Lactate dehydrogenase as prognostic factor in limited and extensive disease stage small cell lung cancer — A retrospective single institution analysis

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Received 26 May 2010; accepted 21 July 2010
Available online 16 August 2010

KEYWORDS
LDH;
Small cell lung cancer;
Survival;
Prognostic factor

Summary
Purpose: The aim of this retrospective study is to present data on clinical significance of lactate dehydrogenase (LDH) serum levels in an unselected contemporary patient population with small cell lung cancer (SCLC) in limited disease (LD) and extensive disease stage (ED).

Patients and methods: From June 2004 to June 2008, our electronic database including all in-patient and out-patient contacts was searched for patients with newly diagnosed LD and ED SCLC. 397 cases were identified. We collected data on patient characteristics including clinical performance status and LDH serum levels, metastatic sites, efficacy of first line chemotherapy and survival.

Results: In both limited and extensive disease SCLC, elevated LDH serum levels resulted in significantly shorter median survival. The effect was most pronounced if levels were 300 U/l or higher. In patients with limited disease and normal LDH levels, median survival was 18.0 months. If LDH was higher than 300 U/l, overall survival was reduced to 12 months. In cases with extensive disease, overall survival was significantly lower in patients with elevated LDH serum levels with an additional reduction in overall survival in patients with LDH levels above 300 U/l. (7.0 vs. 12.0 months, p = <0.001). Multivariate Cox regression analyses revealed LDH levels to be an independent predictor of mortality after adjustment for age and Performance Status in LD and ED SCLC (HR 1.003, p = 0.017; HR 1.001, p = 0.002 respectively). However, categorizing LDH levels revealed no significant difference in LD SCLC.

Conclusion: In our contemporary comprehensive patient population, LDH is proved to be a strong, independent predictive factor of median survival in patients with LD and ED SCLC.

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Introduction

Lung cancer is still the leading cause of death in patients with cancer. It accounts for over 800,000 deaths worldwide every year. The frequency of SCLC has been slightly decreasing over the last 20 years. The prognosis of SCLC has not changed much since the seventies, until the value of prophylactic brain irradiation in treatment responders was demonstrated. In extensive disease stage patients without treatment, median survival is about 6–8 weeks after establishment of diagnosis. With chemotherapy, median survival reaches 9–11 months. In limited stage SCLC, median survival without treatment is 15–17 weeks. With combined radiochemotherapy, 22–27 months are achievable. The most important prognostic factors in SCLC are disease stage, clinical performance status (PS) and lactate dehydrogenase (LDH). Pre-treatment serum levels of albumin, neuron-specific enolase and carcinoembryonal antigen are less useful in determining the course of the disease but might be used as additional tools in a follow-up setting.

The significance of LDH had been examined for patients with lymphoma, sarcoma and multiple myeloma. The role of LDH as prognostic factor in SCLC has been established in the last decades and was proven again. The aim of our study was to examine the clinical importance of pre-treatment LDH serum levels on overall survival in an unselected patient population with LD and ED SCLC at our institution.

Patients and methods

Our electronic database including all in-patient and outpatient contacts was searched for patients with newly diagnosed LD and ED SCLC from June 2004 to December 2008. We identified 397 patients. All patients had SCLC confirmed by histology or cytology. Previous chemotherapy, radiotherapy or surgery was not performed before staging and evaluation of LDH serum levels. Performance status ranged from 0 to 3 on the Eastern Cooperative Oncology Group (ECOG) scale. There were 4 patients with other malignancies in the past, all of these patients had normal LDH serum levels. At base line, no patient suffered of acute heart failure, acute coronary syndrome or severe hepatic dysfunction. Renal and hematologic parameters were normal. Thus, relevant possible confounding factors for elevated LDH serum levels were eliminated as far as possible in a clinical setting.

All patients with newly diagnosed SCLC had a complete history and physical examination taken. Performance status was evaluated at base line. A staging procedure was performed including bronchoscopy, CT-scan of the chest and upper abdomen, CT-Scan or MRI of the brain, bone scan and a comprehensive laboratory panel including hematologic, renal and hepatic function tests and LDH. In patients with clinical diagnosis of LD SCLC, a bone marrow specimen was obtained by the method of Jamshidi. Serum levels of NSE or other serum tumor markers were not routinely assessed.

LDH serum levels were available in 395 of 397 patients (99.5%).

Of each patient with SCLC, every single electronic report was reviewed. We collected data on age, disease stage, date of initial diagnosis, last observation and survival in months, performance status, levels of lactate dehydrogenase, metastatic sites, and result of first line chemotherapy (complete response, partial response, stable disease and progressive disease).

The vast majority of responses were evaluated using the RECIST criteria. Complete response (CR) is defined as a complete disappearance of all target lesions. Partial response (PR) means a decrease of the sum of the greatest diameter of all target lesions of more than 30% compared with base line measurement. Stable disease (SD) is present if target lesions do not vary in size by more than 20%. Progression of disease was the case in a greater than 20% increase of the above named sum.

Survival time was measured from the date of diagnosis to the date of death. There was a minimum delay between diagnosis and start of chemotherapy ranging from 1 to maximum 5 days.

LDH serum levels were assessed by UV-test. The catalytic activity of LDH was determined by measurement of increased absorbency of nicotine—adenine dinucleotide at 340 nm as a result of catalytic oxidation of lactate to pyruvate. The normal reference range is 135–225 Units per liter (U/l) at our hospital. All LDH measures were performed at our hospitals’ clinical laboratory (COBAS Integra 700, Roche).

The method of Kaplan and Meier was used to calculate survival curves. To assess the statistical significance of differences between survival curves, we performed log-rank tests. Multivariate testing was done by Cox regression analyses. LDH was first categorized into two levels (LDH <225 and LDH >225 U/l). Then we applied a three level categorization with the lowest level as reference (LDH <225, LDH 225–300 and LDH >300 U/l). An adjustment was performed for age, disease stage (limited versus extensive disease) and performance status (PS 0–1 versus 2–4).

Results

Limited disease

155 pts (39%) had limited disease at time of diagnosis. The median age of patients with SCLC LD was 63 years (range 38–83). 138 pts (86%) were in ECOG performance status 0–1; 10 pts (10%) in PS 2 and 6 (4%) in PS 3.

LDH levels were available in all but one patient (99.4%). Range was from 97 to 901 units per liter (U/l) with a median level of 230 U/l. In 98 patients (63%) LDH was equal or below 225 U/l which is the upper normal level at our hospital. In 56 (36%) of the cases the level was higher than 225 U/l. In 25 patients (15%), highly elevated levels (>300 U/l) were detected.

A relevant difference regarding Performance Status (PS) was not seen comparing the cohorts with normal vs. elevated LDH levels (1.10 vs. 1.18).

Equally, age showed no clinically relevant difference (61 vs. 63 years).
In the 98 pts with normal LDH levels, partial response (PR) was reached in 62.6% and complete response (CR) in 12.2%; thus yielding a response rate (RR) of 74.5%. 8.2% had progressive disease (PD) after first line chemotherapy. 20 pts were still alive at time of data analysis. The remaining 71 pts had a median survival of 20.0 months.

In the group with LDH levels higher than 225 U/l, 59.6% had PR as result of first line chemotherapy, CR was achieved in 19.3% (RR: 78.9%). 8.8% were progressive. 11 pts out of 55 were censored. The remaining 44 pts showed a median survival of 14.5 months. There was no statistical significant difference in treatment response between the two LDH categories (Table 1).

Analysis of all cases with LD SCLC including censored events (20%) showed a not statistically significant reduction of median survival in patients with elevated LDH levels compared to the cases with normal LDH levels (Table 2).

We then divided the cases with elevated LDH levels in two groups (LDH 225–300 and LDH <300 U/l). Median survival was markedly reduced in the group with LDH levels above 300 U/l. Again, this difference was not statistically significant (Table 3, Figs. 1 and 2).

However, multivariate Cox regression analyses revealed LDH levels to be an independent predictor of mortality after adjustment for age and Performance Status in LD SCLC (Hazard Ratio 1.003, p = 0.017) (Table 4).

Extensive disease

242 pts (61%) were in extensive disease stage. The median age of patients with SCLC ED was 64 (range 41–81) years. 194 pts (80%) were in performance status 0–1; 37 (15%) in PS 2 and 11 (5%) in PS 3. Main metastatic sites in all patients with SCLC ED were: Liver (42%), brain (22%), bone (29%), adrenal glands (16%) and pleura (16%).

LDH levels could be retrieved for 99.6% of all patients. The median level was 317 U/l (range 99–3575).

In 87 pts (36%), LDH was found to be lower or equal the upper limit normal of 225 U/l. In 153 pts (64%), LDH was higher than 225 U/l. Severe elevated levels (>300 U/l) were seen in 84 patients (35%).

We performed an additional analysis of localization of metastases and number of metastatic sites in patient group with different LDH levels. We observed a considerably higher frequency of liver metastasis (58 vs. 25%) and bone metastasis (34 vs. 20%) in patients with severe elevated LDH levels (>300 U/l) compared to the subset with normal LDH levels. On the other hand, the incidence of brain metastasis was higher in the group with normal LDH levels (29 vs. 14%).

Regarding number of metastatic sites there was a trend toward more metastatic sites in patients with severe elevated LDH levels showing 2 metastatic sites in 34 vs. 26% and 4 or more metastatic sites in 5 vs. 1% (Table 5).

There was no influence on treatment as 98% of all patients with SCLC ED received platinum based therapies with etoposide being the most commonly used second compound (90%).

In the group with normal LDH levels, 65.5% had PR, 6.9% CR, resulting in 72.4% RR. 12.6% had PD as result of first line treatment. 10 pts were censored. The remaining 75 pts presented a median survival of 12.3 months.

Of 154 pts with elevated LDH levels, PR was seen in 63.9%, CR in 2.6%, yielding a RR of 66.5%. PD resulted of first line treatment in 23.1%. Only 6 (3%) were still alive at time of data analysis. Median survival was 9.6 months in this group. As in LD SCLC, there was no statistically significant

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<thead>
<tr>
<th>Table 1</th>
<th>LDH serum levels and treatment response in limited disease SCLC.</th>
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<tbody>
<tr>
<td>Response</td>
<td>LDH &lt;225 U/l</td>
</tr>
<tr>
<td>Complete response</td>
<td>12.2%</td>
</tr>
<tr>
<td>Partial response</td>
<td>62.2%</td>
</tr>
<tr>
<td>Response rate**</td>
<td>74.5%</td>
</tr>
<tr>
<td>Stable disease</td>
<td>17.3%</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>8.2%</td>
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</table>

*Chi-square test.  **Response rate: sum of complete and partial responses.

<table>
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<th>Table 2</th>
<th>Log-rank test for median survival in LD SCLC with normal versus elevated LDH serum levels.</th>
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<tbody>
<tr>
<td>LDH level (U/l)</td>
<td>Median Survival (months)</td>
</tr>
<tr>
<td>LDH ≤ 225</td>
<td>18.0 (13.2–22.8)</td>
</tr>
<tr>
<td>LDH &gt; 225</td>
<td>14.0 (9.8–18.2)</td>
</tr>
</tbody>
</table>

*Reference.
difference in treatment response between the two LDH categories (Table 6).

There was no difference in PS between the patients with normal vs. elevated LDH levels (1.16 vs. 1.29). A slightly higher age was detected in the cohort with elevated LDH levels (62 vs. 65 years).

After inclusion of all censored events into statistical analysis, a significant reduction in median survival was detected in the group with elevated LDH levels compared with cases with LDH level below upper limit normal (Table 7).

Patients with LDH levels above 300 U/l had a significantly shorter survival (7.0 months) (Table 8, Figs. 3 and 4).

Multivariate Cox regression analyses revealed LDH levels to be an independent predictor of mortality after adjustment for age and Performance Status also in ED SCLC (Hazard Ratio 1.001, \( p = 0.002 \)) (Table 9).

Thus, statistical evaluation strongly confirmed an independent prognostic value for LDH in both limited and extensive stage SCLC.

Discussion

The present data confirm the significance of lactate dehydrogenase as a strong independent pre-treatment factor in small cell lung cancer in a large unselected contemporary patient population with limited and extensive stage disease treated at our institution between 2004 and 2009. We had data available on all patients. 48 cases were censored, but included into statistical analyses. In contrast to other published studies, we were able to retrieve LDH levels for almost all (99.5%) patients, and cases with LD and ED SCLC were separately assessed. Elevated LDH levels are known to correlate with inflammation and tumor necrosis, thus reflecting tumor activity. Mayor confounding factors which might have led to elevated LDH levels were largely excluded at base line.

In patients with limited disease SCLC, response rate was not altered by LDH levels. In patients with elevated LDH levels (>225 U/l), survival was significantly reduced. When we further divided these cases into two groups (LDH 225–300 U/l and <300 U/l) there was a considerably shorter median survival in the latter group. However, there were only 25 cases of which 7 were censored. Thus, statistical significance was not reached. This is also visible in Fig. 2 where the line representing LDH levels above 300 U/l ends at 0.2.

The median survival of patients with LD SCLC and elevated LDH levels beyond 300 U/l was actually similar to the median survival in patients with ED SCLC. It might be true that markedly elevated LDH levels are suggestive of higher tumor burden or tumor activity even though distant metastasis cannot be detected by standard staging procedures. We looked at tumor size in this patient group in order to possibly detect bulky thoracic disease as cause for higher tumor burden and thus elevated LDH levels. In 19 of 25 patients, CT-scans were...
obtainable. Mean tumor size was 6.1 cm, thus there was no tale of especially big or bulky lesions in these patients.

Our patients with ED SCLC showed typical frequency and localization of metastases. We noted a correlation between severe elevated LDH levels (>300 U/l) and a higher incidence of liver metastases (58 vs. 25%) and bone metastases (34 vs. 20%) compared to patients with normal LDH levels. In addition, there was a trend toward more metastatic sites in patients with severe elevated LDH levels. Both findings might play a role in the design of future studies on new chemotherapeutic agents in the treatment of small cell lung cancer. A statistically significant increased rate of primary progressive disease as result on first line therapy (12.6 versus 23.2%, \( p = 0.046 \)) was seen in the cases with elevated LDH levels. In patients with ED SCLC and normal LDH serum levels a trend toward higher response rates was detected (\( p = 0.338 \)). Median survival was significantly reduced in patients with elevated LDH levels. After further differentiation of the cases, the group with strongly elevated levels (above 300 U/l) showed an even more pronounced effect on survival. These patients had a median survival of only 7.0 months compared to 12.0 months with normal LDH serum levels.

Determination of LDH levels is advantageous as the method is readily available in routine laboratory panels; actually it is part of most routine laboratory assessment panels in patients with suspected thoracic cancer. The test is inexpensive and standardized.

In earlier reports a certain degree of bone marrow involvement of 10–16% was seen.\(^{26,27}\) In another publication only two of 110 patients with normal LDH levels had bone marrow involvement.\(^{28}\) The question arises whether one might omit bone marrow sampling in patients with normal LDH levels.

Besides LDH levels, disease stage and performance were the two other variables which also were statistically proven to be significant as predictive factors. We additionally analyzed whether gender might be another predictive factor. However, in our comprehensive patient population, gender did not reach statistical significance as prognostic marker.

In conclusion, LDH is an easily obtainable strong pre-treatment predictor of outcome in patients with limited and extensive stage small cell lung cancer using a threshold of 225 U/l as upper limit normal. The independent level of LDH was confirmed by statistical adjustment for the two other most important predictive markers: extend of disease and clinical performance status. There is a trend toward even more reduced overall survival in LD SCLC with LDH levels above 300 U/l. In patients with ED SCLC with such elevated LDH levels, median survival was significantly shorter.

LDH should still be measured in every patient with small cell lung cancer and seriously taken into consideration when assessing prognosis and treatment options in the individual patient.

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<td>12.0 (10.7–13.3)</td>
<td>Ref.</td>
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<td>LDH &gt; 225–&lt;300</td>
<td>11.0 (9.1–12.9)</td>
<td>0.360</td>
</tr>
<tr>
<td>LDH &gt; 300</td>
<td>7.0 (6.0–7.9)</td>
<td>&lt;0.001</td>
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Table 7 Log-rank test for median survival in ED SCLC with normal versus elevated LDH serum levels.

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<td>LDH/C20225</td>
<td>12.0 (10.7–13.3)</td>
<td>Ref.</td>
</tr>
<tr>
<td>LDH &gt; 225</td>
<td>8.0 (6.7–9.3)</td>
<td>.004</td>
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Table 8 Log-rank test for median survival in ED SCLC with different LDH serum levels.

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Table 8 Log-rank test for median survival in ED SCLC with different LDH serum levels.

Figure 3 Median survival in ED SCLC with normal versus elevated LDH levels.

Figure 4 Median survival in ED SCLC with different LDH level subgroups.
Conflict of interest statement

The authors of the present manuscript on LDH as prognostic factor in LD and ED SCLC don’t have any conflicts of interest to disclosure.

References