Small Lymphocytic Lymphoma: A Clinicopathologic Analysis of 268 Cases


We analyzed specimens from 268 patients with small lymphocytic lymphoma (SL) to identify prognostic factors significant for survival. These patients were staged and treated according to the protocols of the Cancer and Leukemia Group B, Eastern Cooperative Oncology Group, Southeastern Cancer Study Group, and the Southwest Oncology Group. Univariate analysis showed that a large-cell grade > 1, WBC > 10,000/μL, hemoglobin (Hgb) < 11 g/dL, age ≥ 55 years, and failure to respond to treatment were all poor prognostic factors. Multivariate analysis showed that large-cell grade, age, degree of capsular invasion, and symptom type were independently associated with survival. Separate analyses of cases with and without leukocytosis indicated differences in survival. In patients without leukocytosis, age, presence or absence of anemia, and treatment response were significant prognostic variables; in patients with leukocytosis, large-cell grade, presence or absence of anemia, symptom type, and treatment response were significantly related to survival. Multivariate analysis showed that age was the only significant independent prognostic variable in patients without leukocytosis; in patients with leukocytosis, symptom type, large-cell grade, and bone marrow involvement were independently associated with survival. We conclude that several parameters, both clinical and pathologic, should be assessed at the initial diagnosis of SL to predict prognosis better.

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SMALL (well-differentiated) lymphocytic lymphoma (SL) is a low-grade malignant lymphoma characterized morphologically by a diffuse proliferation of small, mature-appearing lymphocytes.2,3 It is related clinically to chronic lymphocytic leukemia (CLL) and to Waldenström's macroglobulinemia.3 Although SL is indolent in its course, patients with SL are rarely, if ever, cured by the chemotherapeutic regimens which have been more successful in the treatment of the large-cell non-Hodgkin's malignant lymphomas.4 Furthermore, SL will often transform to an aggressive lymphoma or predispose the patient to life-threatening infection.5,22 Investigators have tried to identify parameters that predict which SL patients would have a better survival.2,23,24 These studies have generally yielded inconclusive results, possibly because most were carried out at single institutions and included only limited numbers of patients. In an attempt to determine whether one can use any clinical or pathologic features at initial diagnosis to predict which patients might have a favorable prognosis, we examined the cases of SL in the files of the Repository Center for Lymphoma Clinical Studies.16 Rather than coming from a single institution, this case material represents the combined experience of four cooperative oncology groups (Cancer and Leukemia Group B (CALGB), Eastern Cooperative Oncology Group (ECOG), Southeastern Cancer Study Group (SECSG), and Southwestern Oncology Group (SWOG)). The cases were referred to the Repository Center for pathologic review and confirmation of the diagnosis at the time of entry into a clinical protocol.

MATERIALS AND METHODS

We evaluated 420 cases of SL on file at the Repository Center for Lymphoma Clinical Studies for inclusion in this study. Thirty-eight cases were contributed by CALGB, 151 by ECOG, 84 by SECSG, and 138 by SWOG. All 420 cases were reviewed initially by two of the authors (J.B-E. and J.S.B.); 149 were eliminated because (a) the only slides available were from extranodal sites (44 cases); (b) a diagnosis other than SL was made (nine cases); (c) the slides available were not of sufficient technical quality to allow us to assess the morphologic parameters of this study, even though the diagnosis of SL could be confirmed (80 cases); or (d) slides were no longer available for review (16 cases). The cases originally classified as SL, but later revised, were changed either to small cleaved cell lymphoma or to malignant lymphoma of intermediate differentiation.11 The lymph node sections from the remaining 271 cases were reviewed independently by the rest of the panel of pathologists (M.D.B., R.K.B., B.N.N., R.W., and B.W.). After this review, an additional three cases were eliminated because the diagnosis of SL could not be confirmed. The 268 cases remaining formed the basis of this study.

Each of the six panel pathologists evaluated the slides from all 268 patients for various histologic features. Since J.B-E. and J.S.B. had initially reviewed the cases simultaneously on a double-headed microscope, their combined evaluation was counted for statistical purposes as one observation. The histologic parameters assessed were architectural pattern, architectural effacement, large cell grading, and capsular invasion.

From the Pathology Panel and Repository Center for Lymphoma Clinical Studies, the Division of Anatomic Pathology, and the Department of Biostatistics, City of Hope National Medical Center, Duarte, CA; Department of Pathology, University of Southern California, Los Angeles; Department of Medicine, University of Minnesota, and VA Medical Center, Minneapolis; Mallory Institute of Pathology, Boston University School of Medicine; and Department of Pathology, Bowman-Gray Medical School, Winston-Salem, NC.

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Address correspondence to Jonathan Ben-Ezra, MD, Department of Pathology, City of Hope National Medical Center, 1500 E Duarte Rd, Duarte, CA 91010.

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Architectural pattern (Fig 1)—Diffuse, pseudofollicular, or truly follicular (nodular). Pseudofollicles were defined as aggregates of lymphoid cells which were larger and stained paler than the surrounding small lymphocytes. Often, these cells had abundant cytoplasm, causing the nuclei to be farther apart than the rest of the lymph node. However, the individual nuclei were morphologically similar to those in the portion of the node involved diffusely by the small lymphocytes. Some of the larger cells had an open, vesicular chromatin pattern and represented prolymphocytes.

Architectural effacement—Complete, incomplete, or not assessable (NA). If effacement was incomplete, we noted whether there were residual germinal centers (GCs), patent sinuses, or a combination of both.

Large-cell grading (Fig 2). The lymphomas were also assessed for the pattern of large cells by a grading system modified from that used by Dick and Maca. In our system, grade I lymph nodes were populated almost completely by small mature-appearing lymphocytes, grade II (Dick and Maca's grade IIA) by small mature lymphocytes with focal aggregates of large cells, grade III (Dick and Maca's grade IIB) by a diffuse admixture of small round lymphocytes and large lymphocytes, and grade IV (Dick and Maca's grade III) by sheets of large cells with minimal numbers of small lympho-
cytes. Large cells were defined as cells larger than the small lymphocytes of SL; some of these cells had a more open or vesicular chromatin pattern than did the small lymphocytes, and some had a prominent central nucleolus. These cells represented prolymphocytes and paraimmunoblasts, respectively.12

Capsular invasion (Fig 3). Low (absent, or only one small focus), high (more than one focus or extensive invasion), or NA (<50% of the node on the section had an intact evaluable capsule). In addition to the above histologic parameters, one of the authors (J.B-E.) independently examined the cases for (a) number of large cells per 20 high-power fields (x450) and (b) number of mitotic figures per 20 high-power fields. The number of large cells were counted in 20 consecutive randomly selected fields and may have included pseudofollicles in the cases that had such structures. This parameter is different from the large-cell grade, since the large-cell grade measures the pattern of arrangement of the large cells, whereas the number of large cells per 20 high-powered fields represents the actual number of large cells, without taking pattern into account. The results of these counts were verified in a simultaneous review with J.S.B.

For statistical analysis, a consensus diagnosis was defined as agreement by four or more of the pathologists. If the six panel pathologists were divided evenly concerning a given parameter, two of the authors (J.B-E. and J.S.B.) evaluated that parameter and arrived at a consensus; this was then entered as the panel’s consensus diagnosis.

The 420 cases reviewed were submitted to the Repository Center from April 1967 through November 1985. The patients had been entered in a variety of treatment protocols over this 18-year period.* Some patients were treated prior to their assignment to a protocol; however, all submitted slides were from pretreatment biopsy specimens. The protocols tended to become more comprehensive with time. Although the Ann Arbor staging system was used throughout, initially the procedures for staging were not uniform among the cooperative groups. Since the early 1970s, however, these procedures and the definitions became more rigorous and uniform.

After morphologic review, clinical data on the study cases were obtained from the statistical centers of the various cooperative groups. The clinical parameters evaluated were age, sex, race, date of diagnosis, initial symptoms, physical findings, stage of disease, hemogram results, response to treatment, status at last follow-up, and survival time. The survival times were measured from the date when the diagnosis of lymphoma was first established by biopsy to the date of death or the date of last follow-up. Survival curves were obtained by the product-limit method of Kaplan and Meier.13 We used the log-rank test to evaluate differences between survival curves.14 Multivariate analysis was performed using Cox’s regression model15; it included only patients for whom we had complete data on all parameters of interest.

RESULTS

Clinical data. The age and sex distribution for the 254 patients for whom data were available are given in Fig 4. The median age was 59 years, and the ratio of males to females was 2.3:1.

Fifty-seven percent of the patients were asymptomatic (A) and 43% had B symptoms (fever, night sweats, and/or weight loss > 10% of body weight). Ninety percent of the patients had generalized lymphadenopathy. Of the 255

*CALGB protocols 7651, 7851, 7951, and 8251; ECOG protocols 1472, 1476, 1477, 1478, 2474, 3474, 4477, and 5477; SECSG protocols 103, 296, and 349; and SWOG protocols 765, 780, 1480, 7204, 7406, 7426, 7432, 7707, 7761, 7860, 7912, 7918, 8005, 8112, 8245, and 8375.

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Fig 3. (A) Lack of capsular invasion; (B) demonstrates extensive infiltration of the lymphoma through the capsule and into the perinodal adipose tissue. (H & E, original magnification x 100; current magnification x 70.)

Fig 4. Age and sex distribution of 268 patients with SL.
patients for whom staging data were available, none was stage I, three (1%) were stage II, 22 (9%) were stage III, and 230 (90%) were stage IV. Eighty-two percent of the study patients were stage IV by virtue of a positive bone marrow biopsy specimen. (The bone marrow biopsy specimens were not available for review at the Repository Center.)

The hemoglobin (Hgb) levels at diagnosis ranged from 4.0 to 19.0 g/dL, with 30 of 255 patients having levels < 11 g/dL. The initial platelet counts ranged from 30 to 540 × 10^9/µL, with nine of 255 patients having values < 100 × 10^9/µL and 97 other patients having platelet counts between 100 and 200 × 10^9/µL. The initial WBC count ranged from 1.6 to 232.7 × 10^9/µL, with a median of 8,500; 170 of the 255 patients had values < 10 × 10^9/µL. The percentage of lymphocytes had not been entered consistently by the cooperative groups for all treatment protocols; therefore, a WBC of 10 × 10^9/µL was considered as indicating an absolute lymphocytosis, with the assumption that at this WBC level 4 × 10^9 lymphocytes/µL would be present.2

Information on the treatment given was available for 253 (94.5%) of the patients; nine (3.5%) received single-agent chemotherapy, one (0.5%) received chemotherapy and surgery, 17 (7%) received chemotherapy and radiotherapy, and 225 (89%) received multiple-agent chemotherapy. The response to therapy was available for 267 of the patients: 32 (12%) had no response, 109 (41%) had a partial response, (12%) had a complete response (no gross residual disease). At last follow-up, 162 (60%) of the patients were alive; the mean survival time was 54.7 months. For 143 of the deceased patients for whom data were available, 106 (74%) died with disease and 37 (26%) died without evidence of disease.

Morphologic observations. The morphologic findings in the 268 cases are summarized in Table 1. Of the biopsy specimens, 108 (40%) had pseudofollicles, whereas 160 (60%) did not; no cases of truly follicular (nodular) SL were identified. Among the 108 cases with pseudofollicles, in 38 (35%) cases the pseudofollicles were composed of small lymphocytes, in 60 (55%) of a mixture of small lymphocytes and large cells, and in two (3%) predominantly of large cells; in eight cases (7%), the cellular composition of the pseudofollicles could not be specified. In 193 (72%) of the cases, the lymph node architecture was completely effaced by SL, whereas germinal centers remained in 21 cases, patent sinuses were identified in 45, and both were evident in five cases; in four cases (2%) effacement could not be assessed. The germinal centers were invariably small and focal and did not have distinct mantle zones because the neoplastic small lymphocytes had obliterated the mantle zones and encroached on the germinal centers. The patent sinuses were also focal and were usually peripheral. Of the residual patent sinuses in 50 cases, one (2%) was devoid of cells, nine (18%) contained histiocytes, and 40 (80%) were filled with small lymphocytes morphologically identical to those in the inter-sinusoidal regions of the node. Capsular invasion was considered low in 122 of the cases (45%) and high in 97 (36%); it could not be assessed in 49 cases (18%).

Two thirds (177) of the cases had an almost pure population of small mature lymphocytes (large-cell grade I). Focal aggregates of large cells (large-cell grade II) were noted in 82 cases (31%), and a diffuse mixture of large and small cells (large-cell grade III) was noted in only seven cases (3%); none were considered to have sheets of large cells (large-cell grade IV), and two cases were considered NA. Table 1 shows that most of the cases had fewer than two large cells and one mitotic figure per high-power field. In only 15 cases (5%) were there significant numbers of lymphocytes with plasmacytoid features.

Survival data. Survival data were available for 253 of the patients. Survival times ranged from 1 to 205 months (mean 54.7 months, median 68.0 months, Fig 5).

We performed univariate analysis of the clinical and histologic parameters to determine whether any of these
Fig 5. Overall survival curve of 268 patients with SL.

would have a significant bearing on survival (Tables 2 and 3). Five parameters were identified as reaching a level of statistical significance of $P \leq 0.05$. Patients with large-cell grade I had a median survival time of 77 months as compared with a median survival time of 56 months for patients with large-cell grade II or III ($P \leq 0.005$) (Fig 6). Patients with an initial WBC $< 10,000/\mu$L had a median survival time of 84 months as compared with 50 months for patients with a higher initial WBC ($P \leq 0.008$) (Fig 7). Patients with an initial Hgb of $< 11.0$ g/dL had a median survival of 37 months as compared with a median survival of 74 months for patients with an Hgb above this level ($P \leq 0.004$) (Fig 8). In addition, patients aged $> 55$ years had a poorer prognosis (median survival 64 months) than did younger patients (88 months, $P \leq 0.008$) (Fig 9). Response to treatment was also a significant factor; patients who achieved a complete response had a longer median survival (104 months) than patients who did not have a complete response (45 months, $P \leq 0.0001$).

Patients whose lymph nodes showed complete architectural effacement had a median survival of 64 months as compared with 82 months for patients with intact sinuses and/or germinal centers; this difference in survival time, however, was not statistically significant ($P \leq 0.07$). No significant differences in survival were found for the following histologic variables: architectural pattern (diffuse vs. pseudofollicular), degree of capsular invasion, presence or absence of plasmacytoid features, number of large cells per 20 high-power fields, and number of mitotic figures per 20 high-power fields. In addition, the following clinical features also had no significant bearing on the prognosis: presence or absence of B symptoms, clinical stage at diagnosis, treatment received, sex, and presence or absence of bone marrow involvement.

Because many of the parameters appeared to be interdependent, we performed a multivariate analysis to ascertain which were the most important. We could not determine that response to therapy was evaluated at the same time after diagnosis for all patients; therefore, we performed the multivariate analysis without taking this variable into account. In this analysis (Table 4), we identified large-cell grade ($P < 0.006$) as being the most important independent determinant of survival. In addition, we found that age ($P \leq 0.02$), degree of capsular invasion ($P \leq 0.03$), and the presence or absence of B symptoms ($P \leq 0.04$) independently influenced survival.

We analyzed the cases with and without leukocytosis (WBC $\geq 10 \times 10^3/\mu$L) separately to determine whether any parameters would reveal survival differences between the

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Category</th>
<th>Overall Survival (mo)</th>
<th>WBC $&lt; 10,000$</th>
<th>WBC $&gt; 10,000$</th>
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</thead>
<tbody>
<tr>
<td>Pattern</td>
<td>Diffuse</td>
<td>78</td>
<td>98 (P $\leq 0.13$)</td>
<td>49 NS</td>
</tr>
<tr>
<td></td>
<td>Pseudofollicular</td>
<td>64</td>
<td>69</td>
<td>51</td>
</tr>
<tr>
<td>Architectural effacement</td>
<td>Complete</td>
<td>64</td>
<td>78 (P $\leq 0.07$)</td>
<td>49 NS</td>
</tr>
<tr>
<td></td>
<td>Incomplete</td>
<td>82</td>
<td>104 (P $\leq 0.15$)</td>
<td>77 NS</td>
</tr>
<tr>
<td>Capsular invasion</td>
<td>Low (0-1+)</td>
<td>80</td>
<td>85 (P $\leq 0.19$)</td>
<td>63 NS</td>
</tr>
<tr>
<td></td>
<td>High (2-3+)</td>
<td>56</td>
<td>78</td>
<td>48 NS</td>
</tr>
<tr>
<td>Large-cell grade</td>
<td>I</td>
<td>77</td>
<td>96 (P $\leq 0.006$)</td>
<td>58 (P $\leq 0.04$)</td>
</tr>
<tr>
<td></td>
<td>II+</td>
<td>56</td>
<td>68 (P $\leq 0.10$)</td>
<td>46</td>
</tr>
<tr>
<td></td>
<td>0-20</td>
<td>67</td>
<td>80</td>
<td>43</td>
</tr>
<tr>
<td></td>
<td>21-50</td>
<td>74</td>
<td>74</td>
<td>77</td>
</tr>
<tr>
<td>Large cells/20 high-power fields</td>
<td>51-100</td>
<td>64</td>
<td>84 NS</td>
<td>58 NS</td>
</tr>
<tr>
<td></td>
<td>101-150</td>
<td>99</td>
<td>214</td>
<td>21</td>
</tr>
<tr>
<td></td>
<td>150+</td>
<td>56</td>
<td>80</td>
<td>43</td>
</tr>
<tr>
<td></td>
<td>0-5</td>
<td>74</td>
<td>86</td>
<td>51</td>
</tr>
<tr>
<td></td>
<td>6-10</td>
<td>66</td>
<td>80</td>
<td>48</td>
</tr>
<tr>
<td>Mitoses/20 high-power fields</td>
<td>11-15</td>
<td>57</td>
<td>57 NS</td>
<td>13 NS</td>
</tr>
<tr>
<td></td>
<td>16-20</td>
<td>42</td>
<td>42</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td>21+</td>
<td>Not reached</td>
<td>10</td>
<td>51</td>
</tr>
<tr>
<td>Plasmacytoid features</td>
<td>With</td>
<td>53</td>
<td>126 NS</td>
<td>54 NS</td>
</tr>
<tr>
<td></td>
<td>Without</td>
<td>69</td>
<td>84 NS</td>
<td>51 NS</td>
</tr>
</tbody>
</table>

NS, not significant.
two groups (Tables 2 through 4). By univariate analysis, patients with leukocytosis, but not those without, had significantly different survival times with regard to large-cell grade \( (P \leq 0.04) \) (Fig 10) and the presence of B symptoms \( (P \leq 0.04) \), whereas the opposite was true with regard to age \( (P \leq 0.02) \). Survival within both groups was correlated with the presence of anemia (WBC < 10 x 10^3/μL, \( P \leq 0.02 \); WBC ≥ 10 x 10^3/μL, \( P \leq 0.04 \)) and response to treatment (WBC < 10 x 10^3/μL, \( P \leq 0.0001 \); WBC ≥ 10 x 10^3/μL, \( P \leq 0.0003 \)). Multivariate analysis of the cases without leukocytosis demonstrated that only age \( (P \leq 0.04) \) influenced survival significantly. A similar analysis of the cases with leukocytosis revealed that B symptoms \( (P \leq 0.01) \), a large-cell grade > I \( (P \leq 0.02) \), and positive bone marrow biopsy \( (P \leq 0.03) \) were all independently associated with a significantly shorter survival time.

**DISCUSSION**

SL is a non-Hodgkin's lymphoma composed of small, mature-appearing lymphocytes. Immunologically, most of
these neoplasms are monoclonal proliferations of B lymphocytes; only rare SLs are derived from T cells.\textsuperscript{16} SL is generally viewed as being the tissue counterpart of CLL,\textsuperscript{3,17} which is composed of similar cells. Clinical features in these two entities often overlap, with CLL patients having tissue involvement that is not distinguishable morphologically from SL.\textsuperscript{1} In contrast to CLL, in which several clinical parameters\textsuperscript{18} and morphologic features of the bone marrow\textsuperscript{19} are predictors of survival and the course of disease, no such variables have yet been defined in SL. SL is typical of the low-grade lymphomas, which characteristically are refractory to curative therapy, with most patients experiencing repeated relapse and, eventually, death. In contrast, patients with many intermediate- and high-grade lymphomas, for which effective chemotherapeutic regimens exist, have a lower relapse rate once complete remission is achieved.\textsuperscript{20} Thus, patients with low-grade lymphomas have longer survival times in the short term than do their counterparts with high-grade lymphomas, but this situation is reversed after 10 to 15 years.

In this study, we attempted to identify pathologic and clinical parameters that might yield important information about survival. The clinical characteristics of our patients, including age, sex, and stage of disease, were similar to those of patients in other series of SL.\textsuperscript{1-3} Our results based on univariate analysis indicate that large-cell grade, a WBC > 10 $\times$ 10\(^3\)/μL, Hgb < 11 g/dL, age > 55 years, and failure to respond to treatment were all poor prognostic indicators. Multivariate analysis showed that two clinical parameters, increased age and the presence of B symptoms, and two pathologic criteria, a high large-cell grade and massive capsular invasion, were associated with shorter survival times.

One interpretation of these results is that several of the parameters, such as large-cell grade, high WBC, low Hgb, B symptoms, and capsular invasion, indicate the presence of

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**Table 4. Multivariate Analysis of SL**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Level of Significance (P Value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All cases</td>
<td></td>
</tr>
<tr>
<td>Large-cell grade</td>
<td>\leq .006</td>
</tr>
<tr>
<td>Age at diagnosis</td>
<td>\leq .02</td>
</tr>
<tr>
<td>Degree of capsular invasion</td>
<td>\leq .03</td>
</tr>
<tr>
<td>Symptom type</td>
<td>\leq .04</td>
</tr>
<tr>
<td>Cases with WBC &lt; 10 $\times$ 10(^3)/μL</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>\leq .04</td>
</tr>
<tr>
<td>Cases with WBC &gt; 10 $\times$ 10(^3)/μL</td>
<td></td>
</tr>
<tr>
<td>Symptom type</td>
<td>\leq .01</td>
</tr>
<tr>
<td>Large-cell grade</td>
<td>\leq .02</td>
</tr>
<tr>
<td>Positive bone marrow biopsy</td>
<td>\leq .03</td>
</tr>
</tbody>
</table>

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**Fig. 8.** Survival of patients with and without anemia (Hgb < 11 g/dL).

**Fig. 9.** Survival by age at diagnosis.

**Fig. 10.** Survival by large-cell grade for SL patients with (A) and without (B) leukocytosis (WBC > 10 $\times$ 10\(^3\)/μL).
more advanced disease. If SL were to progress like many other neoplasms, we would expect it to start at one focus in the lymph node, eventually replace the node, and then invade the surrounding perinodal tissue and possibly the bloodstream. Therefore, patients with advanced disease, which presumably is accompanied by shorter survival times, would be expected to have a high degree of capsular invasion and evidence of peripheralization.

If this hypothesis were correct, we would expect patients with residual normal lymph node architecture, including the presence of germinal centers and patent sinuses, to have an early form of this disease, and hence a longer survival. Although our data indicated a trend in this direction, they did not reach statistical significance (P = .07). This result is identical to that reported by Evans et al.3

Alternatively, one may argue that many of the parameters which we identified are measures of the inherent “aggressiveness” of a SL in a particular case, rather than of the point in its natural evolution. The large-cell grade,8 identified in our study as an important variable in univariate as well as in multivariate analysis, may represent such a measure. However, other traditional indicators of “aggressiveness,” such as the actual number of large cells and mitotic figures per 20 high-power fields, were found not to have a statistically significant relationship to survival.

Clinical variables found to be prognostically significant included symptom type, Hgb level, WBC count, age, and response to treatment. These variables may also be related to the stage in the evolution of the disease, as well as to the ability of the patient to tolerate treatment. Indeed, several investigators20,21 have argued that the apparent survival advantage for patients who have responded to treatment over those who have not may be related to such complicating factors.

In a previous study, Evans et al1 examined many of the variables that we assessed in this study. Like us, they found that age >60 years was an unfavorable prognostic indicator and that there was a trend toward significantly longer survival in patients with residual germinal centers. However, Evans et al reported shorter survival times for patients whose lymphoma had a high mitotic rate, and they found no correlation of survival with capsular invasion, symptom type, treatment response, or absolute lymphocyte count; they did not assess large-cell grade. Our patient populations were similar in regard to clinical parameters, such as age and percentage of individuals with leukocytosis. However, a part of the difference in variables influencing survival may be owing to the difference in sample size (84 vs 268 patients). Other observed differences, such as response to treatment, may be related to the changes in chemotherapeutic regimens and supportive care that have occurred over the past decade. Similarly, Pangalis et al2 found no statistically significant difference in survival times between patients with SL who had lymphocytosis and those who did not.

Dick and Maca8 introduced a large-cell grading system in their evaluation of lymph nodes from patients with CLL. In their study, they found no statistically significant correlation between large-cell grade and outcome. This differs from our finding that large-cell grade was a significant prognostic variable. Moreover, even when we analyzed only patients with WBC > 10 x 10^9/L, who were presumably more similar to the patients of Dick and Maca8 with CLL and lymphadenopathy than our total population with SL, we showed both by univariate and by multivariate analysis that large-cell grade was a significant prognostic factor in our series. This difference in results between the two studies cannot be readily explained.

Since SL and CLL are closely related,2,3,8,17 it is not surprising that several of the same factors correlated with survival in CLL, such as age, Hgb, and WBC count,21 were also significant in our study of SL. However, several clinical parameters, such as thrombocytopenia and gender, which have a significant correlation with survival in CLL, did not reach statistical significance either in our entire SL study group or in the patients with leukocytosis. In addition, several factors which bear on the prognosis in CLL, such as lymphadenopathy and hepatosplenomegaly,21 are not relevant to assessment of SL patients, because almost all such patients have generalized lymphadenopathy.

We could not guarantee that the cases examined with leukocytosis were those of SL and not of CLL. However, these patients clinically had lymphoma and not leukemia, for otherwise they would have been ineligible for the lymphoma protocols. In addition, we analyzed cases with and without leukocytosis separately to ensure that the data would be applicable to a population that did not have an absolute lymphocytosis. Our results indicate that patients with leukocytosis when SL is diagnosed have survival times different from those of patients without leukocytosis in regard to some clinical and histologic variables (Tables 2 through 4). We believe that this does not represent a difference between patients with SL and those with CLL, since our patients with leukocytosis were not clinically different from those without; the WBC also did not prove to be an independent variable when we assessed survival by multivariate analysis.

This multiinstitutional study has certain shortcomings. Significant data, such as absolute lymphocyte count, could not be obtained from the computer files. In addition, diagnostic material other than the original lymph node specimens, eg, bone marrow biopsy specimens, could not be evaluated independently for extent and pattern of involvement. Finally, the patients were treated with different chemotherapeutic regimens over two decades, which further complicates the evaluation. Nonetheless, our analysis of 268 cases of SL yielded important information on the factors related significantly to survival. Clinically, age, symptom type, response to treatment, Hgb level, and WBC were all correlated with outcome. Similarly, the pathologic characteristics of large-cell grade and degree of capsular invasion were both significantly related to survival. Therefore, these variables should be analyzed at the time of diagnosis, with collaboration between the clinician and the pathologist, as an aid in assessment of the prognosis of patients with SL.

REFERENCES

2. Pangalis GA, Nathwani BN, Rappaport H: Malignant lymphoma...


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J Ben-Ezra, JS Burke, WG Swartz, MD Brownell, RK Brynes, LR Hill, BN Nathwani, MM Oken, BC Wolf and R Woodruff