We grouped 162 patients with advanced, diffuse histiocytic lymphoma (DHL) into various morphological subtypes to ascertain whether there were any significant differences in survival among them. These patients were staged and treated from 1972 to 1977 according to the protocols of the Southwest Oncology Group. Of the 159 patients on whom a consensus on the diagnosis was reached, 115 were classified morphologically as having large noncleaved, 26 as B-immunoblastic, 9 as large cleaved, and 6 as T-immunoblastic. The 3 remaining patients did not fit any of these subtypes, but each had a single prominent nucleolus in most tumor cells ("prominent nucleolus" type). Morphological subdivision of DHL did not identify any subgroup of patients with a significantly longer survival, but clinical parameters such as stage, symptoms, and type of treatment significantly influenced survival times.

It is now well established that approximately 40% of the patients diagnosed as having diffuse "histiocytic" lymphoma (DHL) have prolonged disease-free survivals following combination chemotherapy. Since the DHL are now recognized to be morphologically and immunologically heterogeneous, many investigators have attempted, by employing morphological or immunologic methods or both, to identify subgroups of patients with a good prognosis. The results of these studies, however, are controversial.

We report our results on the morphological subdivision of patients with DHL. The results are based on a study of 162 patients who had advanced disease and were treated by the Southwest Oncology Group between 1972 and 1977.

MATERIALS AND METHODS

Two-hundred and seventy-nine cases of advanced DHL from the files of Southwest Oncology Group form the basis of this study. Of these patients, 115 were treated by cyclophosphamide, adriamycin, vincristine, prednisone (CHOP) or adriamycin, vincristine, prednisone (HOP) in a study conducted between 1972 and 1974 and previously reported on by McKelvey et al. A pathology review was carried out on only about half of these cases. The remaining 164 patients were entered on SWOG Study 7426 (COPiCytoxan, oncovin, prednisone)-Bleo; CHOP-Bleo; CHOP-BCG), which was conducted between 1974 and 1977 and was previously reported by Jones et al. A pathology review was completed in about 80% of the cases in this study.

All patients were carefully evaluated for the extent of disease prior to therapy and staged according to criteria of the Ann Arbor conference. Five patients relapsed after initial radiotherapy with stage II disease; all others had stage III or IV disease. None had received prior chemotherapy. Follow-up on patients entered in these two trials was until August 1981. Details of treatment can be found in references 10, 24, and 26. Clinical features and descriptions of treatment options for 162 patients constituting the study population are found in Table 1. Complete response (CR) was judged clinically in the CHOP/HOP study and judged by careful restaging in the second study.

All 279 cases were reviewed by one of us (B.N.N.), and 117 cases were eliminated because (1) the only slides (25 cases) available were from extranodal sites, and therefore, the pattern could not be accurately judged; (2) a diagnosis other than DHL was found (18 cases); (3) residual or minimal nodularity was found (15 cases); or (4) the technical quality of the sections was less than optimal for a precise subclassification of DHL (59 cases). These remaining cases of DHL were classified into subtypes proposed and described by Lukes and Collins. These morphological subtypes were large cleaved, large noncleaved, B-immunoblastic, T-immunoblastic, and true histiocytic types. The designation of B and T is used in a morphological sense only, without immunologic confirmation. The remaining 162 cases, specimens of which were of excellent histologic quality, were reviewed independently at the Repository Center by each of the seven participating pathologists (R.J.H., J.R., G.E.B., W.W.S., H.K., H.R., B.N.N.). A particular subtype was considered as agreed upon when at least four of the seven pathologists concurred; this happened in 129 cases. In the 33 cases in which there was disagreement, the material was reviewed again by all investigators simultaneously on a nine-headed microscope and a consensus diagnosis was reached. For comparative analysis of subtypes, the consensus diagnosis for all cases was used.

A complete statistical analysis was done by the Southwest Oncology Group statistical center. Median survivals were calculated according to the method of Kaplan and Meier. Gehan’s modification of the Wilcoxon test was used for evaluation of the differences between survival curves. To obtain p-values for comparisons of morphological types, adjusted for various clinical features, a generalization of Gehan’s test was employed.
RESULTS

Morphological Observations

When the 162 cases of DHL were subsequently subclassified according to the morphological criteria proposed by Lukes and Collins,12,29 a consensus was achieved in 159 cases. The most common subtype was large noncleaved (72%) (Fig. 1); the second most common was B-immunoblastic (16%) (Fig. 2). Large cleaved (Fig. 3) and T-immunoblastic (Fig. 4) subtypes constituted 6% and 4%, respectively, of the "histiocytic" lymphomas. Three cases were difficult to classify according to the Lukes and Collins criteria because the nuclei had a single prominent nucleolus with scanty cytoplasm. They were tentatively placed in a separate category that was designated as the "prominent nucleolus" (PN) subtype (Fig. 5).

Clinical Correlations

The age, sex, symptoms, stages, and type of treatment of these 159 patients grouped according to the

![Fig. 1. Lymph node showing the morphology of large noncleaved lymphoma. There is a monomorphic proliferation of large lymphoid cells that have multiple small nucleoli and scanty pale staining cytoplasm with well to poorly defined cell borders (H&E, ×730).](image)

![Fig. 2. Lymph node showing the morphology of B-immunoblastic lymphoma. The characteristic nuclear and cytoplasmic features of this type of lymphoma are apparent. Many of the large lymphoid cells have a prominent, centrally placed nucleolus with moderate to abundant quantities of deeply staining cytoplasm (H&E, ×730).](image)

<table>
<thead>
<tr>
<th>Histologic Subtype</th>
<th>LC</th>
<th>LNC</th>
<th>B-IBS</th>
<th>T-IBS</th>
<th>PN</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex M:F</td>
<td>6:3</td>
<td>74:41</td>
<td>14:12</td>
<td>6:0</td>
<td>3:0</td>
<td>103:56</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
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<td>55</td>
<td>53</td>
<td>55</td>
<td>40</td>
<td>53</td>
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<td>4</td>
<td>1</td>
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<td>36</td>
<td>9</td>
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<tr>
<td>IV</td>
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<td>75</td>
<td>16</td>
<td>2</td>
<td>3</td>
<td>99</td>
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<tr>
<td>Symptoms</td>
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<td>11</td>
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<tr>
<td>&quot;B&quot;</td>
<td>5</td>
<td>51</td>
<td>15</td>
<td>4</td>
<td>2</td>
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<td></td>
<td></td>
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<td>CHOP (7204/05)</td>
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<td>24</td>
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<td>1</td>
<td>1</td>
<td>32</td>
</tr>
<tr>
<td>HOP</td>
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<td>20</td>
<td>5</td>
<td>1</td>
<td>1</td>
<td>28</td>
</tr>
<tr>
<td>COP-Bleo (7426-27)</td>
<td>4</td>
<td>18</td>
<td>3</td>
<td>0</td>
<td>1</td>
<td>26</td>
</tr>
<tr>
<td>CHOP-Bleo</td>
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<td>24</td>
<td>8</td>
<td>4</td>
<td>0</td>
<td>37</td>
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<tr>
<td>CHOP-BCG</td>
<td>3 (33%)</td>
<td>29 (25%)</td>
<td>4 (15%)</td>
<td>0</td>
<td>0</td>
<td>36</td>
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<tr>
<td>Total</td>
<td>9</td>
<td>115</td>
<td>26</td>
<td>6</td>
<td>3</td>
<td>159</td>
</tr>
</tbody>
</table>

LC, large cleaved; LNC, large noncleaved; B-IBS, B-immunoblastic; T-IBS, T-immunoblastic; PN, prominent nucleolus subtype.
Fig. 3. Lymph node showing the morphology of large cleaved lymphoma. The nuclei of the large cells show considerable variation in their shape. Nucleoli are either absent or inconspicuous, and cytoplasm is scanty (H&E ×730).

Fig. 4. Lymph node showing the morphology of T-immunoblastic lymphoma. The lymphoma shows a mixture of small, intermediate, and large lymphoid cells, with the last predominating. The large lymphoid cells show moderate to abundant quantities of pale to clear cytoplasm with well defined cell borders. Note the absence of "cleaved" cells and of large cells with plasmacytoid features (H&E, ×730).

Fig. 5. Lymph node showing the morphology of the "prominent nucleolus" subtype. In this instance, the nuclear features are those of a B-immunoblastic lymphoma, but the cytoplasmic features are those of the large noncleaved cell type. The majority of the nuclei show a solitary prominent nucleolus; however, the cytoplasm is scanty (H&E, ×730).

Fig. 6. Survival curve for all 162 patients. The median survival was 20 mo; 54 patients were alive at the last follow-up (Fig. 6).

The plateau in the curve suggests that approximately 28% of patients who were alive at the end of 5 yr were probably cured of the disease. There were no differences in survival based on age and sex of patients. Patients who had stage III disease had significantly longer survivals than did patients who had stage IV disease (42 versus 12 mo, p = 0.005) (Fig. 7). Similarly, patients who were asymptomatic had significantly different subtypes are shown in Table 1. The median age of all patients was 53 yr. There were no significant differences in the relative frequency of the subtypes, in particular, in patients more than 60 yr of age. The male-to-female ratio for the entire group was 1.8:1. Almost all patients had advanced disease (stage III—35%, stage IV—62%), and 48% of the patients were symptomatic.

Survival According to Clinical Parameters and Treatment

The median survival of all 162 patients was 20 mo; 54 patients were alive at the last follow-up (Fig. 6).
**DIFFUSE "HISTIOCYTIC" LYMPHOMA**

**Survival According to Stage**

<table>
<thead>
<tr>
<th>STAGE</th>
<th>TOTAL NO. PATIENTS</th>
<th>FAIL</th>
<th>MEDIAN SURVIVAL MOS</th>
<th>P VALUE</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>57</td>
<td>30</td>
<td>42</td>
<td>P &lt; 0.005</td>
</tr>
<tr>
<td>II</td>
<td>100</td>
<td>75</td>
<td>12</td>
<td></td>
</tr>
</tbody>
</table>

Fig. 7. Patients who had stage IV disease had a significantly shorter survival than did patients who had stage III disease.

longer survival times than did patients who had "B" symptoms (27 versus 11 mo, p = 0.015) (Fig. 8). In both Figs. 7 and 8, there is a plateau in the survival curves for each of the subgroups, indicating that a small percentage of patients who were alive for more than 5 yr were probably cured. The 36 patients who were treated by CHOP-BCG had significantly superior survival times than the remaining 123 patients who were treated by other protocols (p = 0.005). A comparison of survival among these 123 patients, based on other treatment protocols, did not reveal any significant differences among them. Of the 159 patients who received induction treatment, only 73 received maintenance treatment; and when these 73 patients were distributed among different subtypes and different maintenance treatment protocols, it was not possible to make any meaningful comparisons because of the small numbers in many of the subgroups.

**Survival According to Morphology**

The survival curves for the five subtypes of DHL are shown in Fig. 9. Patients with the large cleaved (LC) cell type had the longest median survival (24 mo), and those who were diagnosed as having T-immunoblastic (T-IBS) lymphoma had the shortest survival (3 mo). The median survivals for the large noncleaved (LNC) (19 mo) and B-immunoblastic (B-IBS) (20 mo) types were similar to those for the large cleaved type. A statistical comparison of these different subtypes failed to reveal any significant differences in survival (p > 0.25). However, there appeared to be a trend indicating that the percentage of patients with the large noncleaved subtype surviving for 3 yr or longer may be higher than the corresponding percentage of patients with B-immunoblastic lymphoma.

**Survival According to Clinical Symptoms**

<table>
<thead>
<tr>
<th>SYMPTOMS</th>
<th>TOTAL NO. PATIENTS</th>
<th>FAIL</th>
<th>MEDIAN SURVIVAL MOS</th>
<th>P VALUE</th>
</tr>
</thead>
<tbody>
<tr>
<td>NONE</td>
<td>83</td>
<td>53</td>
<td>27</td>
<td>P &lt; 0.005</td>
</tr>
<tr>
<td>SYST SYMPT</td>
<td>79</td>
<td>55</td>
<td>11</td>
<td></td>
</tr>
</tbody>
</table>

Fig. 8. Patients who did not have any symptoms (none) had a significantly longer survival than did patients who had systemic (syst) symptoms.

Fig. 9. There were no significant differences in survival among the five subtypes of diffuse "histiocytic" lymphoma. LC, large cleaved; LNC, large noncleaved; B-IBS, B-immunoblastic; T-IBS, T-immunoblastic; PN, prominent nucleolus type.
Figure 10 shows no significant difference in survival when a statistical comparison of follicular center cell tumors (large cleaved plus large noncleaved) versus immunoblastic tumors (T and B) was made ($p = 0.23$). Similarly, in a comparison of large noncleaved with all other subtypes, no significant difference was found ($p = 0.36$, Fig. 11).

Since symptoms and stage influenced survival significantly, we matched patients with the same symptoms and stage and compared different subtypes. However, no significant differences were found between follicular center cell and immunoblastic lymphoma, or between large noncleaved and the other subtypes. In addition, although a significant difference among induction treatments was found, adjusting the comparisons for morphological types to account for the difference in induction treatments did not change the overall results. Specifically, the $p$ value for comparing LNC to all other morphological types, adjusted for induction treatment, exceeded 0.5, and for comparing LC and LNC cases to B-IBS and T-IBS cases adjusted for induction treatment, the $p$ value was 0.37.

**DISCUSSION**

Although immunologic techniques\textsuperscript{12-21,23,30,35} are frequently used in the subclassification of lymphoproliferative diseases, these techniques are still not utilized at most medical centers for many reasons. Because morphology remains the basis for the subclassification of malignant lymphomas, it is important to apply well defined, reproducible morphological criteria. This need is clearly evident in the attempts made previously by several investigators to subdivide the DHL morphologically.\textsuperscript{17,20}

Since it has been recognized that DHL is a heterogeneous group clinically, morphologically, and immunologically, many investigators have shown that there are prognostic differences based on these parameters.\textsuperscript{17-23} Although it is generally well accepted that stage, symptoms,\textsuperscript{20,36} and sites of involvement\textsuperscript{20,36} significantly influence survival in DHL, the importance of morphological\textsuperscript{17-20} and immunologic\textsuperscript{21-23} subdivisions has not been clearly established.

An earlier study from the City of Hope on the morphological subdivision of DHL revealed that one subtype—the large cleaved type—was associated with longer survival times than was the large noncleaved type ($p = 0.08$).\textsuperscript{17} In another study at the National Cancer Institute, it was initially reported that there were three prognostic groups—large cleaved with an excellent prognosis, large noncleaved and mixed follicular center cells with an intermediate prognosis, and pleomorphic pyroninophilic and blastic types with a poor prognosis. It was also found that the prognosis for lymphomas of nonfollicular center cell origin was significantly poorer than that for lymphomas of follicular center cell origin at 2 yr ($p < 0.01$).\textsuperscript{18} However, a follow-up study involving larger numbers of cases did not confirm these initial results.\textsuperscript{20}

In contrast, results from the University of Iowa showed that patients with large noncleaved lymphoma had significantly longer survivals than those with each of the other cell types and that the survival times for each of the other subtypes were similar.\textsuperscript{19} According to data from Tufts University, in which a combination of immunologic and morphological criteria was used, the best prognosis was found for patients with the "null" cell type of large noncleaved lymphoma.\textsuperscript{23} The differ-
rences in the results among these different centers may be due to differences in staging and treatment protocols and differences in the morphological criteria employed.\textsuperscript{17-20,22,23}

The present study is based on a patient population that was subjected to relatively uniform staging and treatment in a series of Southwest Oncology Group protocols of patients with advanced disease.\textsuperscript{24,26} The most significant determinants of survival were the stage of the disease, the presence or absence of symptoms, and type of treatment. Patients who had stage III disease had significantly longer survivals than did patients who had stage IV disease ($p = 0.005$, Fig. 7); and patients who were asymptomatic had longer survivals than those who were symptomatic ($p = 0.015$, Fig. 8). Patients who received CHOP-BCG had significantly superior survival than the remaining patients ($p = 0.005$).\textsuperscript{26}

Each of the survival curves in Figs. 7 and 8, as well as the curve for all patients (Fig. 6), show a plateau, suggesting that some patients were cured. These results are in essential agreement with those reported previously.\textsuperscript{3-11}

Our main purpose in performing this study was to ascertain whether morphological subtypes of "histiocytic" lymphoma are independent parameters that influence survival. Our results showed that the median survivals of the five morphological subtypes of DHL did not differ significantly ($p > 0.25$, Fig. 9). In addition, in a comparison between lymphomas of follicular center cell origin (large cleaved, large noncleaved) and lymphomas not of follicular center cell origin (B and T-immunoblastic), no significant differences in survival times were evident (Fig. 10). Similarly, a comparison of the large noncleaved with all the other subtypes did not show any significant difference (Fig. 11). Finally, when the patients were matched for the same stage and symptoms, and when adjustments were made for treatments, no significant differences were found. Thus, our data suggest that, in a carefully staged and aggressively treated patient population, a morphological subdivision of DHL into different subtypes has little clinical relevance, whereas the clinical parameters of stage, symptoms, and type of treatment were considerably more important in determining the prognosis.

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The clinical significance of the morphological subdivision of diffuse "histiocytic" lymphoma: a study of 162 patients treated by the Southwest Oncology Group

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