Cladribine) are related purine analogs with high activity in CLL [83, 94-98]. Unfortunately, there are no studies comparing the relative merits of the different purine analogs in CLL therapy. In single-arm, uncontrolled studies, high response rates have been reported with both fludarabine [81-83] and 2-chlorodeoxyadenosine [83, 97, 98] in patients with and without prior therapy.

The preliminary results from a large randomized study comparing fludarabine vs. chlorambucil in previously untreated patients show a higher CR rate for fludarabine (40/120 33%) than for chlorambucil (9/113, 8%) (P < 0.0001), with the proportion of PR being the same (45/120, 38%, and 40/113, 38%, respectively) [94]. The follow-up of this series is still too short to see whether the higher CR rate obtained with fludarabine will translate into a longer survival. Likewise, in a recently reported trial in which fludarabine has been compared to CAP (cyclophosphamide, doxorubicin, prednisone) in the treatment of patients with intermediate- and high-risk stage CLL (Binet’s B and C stage) a higher response rate to fludarabine was observed in both untreated (71% vs. 60%, P = 0.26) and pretreated (48% vs. 27%, P = 0.036) cases. In the latter group, however, remission duration and survival did not differ between treatment groups, with a median remission duration of 324 days after fludarabine and 179 days after CAP (P = 0.22) and median survival times of 728 and 731 days, respectively. In untreated cases, on the other hand, fludarabine induced significantly longer remissions than CAP, with the median not yet reached after fludarabine and a median of 208 days after CAP (P < 0.001); this effect also translated into a tendency toward a longer overall survival after fludarabine (P = 0.087) [96].

Taken together, these results are encouraging, but currently frontline therapy with fludarabine or other purine analogs should only be considered if forming part of clinical trials. In this context, purine analogs are also being investigated in combination with other drugs (e.g., cyclophosphamide, platinum, etoposide) [83].

The most important side effects of purine analogs are myelosuppression and infections; the latter seem to be more frequent in patients receiving corticosteroids in whom infections due to opportunistic organisms (e.g., legionella, *Pneumocystis carinii*, toxoplasma, listeria) may be observed [99]. This is attributed to the decrease in CD4 lymphocytes caused by these agents. Many groups use some type of antibiotic prophylaxis (e.g., cotrimoxazole, inhaled pentamidine) in patients receiving purine analogs; this is a reasonable approach although there is no formal proof of its effectiveness. Other side effects of concern are the triggering of autoimmune hemolytic anemia [100, 101] and the tumor lysis syndrome [102]. In addition, several cases of transfusional acute graft-versus-host disease have been reported in patients treated with fludarabine [103, 104], which raises the point as to whether blood products should be systematically irradiated in patients receiving purine analogs.

**Biotherapy**

Monoclonal antibodies (MoAbs), either alone (e.g., CAMPATH) or conjugated with toxins (B4-blocked ricin), cytotoxic agents, or radioisotopes (113I) are being investigated; the response is usually partial and transient. MoAbs might be useful to eliminate residual disease in patients achieving good response after chemotherapy [105-108]. Interferon-α (IFN-α) has only demonstrated activity in patients with early disease and no prior therapy, although no CRs are obtained [109]. Whether IFN-α prolongs responses achieved with fludarabine has not been explored in large randomized trials; data reported up to now have given either negative results [110] or some indication toward a beneficial effect of IFN-α in terms of remission duration [111]. This issue should be investigated further. Interleukins (e.g., IL-2, IL-4, IL-6) as well as antisense oligonucleotides are also under study [112-114].

**Transplantation of hematopoietic precursors**

Transplants, both allogeneic and autologous, are increasingly performed in CLL patients [115-117]. In the most recent update of the cases collected by the European and International Bone Marrow Transplant Registries [115], the CR rate in 70 patients autografted was 76%, and in 29 patients autografted 83%, although in the latter group the CR rate of patients who were not transplanted in CR was only 27%. The relapse rates were 11% and 17% in the autografted and the autografted group, respectively. In turn, the five-year survival probability was 42% in patients submitted to allogeneic transplants and 52% in those receiving autotransplants. Of note, 50% of the patients autotransplanted died as a consequence of treatment-related complications, whereas only 7% of the autografted patients did [115]. The higher mortality of autografted patients in this series as compared to that found in single-center studies most likely reflects differences in selection criteria [116, 117]. Interestingly, a likely graft-versus-CLL effect has been recently described [118]. Cytofluorometry and/or molecular biology techniques demonstrate that some of the remissions achieved after trans-
plant are molecular, with no evidence of residual disease [115, 119].

Although the role of transplants in CLL treatment has not yet been defined, the possibility of performing a transplant should be considered in any young patient with high-risk CLL. Since responses achieved with purine analogs may be not only complete but also molecular (e.g., without evidence of residual disease by cytfluorometry and molecular biology studies), autotransplants are increasingly likely to be performed in patients with CLL. All transplanted patients should be reported to the International Registries for a meaningful analysis. In this context, it is also worth emphasizing that younger age by itself is not a criterion for transplantation.

Treatment goals

To prolong survival is the most important aim in CLL therapy. However, since there are subjects with CLL in whom the disease does not affect survival, treatment should not be decided without taking risk factors into consideration. In the majority of the patients with CLL needing treatment, the most reasonable aim is to obtain the highest response with an acceptable toxicity. However, in young patients with poor risk factors, experimental approaches with the cure of the disease as the objective are warranted.

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Correspondence to:
E. Montserrat MD
Hematology Service & Postgraduate School of Hematology 'Farreras Valenti'
Department of Medicine
Hospital Clinic
Villarroel, 170 - 08036 Barcelona
Spain