Introduction

Chronic lymphocytic leukemia (CLL), the most prevalent adult leukemia in the Western world, is characterized by the progressive accumulation of mature B cells, and its clinical course is very heterogeneous. Therefore, the identification of prognostic and predictive factors for CLL is critical and this is a field of active investigation. Genetic abnormalities in particular have the potential to serve as prognostic factors in CLL.

Until recently, the low mitotic index of most CLL cells made the use of metaphase cytogenetics difficult, even when metaphases could be generated, because the cellularity was often poor, and abnormalities were detected in only 40-50% of cases. Recently, analyzable karyotypes have been obtained in patients with CLL using mitogenic stimulation of CLL specimens with CpG oligonucleotides. Furthermore, the analysis of aberrant chromosomal regions using specific DNA probes through fluorescence in situ hybridization (FISH) has made it possible to detect clonal aberrations in more than 80% of CLL patients.

The most common chromosomal abnormalities identified by FISH in CLL are 13q14 deletion (del13q), trisomy 12 (+12), 11q23.3-q23.1 deletion (del11q), and 17p13 deletion (del17p). A recently published prospective cohort study of 1494 patients across 199 US centers has shown that del13q is present in approximately 46% of CLL cases, and +12 is present in 21% of CLL cases. Del17p and del11q are observed in fewer cases: 12% and 18% of CLL cases, respectively. The frequency of detection of each chromosomal abnormality is influenced by several factors, such as the methods and probes used, the frequency of neoplastic B cells in the specimen analyzed, and the cohort of patients investigated.
Here, we review the unique morphological, immunophenotypic, and genetic characteristics of patients with CLL carrying +12.

Cytogenetic abnormalities concomitant with +12

+12 is the second most frequent cytogenetic abnormality identified by FISH in patients with CLL, occurring in 16% of these patients at the time of initial evaluation. When identified by FISH, +12 is the sole aberration in approximately 70% of +12 CLL cases; +12 has been associated with del13q, del11q, or del17p in 18%, 8%, and 4% of +12 CLL cases, respectively. When identified by chromosome banding analysis, +12 is the sole abnormality in 80% of +12 CLL cases, but it can be associated with trisomy 18 (5% of cases) or del11q (5% of cases); associations with t(14;19)(q32;q13), trisomy 19, del17p, del15q, and del11q have also been reported.

+12 is more frequent in patients with small lymphocytic leukemia than in those with CLL (28-36% vs. 13-16%). In fact, increased +12 frequency and reduced del15q frequency may represent specific features of small lymphocytic lymphoma with a different prognosis and may distinguish it from classical CLL.

+12 as a single aberration in CLL confers an intermediate prognostic risk, with a median time to first treatment (TTFT) of 33 months and a median overall survival time (OS) of 114 months. +12 is associated with additional chromosomal abnormalities, including t(14;18)(q32;q21) and trisomy 18, portends a poor prognosis independent of NOTCH1 mutation, which is more common in cases with isolated +12. Patients with CLL who develop Richter syndrome have a particularly poor prognosis, and +12 is frequent in patients with this syndrome, with an incidence of up to 50%. Yi et al. retrospectively analyzed 350 non-selected CLL patients, using a panel DNA probe to detect cytogenetic abnormalities by FISH, 70 patients were positive for +12. In patients who carried a favorable or neutral cytogenetic abnormality, including +12, the co-occurrence of several chromosome abnormalities associated with shorter TTFT and OS. However, in patients with adverse cytogenetic abnormalities, such as del17p or del11q, the co-occurrence of a favorable or neutral clone, including again +12, portended an improved prognosis. This study challenged the classical hierarchical FISH classification used in CLL, highlighting the prognostic relevance of the intra-tumoral cytogenetic heterogeneity.

+12 is not related to a specific abnormality. However, +12 as a ‘driver’ mutation can facilitate the appearance of NOTCH1 and FBXW7 mutations: disruptions of FBXW7 function may lead to constitutional activation of NOTCH1 and then to cell proliferation and evasion from apoptosis. The presence of abnormalities of FBXW7 may be implicated in the pathogenesis of the CLl and determine the selection of treatment-resistant clones.

Cytopenia in patients with +12 CLL

Cytopenias are common in patients with +12 CLL. It has been reported that up to 24% of patients with +12 CLL will develop cytopenias during the course of their disease. Cytopenias in CLL can result from either bone marrow failure or autoimmune disease. Two studies showed that CLL patients with +12 have a higher incidence of autoimmune cytopenias than infiltrative cytopenias.

Morphological features of patients with +12 CLL

Atypical morphology, defined as the presence of cleaved nuclei and/or lymphoplasmacytoid features in more than 15% of cells, can be observed in up to 20% of patients with CLL. Several studies have revealed that +12 is the most common cytogenetic abnormality in these cases.

Athanasiadou et al. evaluated the presence of atypical and typical CLL morphology in a population of 100 CLL patients. In the +12 subgroup, 17 of the 23 cases analyzed (74%) were considered morphologically atypical. Atypical morphology was also frequent in the del11q/del17p subgroup (5 of 7 cases, 71%). All del13q cases and 45 of 51 cases (88%) with normal karyotypes had typical morphology.

Ruptured B cells, or smudge cells, are commonly seen in blood smears of patients with CLL. Levels of smudge cells have been correlated with low CD45 expression on CLL cells by flow cytometry. Smudge cells are believed to reflect intrinsic CLL cell fragility and cytoskeletal abnormalities, linked to reduced expression of vimentin, and some authors have proposed using percentages of smudge cells to stage CLL. In patients with +12 CLL, fewer smudge cells are observed than in patients with CLL overall, along with normal levels of CD45 expression.

Immunophenotype of patients with +12 CLL

Chronic lymphocytic leukemia patients show an immunophenotypic panel that is typically CD5+, CD23-, FMC7-, surface immunoglobulin (sIg)d-, CD20+, sIgM-, CD19+, CD79b+, CD24, CD27, CD79a+, CDS8-, CD38-, CD43. Among various cytogenetic subgroups, the atypical immunophenotypic pattern identified in overall CLL patients was more frequent in the +12 and del17p subgroups and less frequent in the del13q subgroup; the del11q subgroup presented an equal distribution of the typical and atypical patterns.

An atypical immunophenotype can be defined using the Matutes score, which is calculated from the following cell surface markers: positive expression of CD5 and CD23, negative expression of FMC7, and weak expression of CD22 and slg. A modification of the scoring system, called the modified Matutes score, replaces CD22 with CD79b, and this score is considered atypical if less than 4. Interestingly, with the modified Matutes score, +12 defines a subgroup of CLL with more frequent atypical morphology than with the original scoring system.

CD38

CD38 expression is significantly more frequent in the +12 and del11q/del17p subgroups of CLL patients (10 of 26 cases and 5 of 10 cases, respectively) than in patients with normal karyotype or in the del13q subgroup of CLL patients (10 of 72 cases and 1 of 5 cases, respectively). High CD38 expression on CLL cells has been used as a
surrogate marker of unmutated IGHV genes. When the threshold for CD38 positivity was set at the standard 50%, higher expression of CD38 was not associated with a significantly impaired TTFT, but a threshold of 40% for CD38 expression retained its prognostic value for TTFT (P=0.008); so the threshold of CD38 positivity may be raised to 40% in +12 CLL cases to preserve its prognostic value. CD38 inhibitors may have particular efficacy in this cytotagentic subtype. CD38 also showed higher expression among CLL cases with both +12 and del11q, which could explain the adverse prognosis of this subgroup compared to CLL patients with +12.

ZAP-70

The negative prognostic impact of ZAP-70 expression and the association of ZAP-70 with unmutated IGHV are maintained in patients with +12 CLL.

CD20

CLL patients with +12 have higher expression of CD20 than CLL patients with del17p, del11q, del13q, or negative FISH results; this expression of CD20 may predict a better response to rituximab-based regimens.

FMC7

FMC7, an epitope on the CD20 molecule itself, is significantly (P=0.035) more frequent in the +12 subgroup of CLL (32.0%) than in the del13q CLL subgroup, normal patients, and the del11q/del17p CLL subgroup (which 20.0%, 11.1%, and 10.0% were FMC7 positive, respectively).

CD49d

CD49d is expressed in a vast majority of +12 CLL cases and emerged as a negative prognostic factor. Using a 30% cut off, an analysis was performed on 1200 CLL patients: 735 cases (61.2%) were CD49d-, whereas 465 cases (38.8%) were CD49d+. A significantly (P<0.001) higher percentage of cases were CD49d+ (89.4%) in the +12 subgroup than in the other cytogenetic subgroups. Among the CD49d- CLL patients, those with +12 expressed CD49d at higher mean fluorescence intensity (MFI) levels [median MFI 2200; 95% confidence interval (CI) 1810-2546] compared with patients without +12 (median MFI 1386; 95%CI: 1050-1673; P<0.001). CD49d overexpression in +12 CLL is associated with ITGA4 hypomethylation, as shown by quantitative real-time polymerase chain reaction analysis in 74 CLL patients (51 patients who were CD49d- and lacked +12, and 43 patients who were CD49d+ and had +12). Patients with +12 who were CD49d+ showed a shorter TTFT than that of patients with +12 who were CD49d- (P<0.001). A specific tropism of +12 CLL cells toward lymph nodes has been confirmed by the higher proportion of +12 CLL cells in lymph nodes than in peripheral blood or bone marrow. CD49d overexpression may provide a molecular basis for the peculiar biological behavior of +12 CLL and may predict the development of additional cytogenetic lesions.

Adhesion molecules

Other cell surface markers with a possible prognostic role in +12 CLL are CD25 (also called activation-associated interleukin-2 receptor), which has a role in B-cell proliferation; CD54 (i.e. intercellular adhesion molecule-1), which has a role in cell adhesion and in the homing process; and CD95 (i.e. FasR), which has a role in regulation of apoptosis in lymphoid tissues. Patients with levels of 50% or higher of CD25+ B-CLL cells had a shorter median TTFT (P=0.01). Low CD54 expression was associated with a prolonged median TTFT (P=0.004), low leukocyte count (P<0.05), and low serum lactate dehydrogenase level (P=0.08). CD54 could be a prognostic marker for CLL and might be a determinant of whether patients present with localized or widespread lymphadenopathies. High CD95 expression has been correlated with elevated serum lactate dehydrogenase level (P=0.02) and lymphadenopathy (P=0.02). Haljmar et al. correlated these markers on CD19+ cells with the occurrence of +12 and atypical lymphocyte morphology. They found that the mean percentage of CD25+ B cells in CLL with atypical morphology and in patients with +12 was lower than that in CLL with typical morphology (P<0.02) and in patients with dicosmic tumor cells

Integrins

Circulating +12 CLL cells show increased expression of the integrins CD11b, CD18, CD29, and ITGB7, and of the adhesion molecule CD323 compared with other CLL cytogenetic groups. These changes are modulated by NOTCH1 mutation status; NOTCH1-mutated +12 cases have lower expression of CD11a, CD11b, and CD18 than wild-type cases. +12 CLL cells also have upregulation of signaling pathways that increase ligand binding and enhance VLA-4–directed adhesion and motility. Also, increased expression of the α-integrins CD11a and CD11b was associated with a shortened TTFT (P=0.002 for CD11a; P=0.027 for CD11b). The presence of NOTCH1 mutations in the context of +12 was associated with decreased CLL cell expression of CD11a, CD11b, and CD18 to levels similar to those of CLL cells without +12. Notably, the presence of a NOTCH1 mutation had no impact on CD29, CD49d, or ITGB7 expression on CLL cells. The observed heterogeneity of expression of β-integrins in +12 CLL cases can be explained largely by the presence of NOTCH1 mutations. The expression of the β-integrins CD11a/CD18 (LFA-1) and CD11b/CD18 (Mac-1) is down-regulated by the co-existence of NOTCH1 mutations, indicating a novel interaction that may be of importance in aggressive, high-risk CLL.
Stereotyped B-cell receptor prevalence in patients with +12 CLL

Recrrent ‘stereotyped’ patterns \(^{75,76}\) known as subsets, have been reported in +12 CLL patients, including a higher prevalence of IGHV 4-39 gene, commonly in patients who developed Richter Syndrome. \(^{77,79}\) Falisi et al. highlighted the fact that 44% of +12 CLL patients carried stereotyped B-cell receptor and found a significantly higher prevalence of stereotyped IGHV configurations in +12 CLL patients than in controls (27%; \(P=0.01\)). The most prevalent stereotyped subset was subset #1, followed by subsets #6, #10, #28 and #59. The most frequently observed IGHV gene was V4-39*01, followed by V1-3*01. IGHV 4-39*01 was the most common gene in +12 CLL patients in the literature, confirming the strong association between +12, IGHV 4-39*01 stereotype, and Richter syndrome.\(^{77-80}\)

Immunoglobulin heavy chain mutational status in patients with +12 CLL

Chronic lymphocytic leukemia subgroups with del11q/del17p and +12 showed greater percentages of unmutated IGHV cases (80.0% and 53.3%, respectively) than those with del13q or with normal karyotype (37.5% and 31.5%, respectively).\(^{81}\) Cytogenetic subgroups also showed differences in the IGHV repertoire: IGHV4 genes were observed more frequently in the +12 subgroup (26.9%) than in other subgroups (20.0% in del11q/del17p and in del13q subgroups and 12.3% in the normal karyotype). IGHV4 genes were noted at similar frequencies in the +12 subgroup and in the normal group (34.6% and 30.1%, respectively), and they were not identified in any cases in the del11q/del17p subgroup.\(^{82}\)

Molecular abnormalities in patients with +12 CLL

Chronic lymphocytic leukemia patients with +12 or normal karyotype at diagnosis have an approximately 2-fold higher probability of developing poor-risk genetic lesions and entering the intermediate- or high-risk subgroups associated with shorter survival, compared with low-risk CLL patients harboring del13q only.\(^{83}\) Chronic lymphocytic leukemia patients with +12 rarely show TP53 mutations or acquire them over time.\(^{84,85,86}\) On the contrary, NOTCH1 mutations can be identified in 50-40% of CLL patients carrying +12.\(^{87,88}\) NOTCH1 is a human gene encoding a single-pass transmembrane protein, whose signaling network regulates interactions between physically adjacent cells. Following the pivotal study that identified NOTCH1 mutations in CLL and provided initial evidence on the unfavorable clinical outcome associated with NOTCH1 alterations,\(^{89}\) two additional independent studies of the CLL coding genome have identified activating mutations of NOTCH1 gene in approximately 10% of CLL at diagnosis.\(^{90,91}\) The biological contribution of NOTCH1 mutations in determining the aggressive behavior of CLL could be due to the over-representation of genes involved in the cell cycle and proliferation. In at least four series, NOTCH1 mutations had an adverse impact on outcome independently of other clinicobiological features.\(^{92,93}\) In an analysis by Del Giudice et al.,\(^{94}\) NOTCH1 mutations clustered within 104 untreated +12 CLL patients accounted for 24% of those cases, and were frequently detected in cases with unfavorable biological markers, associated with a particular gene expression profile predicting a poor outcome. NOTCH1 mutations are not associated with TP53 disruption or del11q; this mutual exclusivity could be useful in a genetic hierarchical prognostic model.\(^{95}\) NOTCH1 mutations were preferentially associated with unmutated IGHV (84% of cases; \(P=0.003\)).\(^{96}\) NOTCH1 mutations were not associated with sex or ZAP-70 positivity (mutated NOTCH1 cases were 62.5% ZAP-70\(^{+}\), and wild-type NOTCH1 cases were 44.2% ZAP-70\(^{+}\); \(P=0.116\)). NOTCH1 mutations have been reported at CLL diagnosis in approximately 20% of chemoresistant cases.\(^{96}\) NOTCH1 mutations conferred a higher cumulative probability of Richter syndrome.\(^{97,98}\) The impact of NOTCH1 mutations on prognosis is less relevant in the presence of concurrent chromosomal aberrations, as worse outcomes are observed among patients with +12 associated with additional chromosomal abnormalities irrespective of NOTCH1 mutation status.\(^{99}\)

Landau et al. have published the results of a large retrospective cohort study using whole-exome sequencing to analyze the frequency of somatic mutation and copy number abnormalities in 160 patients with CLL. They found that favorable alterations, such as MYD88 mutation, del13q and +12, represented early clonal drivers of disease; instead, more unfavorable alterations, such as ATM, TP53 and SF3B1 mutations, were subclonal during the early stages of disease, and became clonal at time of first treatment or treatment failure. The same group has more recently published prospective genetic data collected from 278 patients with CLL; while confirming previously published retrospective data, this study found also an association between +12 and mutations in BIRC3 and BCOR. Interestingly, neither BIRC3 nor BCOR mutation was associated with worse survival, in contrast to what had previously been published in smaller studies.\(^{100,101}\)

Maura et al. studied the association of CLL with IGFIR expression.\(^{102}\) IGFIR-IGF1/2 interaction is involved in intracellular signaling pathways such as RAS/RAF/MEK/ERK kinases and PI3K-Akt. IGFIR, which is implicated in the activation of the PI3K/Akt and MAPK pathways, was generally over-expressed in CLL cells compared with healthy B cells.\(^{103}\) IGFIR expression was strongly associated with unfavorable/intermediate-risk cytogenetic features, in particular +12, independently from unmutated IGHV, NOTCH1 mutation, or clinical monoclonal B-cell lymphocytosis status. Thus, IGFIR represents a potential novel candidate for specific targeted therapy in +12 CLL patients. In a prospective series, a group of +12 patients, showing low IGFIR expression, mutated IGHV, and wild-type NOTCH1 status had an indolent clinical course, whereas the others, characterized by unmutated IGHV and/or high CD38, mutated NOTCH1, and high IGFIR, had a more aggressive evolution and shorter TTFI. Thus, IGFIR may have a role in discriminating aggressive CLL from intermediate-risk or favorable CLL in the presence of +12.\(^{104}\)

The overexpression of A TF5 in CLL was significantly \((P<0.001)\) associated with chromosomal abnormalities including del11q and +12.\(^{105}\) ATF5 is known for its role in the regulation of cell cycle progression and of differentiation and apoptosis. ATF5 overexpression was most com-
TTF and OS in patients with +12 CLL

Few reports detail the clinical outcomes of CLL cases with +12. Characteristics of the patients in these main series are summarized in Table 1.23,32,33,44 Here, we review data from the two largest series of patients with +12 CLL published so far. Outcomes from these studies are summarized in Table 2.

A multicenter analysis by González-Gascón y Marín et al. included 2561 patients diagnosed with CLL from 25 Spanish institutions, of whom 289 (11.3%) patients showed +12 at diagnosis; the analysis excluded patients with monoclonal B-cell lymphocytosis, patients who acquired +12 as clonal evolution, and patients with inadequate follow up.23,33,34 +12 patients had a median TTF of 42 months (95% CI: 34-49 months) and a median OS of 129 months (95% CI: 100-158 months). The findings in this series are similar to those of previous studies that included a lower frequency of +12 cases, approximately 15-20%, with a median TTF of 32 months and a median OS of 111 months.33 These patients were a median 68 years old, were predominantly male, and had a high frequency of low lymphocyte counts (53%), low β2microglobulin level (71%), early Binet stage (71%), low levels of CD38 (63%), and an absence of significant organomegaly.

González-Gascón y Marín et al.23 correlated the proportion of +12 CLL cells with prognosis and identified 60% as the cut-off value associated with survival. One hundred and seventy-four patients (60.2%) carried +12 in less than 60% of cells, whereas 115 patients (39.8%) carried +12 in 60% or more of cells. The patients with +12 in 60% or more of cells had more marked leukocytosis (P=0.001), higher lymphocyte counts (P=0.006), higher levels of serum lactate dehydrogenase (P=0.03), more pronounced splenomegaly (P=0.001), and more advanced Binet stage (P=0.04). In the cohort of 289 +12 patients, 175 (60.6%) required treatment initiation. The patients with +12 in less than 60% of cells had a lower rate of treatment initiation and longer TTF (51.2% with a median TTF of 49 months) than did patients with +12 in 60% or more of cells (75.7% with a median TTF of 30 months; P<0.001) in both univariate and multivariate analyses. At the time of analysis, 69 patients (25.9%) had died, and there was a significant difference in frequency of deaths (P=0.009) between patients with less than 60% +12 cells (16.7% with a median OS of 159 months) and patients with 60% or more +12 cells (29.6% with a median OS of 96 months). On multivariate analysis, only Binet stage (P=0.04), del11q in addition to +12 (P=0.01), and high β2microglobulin levels (P=0.08) were significantly associated with shorter OS. TTF and OS were shorter in +12 and del11q patients compared with those with +12 as a unique aberration (25 months vs. 44 months, P=0.02 for TTF; 44 months vs. 159 months, P=0.02 for OS), but no difference could be found in TTF or OS when +12 was accompanied by del17p or del15q.

Strati et al. analyzed a single-center experience of 250 untreated CLL patients with +12 followed for nine years and compared their outcomes with those of 516 treatment-naïve CLL patients who lacked common recurrent abnormalities on FISH analysis (negative for del11q, del13q, del17p, and +12), evaluated at the same institution during the same period.24 On multivariate analysis, factors significantly associated with +12 were a platelet count of less than 100x10^9/L [odds ratio (OR) 2.4; P=0.03], positivity for CD38 (OR 2.4; P=0.001), and a Matutes score of less than 4 (OR 2.4; P<0.001). At a median follow

### Table 1. Clinical and laboratory characteristics at diagnosis of patients with +12 chronic lymphocytic leukemia.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>González-Gascón y Marín (n=289)</th>
<th>Strati (n=250)</th>
<th>Del Giudice (n=104)</th>
<th>Fallisi (n=44)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (range), years</td>
<td>68 (22-88)</td>
<td>60 (32-87)</td>
<td>65 (56-72)</td>
<td>62.8 (45-86)</td>
</tr>
<tr>
<td>Male sex</td>
<td>61.0%</td>
<td>58.8%</td>
<td>54 (52%)</td>
<td>32 (73%)</td>
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<tr>
<td>Binet stage A</td>
<td>71.1%</td>
<td>71%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Binet stage B</td>
<td>23.6%</td>
<td>13%</td>
<td>36% Binet B to C</td>
<td></td>
</tr>
<tr>
<td>Binet stage C</td>
<td>5.4%</td>
<td>16%</td>
<td>36% Binet B to C</td>
<td></td>
</tr>
<tr>
<td>Median white blood cell count, x10^9/L</td>
<td>19 (4.5-294.2)</td>
<td>18 (2-681)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absolute lymphocyte count, &gt;30x10^9/L</td>
<td>16.8%</td>
<td>26.0%</td>
<td></td>
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<tr>
<td>Splenomegaly</td>
<td>15.5%</td>
<td>16.0%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatomegaly</td>
<td>5.7%</td>
<td>6.0%</td>
<td></td>
<td></td>
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<tr>
<td>High β2microglobulin</td>
<td>28.9%</td>
<td>18.1%</td>
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<tr>
<td>Unmutated IGHV</td>
<td>53.8%</td>
<td>55.1%</td>
<td>58.0%</td>
<td>70.6%</td>
</tr>
<tr>
<td>CD38 positivity</td>
<td>37.4%</td>
<td>55.0%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ZAP-70 positivity</td>
<td>55.8%</td>
<td>45.1%</td>
<td></td>
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<tr>
<td>+12 and del11q</td>
<td>3.9%</td>
<td>0%</td>
<td>8.0%</td>
<td>4.5%</td>
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<tr>
<td>+12 and del17p</td>
<td>6.1%</td>
<td>0%</td>
<td>5.0%</td>
<td>2.3%</td>
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<tr>
<td>+12 and del13q</td>
<td>17.0%</td>
<td>17.6%</td>
<td>18.0%</td>
<td>9.1%</td>
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</table>

1High β2microglobulin level defined as above normal range; 2High β2microglobulin level defined as ≥4 mg/L.
up of 51 months (range 1-105 months), 142 patients (56.8%) required initiation of treatment. The median TTFT was 38 months (95% CI: 27-48 months), significantly shorter than that of FISH-negative patients (82 months; P<0.001). The multivariable model for TTFT showed that a Rai stage of III-IV (Hazard Ratio (HR) 3.3; P=0.02), palpable splenomegaly (HR 2.3; P=0.007), and chromosome banding analysis positivity for del14q (HR 3.3; P=0.04) were independently associated with TTFT. The estimated median OS was not reached, as only 18 patients died, and did not differ significantly between patients with or without +12 by FISH (P=0.22).

Followed over time, 6 of these patients (2.4%) developed histologically confirmed Richter syndrome after a median ten months (95% CI: 5-15 months) from diagnosis. This incidence was significantly higher in treated than untreated patients (4% vs. 0%; P=0.04) and in patients with +10 compared with the control cohort of patients with normal karyotype (2.0% vs. 0.4%; P=0.02). Twenty-two patients (8.8%) developed a malignancy other than Richter syndrome after a median of 19 months (95% CI: 6-32 months) from diagnosis. Among second neoplasms, 5 were hematologic malignancies, and 17 were non-hematologic malignancies. In the multivariable model, an absolute lymphocyte count of more than 30x10^9/L (HR 14.5; P=0.04) and development of a second malignant neoplasm (HR 23.8; P=0.002) remained independently associated with OS. A correlation between CLL and second malignant neoplasms has been reported, but the mechanism linking +12 to the onset of second neoplasms remains unknown. Eighteen patients (7.2%) died during the observation time, 15 of whom had received treatment for CLL. Seven patients died of CLL-related (n=4) or Richter syndrome-related (n=3) causes; 6 patients died of second neoplasms, and 5 died of unrelated causes. There was no significant difference in distribution of the causes of death between treated and untreated patients (P=0.24). The mortality of patients with +12 was only partly related to complications of CLL; the leading causes of death were Richter syndrome and second malignant neoplasms. However, given the evidence of a worse outcome for second malignant neoplasms in CLL, increased surveillance of patients in this specific group should be considered.

Conclusions

The unique morphology, immunophenotype, and cytogenetics of +12 CLL easily distinguish it from other CLL cytogenetic subtypes. +12 in CLL confers an intermediate prognostic risk, characterized by a median TTFT of 33 months and a median OS of 114 months. Genomic alterations, especially NOTCH1 mutations, can portend a worse prognosis and an increased risk of Richter syndrome.

Acknowledgments

The authors would like to thank Sarah Bronson, ELS Department of Scientific Publications The University of Texas MD Anderson Cancer Center for editorial assistance.

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Chronic lymphocytic leukemia with trisomy 12


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