Prognostic Information From Cytogenetic Analysis in Chronic B-Lymphocytic Leukemia and Leukemic Immunoctoma


Fifty-five patients with a clonal expansion of B lymphocytes in the peripheral blood were studied. According to the Kiel classification, 22 patients had chronic lymphocytic leukemia (CLL), 29 had immunocytoma (IC), two had prolymphocytic leukemia, and one had centrocytic lymphoma. One patient had dup(12). Fifteen patients showed only normal metaphases. and 12 patients were not evaluated cytogenetically. The cytogenetic subgroup pattern did not distinguish between CLL and IC patients. There was no significant difference between the CLL and IC groups as regards clinical findings and prognosis. However, the cytogenetic typing proved to be of prognostic significance. Increasing numbers of chromosomal aberrations within the cell clone were significantly associated with a poorer prognosis, ie, with impairment of survival (P = .04) and therapy-free survival (P < 10^-4). Patients with complex karyotypes (at least clonal aberrations) showed the poorest survival (P = .007). Patients with + 12 required treatment earlier than patients with a normal karyotype (P = .01) and patients with karyotypic changes other than + 12 (P = .006). These latter differences were even more pronounced when only IC patients were considered (P = .005 and P = .002, respectively). A multivariate analysis revealed that + 12 was as strong an indicator of poor survival as advanced Rai or Binet stages and a stronger predictor of therapy-demanding disease.

CHRONIC LYMPHOCYTIC LEUKEMIA (CLL) is known to be a heterogeneous disease with a highly variable prognosis. In recent studies by the Kiel Lymphoma Study Group, subclassification and definition of immunologic phenotype was claimed to give a better prediction of prognosis in CLL. This also allows consideration of the maturation level and origin of the malignant lymphocytes in relation to their normal counterparts. Thus, by morphologic, cytochemical, and immunophenotypic studies on lymph node, blood, and bone marrow specimens, it is possible to subdivide CLLs into several diagnostic entities, such as CLL of the B cell (B-CLL) and T cell (T-CLL) types, immunocytoma (IC), hairy cell leukemia (HCL), prolymphocytic leukemia of the B cell (B-PLL) and T cell (T-PLL) types, Mb Ségéry, and leukemic states of follicle center-cell-derived lymphomas. Within the classic CLL disease, two major groups belonging to the B cell lineage can be distinguished, namely lymphomas with a homogeneous "lymphocytic" differentiation, ie, CLL "proper," and lymphocytic lymphomas including lymphoplasmacytoid cell variants within the malignant clone, ie, IC. This subdivision appears to be of clinical importance, since patients with CLL had a better prognosis than IC patients, and patients with HCL and PLL may need special treatment.

It is now well known that polyclonal B cell activators can also stimulate malignant B lymphocytes to proliferate in vitro, allowing cytogenetic typing of lymphoblastoid cell lines within the malignant clone, ie, IC. We have also shown that the most frequent cytogenetic abnormality in CLL is an extra chromosome 12, a finding confirmed by other groups. This was shown to be of clinical interest, since it appears to predict a progressive disease with an early need for treatment.

The aim of this study was to investigate the clinical importance of chromosomal aberrations within the Kiel subgroups of leukemic B-lymphocytic lymphomas.

MATERIALS AND METHODS

Patients

Fifty-five patients with a leukemic clonal expansion of nonblastic B lymphocytes were studied. Patients 101 to 120 and 130 have been discussed previously. Thirty-five patients were men and 20 were women. Their ages ranged from 38 to 88 years (median, 67 years). Median blood parameters at sampling were hemoglobin, 124 g/L (range, 70 to 57 g/L); lymphocyte count, 38 x 10^9/L (range, 5 to 320 x 10^9/L); platelet count, 181 x 10^9/L (range, 7 to 430 x 10^9/L). Lymphadenopathy was found in 36 patients, and 24 had splenomegaly. Clinical staging according to Rai showed that 10 patients were at stage 0, 20 were at stage I, nine were at stage II, eight were at stage III, and eight were at stage IV. The staging procedure according to Binet revealed 27 patients at stage A, 10 at stage B, and 18 at stage C. Our criteria for established disease were a persistent lymphocytosis of ≥ 5 x 10^9/L, and/or a stable lymph node.
enlargement, later verified as a lymphoma. All patients were leukemic at the time of diagnosis. The cell surface immunoglobulin phenotype was μ in seven cases, μκ in 22, γλ in six, μκ in five, and μδλ in 12; in three cases either heavy or light chain fluorescence was too weak to permit identification.

Patient care was standardized according to the protocol of the Lymphoma Group of Central Sweden. The treatment protocol was not influenced by chromosome data. Indications for treatment were progressive disease with clear B symptoms (fever, night sweats, or weight loss not the result of other causes), progressive disabling lymphadenopathy, progressive anemia or thrombocytopenia, with hemoglobin levels consistently below 100 g/L or platelet counts decreasing below 100 x 10^9/L. Seven patients had received cytostatic drugs before sampling for cytogenetic analysis: patient 153 was on azathioprine therapy because of a renal transplant 14 months before her CLL diagnosis. Sampling was also performed on three patients (No. 104, 105, 106) treated with chlorambucil–prednisolone orally, and on two patients (No. 132 and 151) who had received chlorambucil for short periods more than two years previously. Patient 176 had been treated for several years with courses of combined chemotherapy, and both PLL patients (No. 132, 138) had received radiotherapy of their enlarged spleens more than two years before the cytogenetic analysis.

**Diagnosis**

Morphology and immunocytochemistry were performed according to the Kiel classification on available histologic specimens. The methods for tissue fixation and histologic staining have been published previously. Lymph node biopsy specimens from 30 patients and spleen biopsy specimens from nine patients were studied. In addition, autopsy specimens from three patients (No. 104, 113, 120) were investigated. Seventeen patients were diagnosed solely on the basis of the examination of bone marrow specimens, including periodic acid-Schiff–stained bone marrow sections. In these cases the diagnosis of IC was based upon the finding of a significant number of lymphoplasmacytoid cells and mast cells in the bone marrow smears.

**Cell Suspensions**

Cell suspensions from lymph nodes and spleens were obtained by gently pressing fresh biopsy material through a stainless steel net into a balanced salt solution (BSS). Lymphocytes were isolated from cell suspensions, heparinized peripheral blood and bone marrow by gently pressing fresh biopsy material through a stainless steel net (from Professor lord Holme, Karolinska Institute) was centrifuged, the cells were resuspended in fixative, dropped onto slides, and then air dried. The cells were then stained by the Q-banding technique. Metaphases of good quality for chromosome analysis were photographed in a Zeiss fluorescence microscope. All metaphases were analyzed by conventional karyotyping. A clonal chromosomal abnormality was defined by one of the following criteria: (1) gain of a specific chromosome in at least two cells; (2) loss of a specific chromosome in at least three cells; or (3) identical structural aberration in at least two cells. The patients were considered to have a normal karyotype if a normal karyotype was found in at least 12 cells and if there was no evidence of a clonal aberration.

**Mitogens**

Cells were activated by Epstein-Barr virus (EBV), lipopolysaccharide from *Escherichia coli* (LPS), and tetradecanoxyphorboleactate (TPA). EBV stimulation was performed by preincubating the cells with 1 mL of supernatant from the B95-8 cell line (from Professor Georg Klein, Karolinska Institute, Stockholm) per 10^7 cells for one hour at 37 °C in humidified air containing 5% CO₂. Thereafter the cells were washed and cultured. LPS from *E. coli* (055:B5) (from Professor Tord Holme, Karolinska Institute) was used at a final concentration of 100 μg/mL. TPA (Sigma Chemical Co, St Louis) was used at a final concentration of 2 x 10⁻⁶ mol/L. In addition, cells from patient 175 were also activated by cytochalasin B (Sigma) and used at a final concentration of 1.0 μg/mL.

**Culture Conditions**

The cells were cultured at a concentration of 2 x 10⁶/mL in Eagle’s medium containing 10% heat-inactivated human AB-serum. Cultures of 4 mL were set up in 50-mL plastic flasks (Falcon 3031, Falcon Plastics, Oxnard, Calif) and incubated at 37 °C in humidified air containing 5% CO₂.

**Chromosome Analysis**

Cell cultures were harvested on day 4. During the last 90 minutes of culture, the cells were treated with colchicine at a final concentration of 0.05 μg/mL. Hypotonic treatment was performed with a 0.56% solution of potassium chloride for five minutes. The cells were then fixed in methanol/acetic acid (3:1) for 40 minutes. After centrifugation, the cells were resuspended in fixative, dropped onto slides, and then air dried. The cells were then stained by the Q-banding technique. Metaphases of good quality for chromosome analysis were photographed in a Zeiss fluorescence microscope. All metaphases were analyzed by conventional karyotyping. A clonal chromosomal abnormality was defined by one of the following criteria: (1) gain of a specific chromosome in at least two cells; (2) loss of a specific chromosome in at least three cells; or (3) identical structural aberration in at least two cells. The patients were considered to have a normal karyotype if a normal karyotype was found in at least 12 cells and if there was no evidence of a clonal aberration.

**Statistical Analysis**

Survival data were analyzed with respect to survival from date of established disease and survival without therapy. The differences in prognosis between the subgroups were analyzed using the log-rank test as described by Petö et al. Furthermore, Cox's regression analysis was used in a multivariate analysis.

**RESULTS**

**Diagnosis**

According to the Kiel classification, 22 patients had CLL, 29 had IC, two had PLL, and one had centrocytic (CC) lymphoma; one was not subclassified. In the 37 cases where histologic specimens were available, there was congruence with regard to diagnosis and immunophenotype in specimens from lymph node and bone marrow. In 17 patients, the diagnosis was based upon the examination of bone marrow specimens only; in two of these the IC diagnosis was corroborated by the presence of a monoclonal serum immunoglobulin spike. Of the remaining 15 patients diagnosed without histologic studies, seven had CLL, seven had IC, and one had PLL.

The CLL and IC groups did not differ significantly with regard to hemoglobin levels, platelet counts, Rai and Binet stage, sex, age, and degree of lymphoedema. The CLL patients, however, had a higher blood lymphocyte count (mean CLL = 79 x 10⁹/L, IC = 46 x 10⁹/L, P = .08), and the IC patients had more splenomegaly (P = .10).

**Prognosis**

Fourteen patients died during the observation period (CLL, six; IC, six; PLL, one; not subclassified, one). The median survival for these patients was 53 months (mean, 46 months; range, four to 85 months; CLL, mean, 45 months; IC, mean, 54 months). Surviving
### Table 1. Clonal Chromosomal Aberrations

<table>
<thead>
<tr>
<th>Patient and Status</th>
<th>Stage at Sampling</th>
<th>Number of Metaphases</th>
<th>Clonal Aberration</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Total</td>
<td>Abnormal</td>
</tr>
<tr>
<td>CLL patients</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>137*</td>
<td>I/A</td>
<td>37</td>
<td>4</td>
</tr>
<tr>
<td>158†</td>
<td>I/A</td>
<td>17</td>
<td>15</td>
</tr>
<tr>
<td>119†</td>
<td>I/A</td>
<td>18</td>
<td>17</td>
</tr>
<tr>
<td>126†</td>
<td>I/A</td>
<td>32</td>
<td>10</td>
</tr>
<tr>
<td>153*</td>
<td>III/C</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td>106*</td>
<td>IV/C</td>
<td>49</td>
<td>19</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IC patients</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>105†</td>
<td>O/A</td>
<td>36</td>
<td>9</td>
</tr>
<tr>
<td>124†</td>
<td>III/C</td>
<td>15</td>
<td>2</td>
</tr>
<tr>
<td>151†</td>
<td>III/C</td>
<td>31</td>
<td>6</td>
</tr>
<tr>
<td>176†</td>
<td>IV/C</td>
<td>16</td>
<td>5</td>
</tr>
<tr>
<td>156*</td>
<td>III/C</td>
<td>25</td>
<td>10</td>
</tr>
<tr>
<td>108†</td>
<td>I/B</td>
<td>40</td>
<td>31</td>
</tr>
<tr>
<td>110†</td>
<td>II/B</td>
<td>33</td>
<td>24</td>
</tr>
<tr>
<td>118†</td>
<td>I/A</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td>175‡</td>
<td>II/B</td>
<td>22</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PLL patients</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>132†</td>
<td>III/C</td>
<td>19</td>
<td>12</td>
</tr>
<tr>
<td>130†</td>
<td>III/C</td>
<td>42</td>
<td>13</td>
</tr>
<tr>
<td>180†</td>
<td>II/B</td>
<td>15</td>
<td>3</td>
</tr>
<tr>
<td>101†</td>
<td>II/A</td>
<td>60</td>
<td>3</td>
</tr>
<tr>
<td>117†</td>
<td>I/A</td>
<td>15</td>
<td>3</td>
</tr>
<tr>
<td>140‡</td>
<td>I/A</td>
<td>13</td>
<td>6</td>
</tr>
<tr>
<td>166‡</td>
<td>O/A</td>
<td>8</td>
<td>4</td>
</tr>
<tr>
<td>120*</td>
<td>IV/C</td>
<td>15</td>
<td>15</td>
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</tr>
</tbody>
</table>
patients were observed for a median of 55 months (mean, 50 months; range, ten to 155 months; two patients less than 12 months). In this material no significant difference in prognosis was found between the CLL and IC patients. The five-year probability of survival for the CLL group was 0.72, and for the IC group it was .87 \((P = .09)\). If therapy-free survival was considered, the five-year probabilities for the two groups were .42 and .44, respectively \((P = .69)\). The median therapy-free survival for the CLL group was 54 months, and for the IC group it was 44 months.

Chromosomes

All clonal aberrations are listed in Table 1. In 43 of the patients, a sufficient number of metaphases could be evaluated. Six patients had an extra chromosome 12 as the sole abnormality. In addition, patient 176 showed a pure \(+12\) karyotype in two metaphases, whereas in three metaphases this extra chromosome 12 was deleted with a breakpoint at 12q22. Another nine patients had \(+12\) together with various other aberrations. Patient 130, as previously reported,\(^24\) had a duplication of the chromosome 12 segment q13-q22, i.e., a trisomy of this segment, and is in the following presentation included in the \(+12\) group. Patient 120 had a clonal translocation involving chromosome 12, but in this karyotype no extra chromosome 12 material was present. Patient 131 showed clonally fragmented metaphases. Six patients had 14q+, and three patients had a deletion of chromosome 11, two with the same breakpoint—q22. Five different breakpoints on chromosome 6 were seen. Del(3)(p13) was seen twice. Seven patients (No. 106, 118, 120, 132, 138, 153, and 175) had complex karyotypes with three clonal aberrations or more. All chromosomes except for No. 5, 15, 16, 19, and 23 were involved in clonal aberrations. Several patients had more than one specific clone, but in all but one case (No. 106) all the clones of a single patient shared one or more abnormalities. In five patients with \(+12\) (No. 106, 110, 119, 153, and 175) this specific aberration was missing in some clonally abnormal metaphases.

Eleven patients revealed only normal karyotypes in more than 12 metaphases studied. In cultures from 12 patients without clonal aberrations the mitogens used induced only seven or less metaphases that could be evaluated in each case. These cultures were therefore considered to be inadequate for cytogenetic evaluation.

Except for spleen size, no distinguishing correlation \((P > .2)\) with clinical findings at sampling was seen when comparing the following cytogenetic subgroups: (A) patients with \(+12\), (B) patients with chromosomal aberrations other than \(+12\), (C) patients with normal karyotype, and (D) uncharacterized patients. Patients in groups B and C had less splenomegaly than those in groups A and D \((P = .05)\).

Diagnosis and Chromosome Correlations

Both PLL patients had \(+\text{del}(3)(p13)\) together with other clonal aberrations. No other correlation between diagnosis and karyotype was seen. The cytogenetic subgroup pattern was similar in the CLL and IC groups (Table 2).

**Table 2. Cytogenetic Subgroup Pattern**

<table>
<thead>
<tr>
<th>No. of Patients</th>
<th>CLL</th>
<th>IC</th>
<th>Other</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total No.</td>
<td>22</td>
<td>29</td>
<td>4</td>
<td>55</td>
</tr>
<tr>
<td>Total evaluated</td>
<td>17</td>
<td>22</td>
<td>4</td>
<td>43</td>
</tr>
<tr>
<td>Total with clonal aberrations</td>
<td>12</td>
<td>16</td>
<td>4</td>
<td>32</td>
</tr>
<tr>
<td>+12 alone</td>
<td>2</td>
<td>3</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>+12 with other aberrations</td>
<td>4</td>
<td>7</td>
<td>0</td>
<td>11</td>
</tr>
<tr>
<td>Clonal aberrations without +12</td>
<td>6</td>
<td>6</td>
<td>3</td>
<td>15</td>
</tr>
</tbody>
</table>
DISCUSSION

Cytogenetic analysis has previously been shown to give prognostic information in CLL. Patients with an abnormal karyotype had a poorer survival, and +12 was the strongest marker for disease progression. In the present study, +12 was also found to be significantly associated with poor survival, with a P-value of <0.01. Patients with +12 had significantly worse survival compared to patients without +12 (P < 0.01). These differences were even more pronounced when only the IC patients were considered. IC patients with +12 had a significantly higher risk of progression than IC patients without +12 (P < 0.01). These findings are consistent with previous reports indicating that +12 is an independent predictor of poor prognosis in CLL.

The observed differences in survival were also evident when the patients were subdivided according to the number of clonal aberrations. Patients with +12 had a significantly worse prognosis compared to patients without +12 (P < 0.01). These results are consistent with previous studies that have reported that the complexity of the karyotype is a significant predictor of survival in CLL.

In summary, the present study confirms that +12 is a strong predictor of poor prognosis in CLL. The findings suggest that cytogenetic analysis can be used to identify patients at high risk of progression who may benefit from more intensive therapy. Further studies are needed to evaluate the potential role of targeted therapies in patients with +12.
patients with +12 had a more rapidly progressing disease and required early treatment. In the present, more extensive study, we have further examined the prognostic implications of the karyotypic pattern and its relation to the Kiel class of leukemic B-lymphocytic lymphomas. A multivariate analysis revealed that the +12 aberration was as strong an indicator of poor prognosis as advanced Rai or Binet stage. However, the complexity of the karyotype was of the greatest prognostic importance. Furthermore, the present data seem to indicate that the cytogenetic typing is of prognostic importance mainly in the IC group.

It should be emphasized that the IC group in the present material had a somewhat better prognosis than the CLL group. This is in contrast to the findings of other groups, which indicate a poorer survival for IC patients. This might be explained by differences in the method of selecting patients. For two reasons, we presume that our patients are representative for the disease. First, our hospital is the primary institution for referral of all leukemia patients in the local area. Secondly, we have attempted to include and Kiel-classify all "CLL" patients, even those with an indolent disease. In fact, several of these patients showed a lymphoplasmacytoid differentiation of their malignant clone in bone marrow and lymph node specimens. It is possible that IC patients with a benign course of the disease have been undiagnosed or not included in other studies of the prognosis in CLL and IC.

An extra chromosome 12 was again found to be the most specific aberration in "CLL." Here we found it evenly distributed among patients with CLL and leukemic IC (Table 2). Furthermore, +12 has been found in several other lymphocytic lymphomas, such as HCL, PLL, nonleukemic IC (G. Juliusson, G. Gahrton, unpublished observations), centroblastocentrocytic lymphoma (G. Juliusson, G. Gahrton, unpublished observations), T-CLL, and, according to the Working Formulation, lymphomas of follicular large and mixed cell types and the CLL-like small-cell lymphocytic lymphoma. Only occasionally is +12 reported in other malignancies, such as chronic myelocytic leukemia in the blastic phase, polycythemia vera, and large bowel cancer. Therefore, it seems that the +12 abnormality is a marker for the lymphocytic lymphomas in general rather than for CLL only.

It has previously been suggested by us and others that the +12 abnormality is the primary chromosomal aberration in CLL cells having this abnormality. However, in this material five patients with +12 (No. 106, 110, 119, 153, and 175) also showed clonal aberrations without +12, suggesting that in some cases +12 can be a secondary aberration. This is supported by the finding in PLL cells. However, it cannot be excluded that +12, although present in the primary clone, can be lost during further clonal evolution. This problem is currently under investigation by repeated cytogenetic typings during the course of the disease in some of our patients.

The number of clonal aberrations was here found to be an important prognostic marker. Complex karyotypes (at least clonal aberrations) were strongly associated with an aggressive disease (Fig 1, P < 10^-6; Fig 2, P = .007). This is consistent with previous data from acute leukemias and is also in agreement with flow cytometry data from solid tumors, eg, carcinoma of the urinary bladder. In B-CLL, this was supported by the findings of Han et al, who found that five patients with +12 together with other aberrations had a poorer survival than eight patients with pure +12 (no significance).

However, since Han et al found no impairment of survival in the pure +12 group, they suggested that any chromosomal aberration except +12 would indicate a poor prognosis. This suggestion was based on a study that, like ours, included B-CLL, PLL, and probably also IC patients. One of eight pure +12 patients (two of whom were followed for less than 30 months from diagnosis and only one followed for more than two years from sampling) died during the observation period, compared with three of 32 patients with a normal karyotype and three of eight patients with other chromosomal aberrations (two of whom had a complex karyotype). When discussing the prognosis of pure +12 patients, one must consider the long survival expectancy for all patients with a single chromosomal aberration. Regarding therapy-free survival, we have recently demonstrated that pure +12 patients had a significantly poorer prognosis than patients with single aberrations other than +12 (P = .01). With prolonged observation, this might lead to an impaired long-term survival for pure +12 patients. Altogether, we find the data of Han et al compatible with ours, which clearly suggests that the +12 abnormality is a marker for the aggressive disease.

Why +12 is associated with a poor prognosis is as yet unclear. The role of gene dosage in carcinogenesis has been discussed, particularly with regard to the recently developed concept of the oncogenes (for review see Chaganti). One interesting finding is that the c-ras oncogene is located on chromosome 12, indicating a 50% increase in the amount of this oncogene in cells having +12. However, one suggested site of c-ras is 12q24.2, which is not included in the segment 12q13-q22 that was duplicated in the cells of patient 130. This segment encodes for serinhydrox...
y methyltransferase, an enzyme previously found to be elevated in "classical" CLL. Therefore, it seems that this segment can be activated in some cases of CLL. Nevertheless, the breakpoint 12q22, found in the cells from patients 130 and 176, is very near to the suggested site of the oncogene. Modes of gene activation other than gene dosage have been suggested, in Burkitt’s lymphomas, where one of the specific translocation breakpoints is at the site of the immunoglobulin heavy chain gene. Thus, both gene dosage and gene activation by chromosome breakage might be of importance in these malignancies.

An unexpected finding in the present study was that the +12 abnormality indicated an aggressive disease mainly in the IC group, whereas less prognostic information was associated with +12 in the CLL group. Thus, we postulate that the clinical importance of the chromosomal aberrations might not be the same in all types of lymphoma. The reason for this is unclear. However, considering our previous observations suggesting that cells of IC clones may correspond to activated CLL cells, one might speculate that +12 is an aggressive determinant mainly in the activated lymphoma cell, though it does not initiate activation or progression into any particular lymphoma subtype. Correspondingly, in CLL proper the basic chromosomal damage might play a smaller role in determining the clinical picture than in IC, which has a broader, more heterogeneous intracellular differentiation profile.

The better prognosis of cytogenetically unevaluated patients (Figs 3 and 4) may be a reflection of the fact that the malignant cells from these patients were unresponsive to our activating signal in vitro, probably indicating that these cells reside in a resting phase also in vivo. This is also in agreement with previous and recent findings that "CLL" with in vitro B cell mitogen-responsive malignant cells had a more aggressive course than "CLL" with nonresponding cells.

In conclusion, cytogenetic typing of malignant lymphocytes in CLL and IC was shown to be of prognostic importance. The predictive power of the karyotype was as great as that of staging procedures. Its value seems to be greater in IC than in CLL proper. Thus, morphologic and cytogenetic results are prognostic variables that seem to be of additional clinical importance.

REFERENCES


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