CONCISE REPORT

Serum Lactic Dehydrogenase as a Prognostic Tool for Non-Hodgkin Lymphomas

By A. M. Ferraris, P. Giuntini, and G. F. Gaetani

Serum LDH levels have been found to be significantly increased in non-Hodgkin lymphoma (NHL) patients, both histiocytic and lymphocytic. The duration of survival of NHL negatively correlates with the level of serum lactic dehydrogenase (LDH), and statistical analysis reveals that patients with lower levels of LDH have a longer survival rate than the patients with higher LDH activity, irrespective of their histologic classification. The analysis of the results by the Test for Trend in Prognosis allows us to establish that the correlation of the rate of survival and LDH levels is independent from other clinical parameters.

SERUM LACTIC DEHYDROGENASE, LDH, (L-lactate: NAD oxidoreductase, E.C. 1.1.1.27) activity has been reported to be increased in a broad spectrum of diseases, and isoenzyme patterns are thought to be a useful aid in defining abnormal conditions related to pathologic involvement of different tissues. High levels of serum LDH have also been observed in patients with cancer, leukemia, and lymphoma, although no clear correlation has been established with any specific neoplastic disease or with any clinical or histologic parameter.

In this study, the measurement of the level of LDH activity in the serum has been performed on patients with non-Hodgkin lymphomas (NHL) in order to establish a possible correlation between LDH levels, the duration of survival and the histologic classification.

MATERIALS AND METHODS

Forty-one patients with NHL were entered into the study and their disease classified according to the scheme of Rappaport. Their distribution according to the histologic classification and staging is reported in Table I. All patients were staged and treated in a uniform manner. Patients with earlier stage disease received combination chemotherapy that included cyclophosphamide, vincristine, and prednisone (COP), and patients with advanced disease received adriamycin in addition (CHOP).

The serum LDH levels in 34 normal subjects, chosen to match the NHL patients in age and sex distribution, served as controls.

Serum LDH levels were determined according to Wroblewsky et al. at the time of the diagnosis. Activity was measured at 25°C on a Beckman 25K Spectrophotometer (Beckman Instruments, Palo Alto, Calif.) with a recording system and expressed as mU/ml serum. All samples were screened for isoenzyme pattern using a Titan III cellulose acetate plate according to the method recommended by Golias.

Since serum LDH concentration in NHL have a skew distribution (Fig. 1), differences between the groups tested were determined by Student’s t test using the logarithmically transformed values. Life Table estimates of percent of survivors among different groups were calculated according to Peto et al.
Table 1. Distribution According to Histologic Type and Staging

<table>
<thead>
<tr>
<th></th>
<th>Stage I</th>
<th>Stage II</th>
<th>Stage III</th>
<th>Stage IV</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Histiocytic</td>
<td>0</td>
<td>4</td>
<td>5</td>
<td>7</td>
<td>16</td>
</tr>
<tr>
<td>Lymphocytic</td>
<td>1</td>
<td>5</td>
<td>13</td>
<td>6</td>
<td>25</td>
</tr>
</tbody>
</table>

The \( \chi^2 \) test was used to determine if a statistically significant heterogeneity between groups was present; a correlation between LDH values and survival was verified with the Test for Trend in Prognosis.6

RESULTS

Serum LDH values for normals and NHL patients are recorded in Table 2. The difference between the log mean of the LDH values for normals and NHL is highly significant \((p < 0.0005)\). Similarly, the difference between the log means for the histiocytic and lymphocytic subgroups are also significant \((p < 0.0005)\).

The NHL patients, without considering their histologic classification, were subdivided with respect to the LDH values into three subgroups, each representing approximately one-third of the total distribution.6 The limits of the 3 groups were 0–220 mU, 220–460 mU, and over 460 mU. The survival of the patients among the three groups was evaluated using the \( \chi^2 \) test for the heterogeneity, and the Test for Trend in Prognosis; \( p \) values for both calculations were statistically significant \((p < 0.005)\).

Life Table estimates of percent of survivors of the three subgroups are shown in Fig. 2. The median survival time was 72.5 mo for the 0–220 mU group, 31.1 mo for the 220–460 mU, and 4.6 mo for the over 460 mU group.

The NHL patients were then subdivided according to their histologic classifica-

*Each logarithmic transformed LDH value was plotted according to the distribution, obtaining a Gaussian slope. The area under the curve was divided on the basis of the log mean ± one-half standard deviation, obtaining 3 groups, each representing the 33.3% of the observations. Accordingly, the limits of the three groups were 0–220 mU, 220–460 mU, and over 460 mU.
tion; the histiocytic and lymphocytic groups were divided into two classes (high and low LDH) on the basis of the mean LDH value reported for the NHL (316 mU/ml, Table 2). Life Table estimates for the 4 subgroups are reported in Fig. 3. The median survival time of the histiocytic lymphomas was 8 mo for the high LDH and 47 mo for the low LDH subgroup. The median survival time of the lymphocytic lymphomas was 66 mo for the low LDH, while only 10 mo for the high LDH subgroup. Taking into account the histologic classification only, the duration of survival of the histiocytic versus lymphocytic group, compared with the χ² test, was significantly different (p < 0.05).

Analysis of LDH electrophoresis did not reveal a significant modification of isoenzyme pattern distribution in the NHL patients.

DISCUSSION

A series of articles has recently outlined the need for a new classification for NHL based on a multiparameter approach that includes cell marker studies,

Table 2. Serum LDH Levels in Normal Subjects and in NHL Patients

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>Mean Age</th>
<th>LDH Range (mU/ml)</th>
<th>Log Mean ± SEM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normals</td>
<td>34</td>
<td>49</td>
<td>100–240</td>
<td>2.22 ± 0.02</td>
</tr>
<tr>
<td>NHL</td>
<td>41</td>
<td>52</td>
<td>90–1,950</td>
<td>2.50 ± 0.05</td>
</tr>
<tr>
<td>Histiocytic</td>
<td>16</td>
<td>51</td>
<td>130–1,950</td>
<td>2.71 ± 0.09</td>
</tr>
<tr>
<td>Lymphocytic</td>
<td>25</td>
<td>58</td>
<td>90–840</td>
<td>2.36 ± 0.04</td>
</tr>
</tbody>
</table>

Fig. 2. Life Table for the three subgroups. (△) NHL with LDH level less than 220 mU/ml; (○) NHL with LDH level between 220 and 460 mU/ml; (□) NHL with LDH level higher than 460 mU/ml. Open dots indicate living patients, closed dots dead ones.
LACTATE DEHYDROGENASE IN NHL

Fig. 3. Life Table for the four subgroups. (0—0) Lymphocytic NHL with LDH level less than 320 mU/ml; (O—O) lymphocytic NHL with LDH level higher than 320 mU/ml; (Δ—Δ) histiocytic NHL with LDH level less than 320 mU/ml; (Δ—Δ) histiocytic NHL with LDH level higher than 320 mU/ml. Open dots indicate living patients. closed dots dead ones.

cytochemistry, enzyme assays, etc., in order to recognize subgroups that could correlate with behavior and prognosis. In this study, an attempt has been made to establish the contribution that serum LDH determination might give.

A marked increase in serum LDH level has been observed in the past in neoplastic diseases by several authors, although no clear correlation has been established either with a specific disease or any clinical parameter. Bierman et al. reported increases in LDH activity in the serum of 34 of 50 patients with lymphoma, but no consideration was given to the histological appearances found in the group.

In the present study, serum LDH levels have been evaluated in 41 NHL patients at the time of diagnosis in order to establish possible correlations with the clinical and prognostic aspects of the disease. Serum LDH was increased in 63% of all patients with NHL; 75% of the histiocytic and 56% of the lymphocytic NHL presented a high LDH level.

Further investigation of the LDH values among patients with NHL was carried out in order to establish whether there was a relationship between the LDH level at the time of diagnosis and the survival rate. The most interesting finding was a negative correlation between the LDH level and the duration of survival. Figure 2 demonstrates the difference between the duration of survival of the three groups of NHL patients when subdivided according to the level of LDH activity irrespective of their histologic classification; the median survival time of the 0–220 mU group is 15 times that of the over 460 mU group. The analysis of the results of the Test for Trend in Prognosis allows us to confirm that the correlation between LDH values and duration of survival is independent from other parameters.

Although our data for the different rate of survival between the histiocytic and lymphocytic subgroups confirm a slight difference (p < 0.05), this could be
explained by the fact that 75% of the histiocytic have an LDH level higher than normal, while 45% of the lymphocytic have normal activity.

These results are further corroborated by the analysis of Fig. 3, where the Life Table of the histiocytic and lymphocytic lymphomas, subdivided on the basis of the mean LDH value, are separately reported. The median survival time for the high LDH and the low LDH groups is similar both for histiocytic and lymphocytic lymphomas. The correlation of LDH values at presentation with the survival time is therefore more significant than that which exists between survival time and the histologic classification only.

On the basis of the analysis performed in this study, it is possible to conclude that the evaluation of LDH level in NHL patients could represent an additional and useful parameter in defining the clinical and prognostic aspects of the disease.

ACKNOWLEDGMENT

The authors thank Dr. John Haybittle, University of Cambridge, for statistical advice and Mauro Fella for setting a computer program for the Test for Trend in Prognosis.

REFERENCES

Serum lactic dehydrogenase as a prognostic tool for non-Hodgkin lymphomas

AM Ferraris, P Giuntini and GF Gaetani

Updated information and services can be found at:
http://www.bloodjournal.org/content/54/4/928.full.html

Articles on similar topics can be found in the following Blood collections

Information about reproducing this article in parts or in its entirety may be found online at:
http://www.bloodjournal.org/site/misc/rights.xhtml#repub_requests

Information about ordering reprints may be found online at:
http://www.bloodjournal.org/site/misc/rights.xhtml#reprints

Information about subscriptions and ASH membership may be found online at:
http://www.bloodjournal.org/site/subscriptions/index.xhtml