Prognostic Factors and Treatment of Patients with T-Cell Non-Hodgkin Lymphoma

The M. D. Anderson Cancer Center Experience

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BACKGROUND. T-cell non-Hodgkin lymphomas (T-NHL) are more aggressive and patients have a poorer prognosis compared with patients with the corresponding B-cell lymphomas. Although intensive treatments have been developed, it is unknown whether they are more effective than CHOP chemotherapy (cyclophosphamide, doxorubicin, oncovorin, and prednisone).

METHODS. The authors’ retrospective study evaluated the clinical outcome of 135 previously untreated patients with T-NHL who were treated at The University of Texas M. D. Anderson Cancer Center (Houston, TX) between 1996 and 2002. Lymphomas with T-cell histologies with the exception of mycosis fungoides were included.

RESULTS. The estimated median overall survival was 46 months. Thirty-seven percent of the patients received CHOP therapy, 48% received intensive therapy, and 15% received other therapy. The estimated 3-year overall survival rates were 62% for the patients treated with CHOP therapy and 56% for the patients who received intensive therapy. After the exclusion of patients with anaplastic large cell lymphoma (ALCL), who are known to have a better prognosis than patients with other T-NHLs, the estimated 3-year overall survival rates were 43% for the patients treated with CHOP therapy and 49% for the patients who received intensive therapy. Parameters that may be independent prognostic factors for survival in T-NHL, excluding ALCL, included ECOG performance status ≥ 2, beta-2-microglobulin level > 2 mg/L, lactate dehydrogenase level higher than normal, bulky disease ≥ 7 cm, and a higher international prognostic index and tumor score.

CONCLUSIONS. The current study data suggested that patients treated with intensive therapies did not fare better than those treated with CHOP therapy. New treatment regimens need to be developed for patients with T-NHL.


KEYWORDS: T-cell lymphoma, anaplastic large cell lymphoma, international prognostic index, prognostic factors, tumor score, peripheral T-cell lymphoma, non-Hodgkin lymphoma.

T-cell non-Hodgkin lymphomas (T-NHL) are a heterogeneous group of diseases, accounting for 10% of aggressive lymphomas in the U.S. and Europe.¹⁻³ Patients with T-NHLs present with diverse biologic and clinical features, including systemic symptoms and generalized lymphadenopathy, as well as frequent involvement of the skin, spleen, bone marrow, and blood. With the exception of a few series,⁴⁻⁵ most published studies have demonstrated that T-cell lymphoid malignancies generally are more aggressive and confer a poorer prognosis than the corresponding B-cell lymphomas.¹⁻²⁻⁴⁻⁹ In many analyses, the T-cell immunophenotype, with the exception of CD30-
positive ALK-1-positive T-cell anaplastic large cell lymphoma (ALCL), is clinically relevant because it is an independent and significant adverse prognostic factor for disease in all of the risk groups of the international prognostic index (IPI) or tumor score.

Because patients with T-NHL treated with conventional chemotherapy comprised of the regimen of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) have a poor prognosis, investigators at The University of Texas M. D. Anderson Cancer Center (MDACC; Houston, TX), and colleagues from other institutions, have been searching for more effective treatments. Generally, these treatments are more intensive than the CHOP regimen. High-dose chemotherapy followed by autologous stem cell transplantation appears promising, but has only been evaluated in a few patients. For these reasons, we conducted a chart review of 135 patients with non-mycosis fungoides T-NHL presenting to the Department of Lymphoma at MDACC, from 1996 to 2002, 95 of whom had T-cell lymphomas other than ALCL. The goals of the current study were to identify significant prognostic factors and to compare the outcomes of different therapeutic regimens used at MDACC to treat patients with T-NHL.

MATERIALS AND METHODS

Patients with untreated T-NHL who presented to MDACC from 1996 to 2002 were included in the retrospective chart review. Informed consent was obtained per institutional regulations. To facilitate data acquisition, information was gathered from the electronic charts. When necessary, the paper charts were reviewed. If survival status was still unclear, the Social Security Death Index was consulted (available from URL: http://www.ancestry.com/search/rectype/vital/ssdi/main.htm [access date]). As a final resort, the patient or the patient’s family was contacted via telephone. The patients received three types of treatment: CHOP, intense regimens, and others (Table 1). Patient characteristics are provided in Table 2. Patients were staged according to the Ann Arbor staging system. Performance status was assessed according to the Eastern Cooperative Oncology Group scale. The IPI was calculated based on age, ECOG performance status, lactate dehydrogenase (LDH) level, number of extranodal sites involved, and stage. The tumor score was based on presence of bulky disease (defined here as ≥ 7 cm in any one dimension), beta-2-microglobulin (β-2M) levels, the presence of B symptoms (fever, night sweats, or weight loss), LDH level, and stage.

Statistical Analysis

Survival duration was measured from the date of initiation of therapy for T-NHL to the date of death from any cause or the date of last follow-up. Overall survival (OS) was estimated using the Kaplan–Meier product-limit method. The two-sided log-rank test was used to test the association between variables and OS. All P values presented are two sided, and P < 0.05 was considered statistically significant. Statistical analyses
RESULTS

All T-NHL Patients

The median age of our patient population was 55 years (range, 17–87 years). The male-to-female ratio was 2:1. Most patients had advanced-stage disease at presentation: 19% had Stage I disease, 13% had Stage II disease, 20% had Stage III disease, and 48% had Stage IV disease. Forty percent of the patients had B symptoms at the time of diagnosis. Fifty patients had peripheral T-cell lymphoma (PTCL). Of the 50 patients with PTCL, 31 received intensive treatment, 12 were treated with CHOP, and 7 received other therapies. Table 2 shows the histologies of the lymphomas of the patients with T-NHL included in our study.

The median length of follow-up for the patients included in the current study was 37 months. All patients were followed up for ≥ 13 months. Of the 135 patients, 65 had died before the end of the follow-up period. The estimated median OS rate of the cohort was 46 months (Fig. 1). There was no significant difference in OS between patients treated with CHOP and with intensive regimens: the 3-year OS rates were 62% for the patients treated with CHOP and 56% for the patients treated with intensive therapy (Fig. 2).

The few patients treated with other therapy had a worse survival. Some of these patients presented in unusual ways. One patient presented with a rash and Bell’s palsy that was treated with steroids and antibiotics. This patient’s lymphadenopathy initially decreased in size, delaying definitive diagnosis and treatment by several months. A few patients did not receive conventional chemotherapy because of comorbidities such as cardiomyopathy. Nine patients were treated with unconventional modalities such as surgery, radiotherapy, photopheresis, retinoic acid, and interferon alone or in combination with other agents.

Several prognostic factors were associated with worse survival. The estimated median OS period for patients > 60 years was 21 months compared with 63

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**TABLE 2**

<table>
<thead>
<tr>
<th>Feature</th>
<th>All patients with T-NHL</th>
<th>No. of patients with T-NHL without ALCL</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Total</td>
<td>CHOP</td>
</tr>
<tr>
<td>Total</td>
<td>135</td>
<td>95</td>
</tr>
<tr>
<td>Age &gt; 60 yrs</td>
<td>50</td>
<td>44</td>
</tr>
<tr>
<td>Histology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peripheral T-cell</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>Anaplastic large cell</td>
<td>40</td>
<td></td>
</tr>
<tr>
<td>Angioimmunoblastic</td>
<td>14</td>
<td>14</td>
</tr>
<tr>
<td>Sezary syndrome</td>
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<td>6</td>
</tr>
<tr>
<td>gd-hepatosplenic</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Subcutaneous panniculitic</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>T-cell small lymphocytic</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Precursor T-cell</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Intestinal T-cell</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Angiocentric T/natural killer cell lymphoma</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>Large granular lymphoproliferative disease</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Stage III–IV</td>
<td>92</td>
<td>71</td>
</tr>
<tr>
<td>Extranodal ≥ 2 sites</td>
<td>33</td>
<td>26</td>
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<tr>
<td>Performance status ≥ 2</td>
<td>21</td>
<td>15</td>
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<tr>
<td>LDH &gt; 585</td>
<td>67</td>
<td>46</td>
</tr>
<tr>
<td>β-2M: &gt; 3.0</td>
<td>65</td>
<td>48</td>
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<tr>
<td>Bulk ≥ 5 cm</td>
<td>26</td>
<td>17</td>
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<tr>
<td>IPI</td>
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<td></td>
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<tr>
<td>0–1</td>
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<td>38</td>
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<tr>
<td>2</td>
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<tr>
<td>Tumor score</td>
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<tr>
<td>0–2</td>
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<td>58</td>
</tr>
<tr>
<td>≥ 3</td>
<td>54</td>
<td>37</td>
</tr>
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</table>

months for younger patients (\(P = 0.02\)). Patients with hemoglobin values < 10 g/dL at diagnosis had a median OS period of 16 months, whereas those with higher hemoglobin values had a median OS period of 56 months (\(P = 0.02\)). \(\beta\)-2M levels > 2.0 mg/L also conferred an unfavorable prognosis, with a median OS of 22 months versus 63 months (\(P = 0.01\)). Patients with an LDH level greater than normal at diagnosis had a median OS of 16 months compared with 51 months for patients with a lower LDH level (\(P = 0.03\)). The number of extranodal sites (\(P = 0.01\)) and performance status (\(P < 0.01\)) were also significantly associated with worse survival (Table 3).

Patients with precursor T-cell lymphoblastic lymphoma (TLL) may have a different clinical course than patients with mature T-cell histologies. For this reason, we repeated the OS analysis, excluding the four patients with precursor TLL. The median OS time of this cohort is slightly decreased at 43 months, with the OS rates at 6.5 and 13 months being 87% and 71%, respectively.
T-NHL Patients without ALCL

Of the 135 patients with T-NHL included in the current study, 95 did not have ALCL. The median age of these patients was 60 years (range, 18–87 years). The male-to-female ratio was 2:1. Most of the patients had advanced-stage disease at presentation: 15% had Stage I disease, 9% had Stage II disease, 22% had Stage III disease, and 54% had Stage IV disease. Thirty-five percent of the patients had B symptoms at the time of diagnosis.

The majority of patients with non-ALCL T-NHL (55%) were treated with an intense regimen. Seven patients were treated with the hyper-CVAD (fractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone) regimen. Two of these patients, one with Stage I angiocentric T/natural killer cell lymphoma and the other with Stage IV precursor TLL, developed progressive disease and died during treatment. One other patient with Stage IV angiocentric T/natural killer cell lymphoma had complete disease remission that lasted almost 2 years and died shortly after disease recurrence. The other four patients experienced complete disease remission after hyper-CVAD chemotherapy and are alive without disease. These patients have been followed up for 91 months, 59 months, 18 months, and 10 months, respectively. These patients included one patient with Stage I precursor lymphoblastic lymphoma, two patients with Stage II precursor lymphoblastic lymphoma, and one patient with Stage IV angiocentric T/natural killer cell lymphoma.

When the subset of 40 patients with ALCL was excluded, the estimated median OS of the remaining patients was 21 months (Fig. 3). The 3-year OS rates for the patients with T-NHL excluding ALCL by treatment category were 43% for CHOP, 49% for more intense therapy, and 14% for other (Fig. 3). Fewer patients treated with intensive regimens died while in complete disease remission (35% vs. 42%, $P = 0.96$). More patients treated with intensive regimens had progressive disease while receiving treatment (30% vs. 21%, $P = 0.58$). The complete disease remission rates were similar between the groups (58% vs. 59%, $P = 0.99$). When we excluded patients with ALCL from the analysis, the differences in survival outcomes associated with several prognostic factors in the total group of patients with T-NHL were smaller for the patients without ALCL (Table 3). The factors that remained statistically significant included performance status and $\beta$-2M and LDH levels. One additional factor, bulky disease ($\geq 7$ cm in diameter), reached statistical significance, with patients with bulky disease having a median OS of 8 months compared with 24 months for those without bulky disease ($P = 0.03$).

Patients without ALCL with an IPI score of 0 or 1 had an estimated median OS of 43 months (Table 4). Those with an IPI score of 2 had a median OS of 25 months and those with an IPI score of $\geq 3$ had a median OS of 10 months ($P = 0.02$). Patients with tumor scores of 0–2 had a median OS of 24 months and those with a tumor score of $\geq 3$ had a median OS of 12 months. This difference was also statistically significant, with $P = 0.04$.
Patients with precursor TLL and T-cell small lymphocytic lymphoma (T-SLL) had longer survival times than patients with other T-cell lymphomas. The median OS time for all patients with T-NHL without ALCL after excluding precursor TLL is 21 months, with the OS rates at 6.5 and 13 months being 83% and 64%, respectively (Fig. 4). The median OS time for all patients with T-NHL without ALCL after excluding precursor TLL and T-SLL is 21 months, with the OS rates at 6.5 and 13 months being 84% and 64%, respectively (Fig. 5).

T-NHL Patients with ALCL

The median age of the 40 patients with ALCL was 49 years (range, 17–76 years). The male-to-female ratio was 1.7:1. B symptoms were initially present in 33% of the patients. At diagnosis, 30% of the patients had Stage I disease, 20% had Stage II disease, 15% had Stage III disease, and 35% had Stage IV disease. Follow-up was not sufficient to estimate median survival. At 3 years, the estimated survival rate was 83%. This observation is consistent with previous data showing a more favorable prognosis associated with ALCL histology.17,18 Most of the Patients with ALCL were treated with CHOP chemotherapy (65%).

Patients with ALCL with ALK-1–positive disease are believed to have a better prognosis than those with ALK-1–negative disease.19 The ALK-1 status was known for 31 of the 40 patients with ALCL. Of those, 19 (61%) had ALK-1–negative disease. There was a strong trend towards longer survival for patients with ALK-1–positive disease, with \( P = 0.06 \) (Fig. 6). The estimated 3-year OS rates were 70% and 100% for patients with ALK-1–negative and ALK-1–positive disease, respectively.

Because patients with ALK-1–negative ALCL limited to the skin tend to have a better prognosis and longer survival times, the OS analysis was repeated with these 3 patients excluded. The estimated 3-year OS rates were 66% and 100% for patients with ALK-1–negative and ALK-1–positive disease, respectively, with \( P = 0.04 \) (Fig. 7).

Of the 26 patients with ALCL treated with CHOP, 7 had ALK-1–positive disease, 11 had ALK-1–negative disease, and the status of 8 patients was unknown. Of the remaining patients treated with a non-CHOP regimen, 5 had ALK-1–positive disease, 6 had ALK-1–negative disease, and the status of 3 was unknown.
DISCUSSION

In the current study, we report several factors of prognostic significance in patients with non-ALCL T-NHL. They include performance status, \( \beta-2M > 2 \text{ mg/L} \), LDH greater than normal, any site of disease \( \geq 7 \text{ cm in dimension} \), and increasing IPI and tumor scores. Although all of these markers, especially the IPI, are well established and widely used for prognostication and therapeutic decision-making in lymphomas of B-cell origin, to our knowledge their roles in T-NHL are not as clearly defined because few published studies have evaluated prognostic factors in T-NHL. Rudiger et al.\(^9\) examined the 96 patients with non-ALCL T-NHL included in a larger study conducted by the Non-Hodgkin’s Lymphoma Classification Project and found statistically significant differences in OS between 2 IPI groups: 35% for those with an IPI of 0 – 2 compared with 8% for those with an IPI of 3 – 5 (\( P = 0.021 \)). None of the individual components of the IPI (age, LDH level, stage, performance status, and number of extranodal sites) were found to be of prognostic significance in their study. Higher IPI scores were also associated with lower OS of patients with T-NHL in a study by Reiser et al.\(^{20}\) Elevated LDH levels, B symptoms, and extranodal involvement also were found to be predictive factors. The current study results indicated that increasing IPI, and elevated LDH levels and poor performance status (two components of the IPI), were poor prognostic indicators for T-cell lymphomas. We believe the current study is novel in its investigation of the tumor score in this patient population. We found that a higher tumor score and elevated \( \beta-2M \) levels and the presence of bulky disease (2 components of the tumor score) also were associated with worse OS in patients with non-ALCL T-NHL.

As expected, patients with ALCL had higher OS rates than patients with other T-cell histologies and patients with ALK-1–positive ALCL tended to have the best prognosis. Patients with ALK-1–negative ALCL had higher OS rates than patients with other T-cell lymphomas (3-year OS rates of 68% compared with 40%, respectively). The results in this small group of patients differ from those of other published studies that report that the favorable prognosis linked to ALCL is seen only when a tumor is ALK-1 positive and that, conversely, ALK-1–negative ALCL has an OS similar to that of other T-cell lymphomas.\(^{21,22}\) This finding did not change substantially when patients with ALK-1–negative disease limited only to the skin were excluded. Evaluating survival after excluding these patients, we found that the estimated 3-year OS of patients with ALK-1–negative disease decreased only slightly from 70% to 66%. An explanation for the apparent greater survival noted in the current study of ALk-1–negative patients with ALCL compared with previously published work may be due to the relatively few patients within this subset and the retrospective nature of our analysis.

With the notable exception of ALCL treatments, results of current treatment strategies for T-NHL have been disappointing. Alternating triple therapy, hyper-CHOP, hyper-CVAD, and early transplantation strategies produced no better results than CHOP in this cohort of patients. Several factors probably contribute to this observation. First, as this was not a randomized, controlled trial, the results may be due to selection bias. The patients’ physicians may have recommended more intensive regimens to better control more aggressive and advanced-stage disease. In fact, the patients who were treated with intensive regimens generally had later-stage disease, higher LDH and \( \beta-2M \) levels, more extranodal site involvement, and more bulky disease (Table 2).

Another possible reason why the intensive regimens appeared no better than CHOP therapy in efficacy is that the group treated with the intensive therapies could have had more early deaths as a result of the greater toxicity of the treatment itself. In Figure 2, the slope of the survival curve of the patients treated with intensive regimens is slightly steeper than that of patients treated with CHOP, which suggests that the patients receiving intensive regimens were dying at a faster rate initially. However, fewer patients treated with intensive regimens died in disease remission. In addition, more patients treated with intensive regimens had progressive disease while receiving treat-
ment, and the complete disease remission rates were similar between the groups. These results strongly suggested that the greater toxicity of the intensive regimens was not masking a superior response rate. A third, and most likely, explanation for the lack of difference in efficacy among the various treatment strategies for T-NHL is that current treatment modalities are not the optimal therapy for this group of neoplasms. The current study data would suggest that past usage of combination cytotoxic chemotherapy at varying intensity is not effective in the treatment of most T-cell lymphomas and that new treatment modalities are needed. Future efforts should be devoted to the development of rational treatment strategies that take advantage of our growing knowledge of tumor biology and specifically target molecular pathways involved in disease pathogenesis. Novel therapies for patients with non-ALCL T-NHL should ultimately be explored in randomized, prospective trials, and such patients should be encouraged to enroll in these clinical studies whenever possible.

REFERENCES