Original article

Pretreatment serum LDH as additional staging parameter in small-cell lung carcinoma

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Abstract

Background: In patients with limited disease staged small-cell lung cancer (SCLC), overall survival is still poor. Therefore, a retrospective study was carried out of 48 patients with limited disease staged SCLC to select a parameter which can identify prognostic subgroups at the time of diagnosis.

Materials and methods: Follow-up varied from 3 to 96 months during which 38 patients died. Based on clinical outcome, patients were clustered into three groups: complete remission (CR) (n = 16); local recurrence (LOC) (n = 7); and distant recurrence (DIS) (n = 25). Age, gender and pretreatment biochemical parameters were correlated with clinical outcome and survival.

Results: No differences in survival were found in patients with LOC (14% 2-year survival) and DIS (16% 2-year survival) (P = 0.67). Patients with complete remission demonstrated a significantly better survival (75% 2-year survival). LDH was found to be the only significant correlate of both tumour progression and survival. All patients with pretreatment LDH levels > 240 IU/l (n = 13) demonstrated tumour recurrence. The survival rate of patients with LDH levels < 240 IU/l (41% 2-year survival) was much better than that of patients with LDH levels > 240 IU/l (8% 2-year survival) (P = 0.0001).

Conclusion: LDH may be used for the identification of prognostic subgroups in limited disease SCLC. Patients showing pretreatment LDH levels > 240 IU/l have an extremely high risk of tumour recurrence, whereas survival is poor. In patients with LDH levels, < 240 IU/l survival is significantly better. © 1998 Elsevier Science B.V.

Keywords: Small cell lung cancer; Limited disease; Occult metastasis; Lactate dehydrogenase

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1. Introduction

Small-cell lung carcinoma (SCLC) is conventionally staged as limited or extensive disease and the identification of these subgroups has well-established prognostic significance. While only 5% of patients with extensive disease achieve 2-year survival, 2-year survival in limited disease may exceed 20% and 5-year survival may approach 12% [1,2]. Since the poor outcome in limited disease is probably due to occult metastatic disease not detected by currently used imaging modalities [3–5], more accurate parameters are needed to improve identification of subgroups.

The aim of this retrospective study was to investigate whether, in addition to imaging modalities, a single parameter or a combination of parameters could be selected which can identify prognostic subgroups at the time of diagnosis.

2. Materials and methods

2.1. Patients and methods

A retrospective study was carried out of 51 patients (9 female, 42 male) who came under observation at our hospital between January 1988 and January 1994 because of newly diagnosed limited disease, staged SCLC. In all patients, the diagnosis of SCLC was established by biopsy and histological examination. In two patients, insufficient biochemical data were available for evaluation, while one patient died during the first course of chemotherapy due to a sepsis. Of 48 patients, sufficient data were available for further evaluation. Follow-up ranged from 3 to 96 months (mean 24 months) during which 38 patients died. The staging procedure at the time of diagnosis included chest radiography, CT scan of the chest, ultrasonography of the liver, bone scintigraphy and iliac crest bone marrow biopsy. In this selected group of patients, a CT scan of the brain was not performed at the initial stage because of the absence of neurological symptoms. However, in the case of symptoms during follow-up, which were confirmed by an experienced neurologist, a CT scan of the brain was performed. All patients were initially treated with chemotherapy including cyclophosphamide, etoposide and doxorubicin. Four patients received five courses of chemotherapy or less without radiotherapy, while 44 patients underwent additional radiotherapy of the chest and brain. Based on clinical outcome, patients were clustered into three groups: complete remission (CR); distant recurrence (DIS); and local recurrence (LOC). Unfortunately, data on performance status and pretreatment weight loss were not available in many patients.

Table 1

| Pretreatment characteristics of 48 patients with initially limited staged SCLC |
|-----------------------------|-----------------------------|-----------------------------|
| Clinical outcome | DIS (n = 25) | LOC (n = 7) |
| Age (years) | 66.8 ± 6.6 (55–78) | 61.0 ± 9.3 (37–83) | 64.4 ± 7.7 (55–76) |
| Female gender; n (%) | 5 (20) | 0 (0) | 0.096 |
| AP (IU/l) | 56 ± 17 (34–83) | 54 ± 19 (33–114) | 45 ± 4 (38–49) |
| LDH (IU/l) | 170 ± 29 (119–229) | 251 ± 81 (147–446) | 155 ± 26 (107–185) |
| γ-GT (IU/l) | 16.5 ± 6.6 (5–24) | 16.36 ± 7.29 (10–33) | 20.2 ± 13.4 (6–35) |
| AST (IU/l) | 10.2 ± 2.99 (7–17) | 9.93 ± 2.66 (6–17) | 8.4 ± 1.95 (6–11) |
| ALT (IU/l) | 9.3 ± 4.17 (3–14) | 11.79 ± 6.76 (4–31) | 8.60 ± 2.3 (5–11) |
| Protein (g/l) | 68 ± 3.0 (63–74) | 70 ± 6.5 (59–83) | 69 ± 6.2 (60–80) |
| Albumin (g/l) | 42 ± 4 (32–51) | 43 ± 5 (31–50) | 41 ± 3 (37–46) |

Except for female gender values, values are mean ± S.D. with range given in parentheses. S.D. = standard deviation; CR = complete remission; DIS = distant recurrence; LOC = local recurrence; n = sample size; LDH = lactate dehydrogenase; AP = alkaline phosphatase; Ca = calcium; AST = aspartate aminotransferase; ALT = alanine aminotransferase; γ-GT = γ-glutamyl transpeptidase; leuco = leucocyte count.

*P-value of Student’s t-test, Mann–Whitney test or χ²-test.
Table 2
Organs involved in metastatic disease during follow-up in patients with initially limited disease staged SCLC

<table>
<thead>
<tr>
<th>Site</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone</td>
<td>5 (10)</td>
</tr>
<tr>
<td>Brain</td>
<td>15 (31)</td>
</tr>
<tr>
<td>Liver</td>
<td>10 (21)</td>
</tr>
<tr>
<td>Lungs</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Adrenals</td>
<td>3 (6)</td>
</tr>
</tbody>
</table>

n = sample size; n.d. = not determined.

2.2. Biochemistry

Values of commonly tested biochemical parameters, such as lactate dehydrogenase (LDH; normal value < 160 IU/l), alkaline phosphatase (AP; normal range 15–60 IU/l), calcium (Ca; normal range 2.25–2.55 mmol/l), protein (normal range 60–80 g/l), albumin (normal range 40–50 g/l), γ-glutamyl transpeptidase (γ-GT; normal range men 6–28 IU/l, women 14–18 IU/l), aspartate aminotransferase (AST; normal range 215 IU/l) and alanine aminotransferase (ALT; normal range 216 IU/l) were gathered.

2.3. Statistical methods

All clinical and biochemical parameters were correlated with the development of metastases and survival. Patient groups were compared using the Student’s t-test, the Mann–Whitney test or χ²-square test where appropriate. Quantitative variables were summarized with their mean, standard deviation and range. Multivariate analysis with respect to tumour recurrence were done with the logistic regression model. The predictive value of the patient characteristics for the result of follow-up was quantified with the odds ratio and its 95% confidence level. Multivariate analyses with respect to survival was done with the Cox regression model. The prognostic value of the patient characteristics was quantified with the hazard ratio and its 95% confidence level and illustrated with Kaplan–Meier curves. Throughout, a P-value of 0.05 or less was considered statistically significant.

3. Results

Table 1 lists the pretreatment characteristics of the 3 groups of patients. Sixteen patients achieved complete remission (33%). In 25 of 48 (52%) patients, distant recurrence was found during follow-up, while 7 (15%), showed local recurrence. The sites of metastases during follow-up were brain (31%), liver (21%), bone (10%), adrenals (6%) and lungs (2%) (Table 2). In 19 patients with solitary distant recurrence, the brain was the most commonly involved site (n = 9). Of all pretreatment variables tested, LDH was the only parameter showing a significant...
Fig. 3. Survival curves of patients with limited disease and LDH levels $< 240$ IU/l (dotted line) and LDH levels $> 240$ IU/l (solid line).

\(P < 0.0001\) correlation with tumour recurrence and survival. Its odds ratio for tumour progression, i.e. local or distant recurrence was 1.02 (95% CI 0.891.16) \((P = 0.0224)\). In addition, all patients with a pretreatment LDH $> 240$ IU/l \((n = 13)\) developed metastases compared to 31% of the patients with a LDH $< 240$ IU/l. In the 19 patients with a solitary site of metastatic disease, 18 had elevated LDH levels. Using LDH measured at the time of diagnosis, a statistical model was developed that allowed the probability of progression during follow-up to be estimated (Fig. 1). These data show that patients with limited staged disease, in combination with a pretreatment elevated serum LDH, have a high risk of tumour recurrence. However, no correlation was found between a biochemical parameter or a combination of parameters and a specific site of distant recurrence.

Kaplan–Meier curves of the subgroups of patients are shown in Fig. 2. Patients with complete remission demonstrated a significantly better survival (75% 2-year survival, \(P < 0.001\)) than the other groups. No differences in survival were found \((P = 0.67)\) in patients with local recurrence (14% 2-year survival) and patients developing metastases (16% 2-year survival) during follow-up. Patients with LDH levels $< 240$ IU/l demonstrated a significantly better survival (41% 2-year survival) than patients with LDH levels $> 240$ IU/l (8% 2-year survival) \((P = 0.0001)\). The hazard rate of LDH $> 240$ IU/l was 2.83 (95% CI 1.40 5.72) \((P = 0.0039)\). Survival curves based on LDH levels are shown in Fig. 3. To exclude infection as a cause of elevated LDH levels, leucocyte counts were studied, but no significant correlation was found between both variables \((P = 0.87)\).

4. Discussion

A number of investigators have dealt with the identification of prognostic factors in patients with small-cell lung cancer (SCLC). It has been reported that one of the most important determinants of outcome is tumour extension. Patients with limited disease demonstrate significantly better survival than patients with extensive disease. Combination chemotherapy results in median survival times of approximately 8–11 months for patients with extensive disease and 12–16 months for patients with limited disease [6,7]. In the present study, however, in the patients initially staged as having limited disease, more than 50% developed metastases and 15% showed local recurrence, which is in agreement with other studies [8,9]. Since patients with tumour progression have a much poorer prognosis than the patients with complete remission, patient management would benefit from having access to parameters that can identify prognostic subgroups at the initial stage.

Our results show that LDH is a significant, independent pretreatment prognostic variable in patients.
with SCLC. Patients initially staged as having limited disease, but with elevated LDH levels, have a significantly increased risk of tumour recurrence. Our results suggest that pretreatment LDH levels may be a tumour marker for occult disease not detected by current imaging modalities. Elevated levels of LDH have been documented in association with enhanced metabolic activity. In neoplasia, elevation of LDH may reflect the release secondary to tumour necrosis.

In patients with SCLC, correlations between biochemical parameters and specific sites of metastases have been suggested [10]. In this respect, the evaluation of metastases in the liver from biochemical parameters is a particular problem because the blood tests commonly used for this purpose, such as transaminases, are not very sensitive and are extremely non-specific. Troell et al. [11] described that even in late metastatic disease, only 25% of patients had increased transaminase values. Beck et al. described that γ-GT is a more sensitive indicator of liver involvement [12]. These authors reported that in addition to the increase in γ-GT with progress of metastatic disease, a greater proportion of enzyme activities was elevated. Despite the fact that more than 20% of the patients developed metastases in the liver, no correlation was found with the liver function tests or a combination of these tests. A negatively correlated relationship between serum LDH levels and brain involvement has been described by Sagman et al. [13]. These authors suggested that this finding may relate to factors governed by the blood–brain barrier. In the present study, the brain was found to be the most commonly involved site in this selected group of patients. Almost one in three patients developed brain metastases. However, a correlation between LDH and brain involvement was not found. In the 19 patients with a solitary site of metastatic disease, 18 had elevated LDH levels. Therefore, unfavourable prognosis in patients with elevated levels of LDH may not only reflect tumour mass, but also malignancy grade. This finding is in agreement with the LDH levels found in malignant lymphoma, in which higher levels were found in high- versus low-grade tumours [14]. Therefore, LDH may serve as a measure of overall disease activity.

In our study, survival of patients demonstrating local recurrence was not significantly different from patients showing distant recurrence. Consequently, these patients can be considered as one group when assessing prognosis, which is in agreement with the results described by Shepherd et al. [15]. In contrast, patients with complete remission showed an extremely good prognosis with a two-year survival rate of 75%. These results confirm the necessity of having additional parameters for the identification of prognostic subgroups. In the present study, by using a multivariate analysis, LDH was found to be the most predictive parameter of outcome in patients with SCLC, which is in agreement with other studies [6,16,17]. In contrast to previous studies [18,19], we did not find a correlation between albumin and survival. This may be due to the patient selection. In addition, CEA has been reported to be of prognostic value [20], but this parameter was not routinely tested in our patient group and therefore could not be analyzed.

Although performance status has been found to have prognostic value in most other studies [6,9,21], it was not analyzed in the present retrospective study, because it was not available in many patients. In contrast with the objective clinical and biochemical parameters, performance status is a factor that depends on both qualitative and quantitative aspects of the disease and on the general health of the patient. In addition, poor performance status has no statistically adverse effect on the complete response rate [9,13]. Furthermore, Albain et al. [6] suggested a superiority of LDH over performance status with respect to the assessment of prognosis. The LDH emerged as a highly significant factor for the identification of prognostic subgroups, whereas performance status did not.

Finally, the absence of mediastinal or supraclavicular lymph node metastases and no pleural effusion have been reported as significant prognostic factors for patients with limited disease [6,15,22,23]. Based on the presence or absence of lymph node involvement, pleural effusion and atelectasis, Shepherd et al. [15] identified three prognostic subgroups of patients with limited SCLC. Patients with very limited disease, i.e. without lymphadenopathy, pleural effusion or atelectasis, had a significantly better prognosis than patients with mediastinal lymphadenopathy. Sagman et al. [24] identified the absence of mediastinal lymph nodes and plasma LDH as significant
prognostic factors for patients with limited disease. The most favourable class was defined by limited stage, age less than 70 years and absence of mediastinal lymph nodes. However, limited disease patients with positive mediastinal nodes also demonstrated favourable survival provided they were of female sex and had a normal pretreatment LDH. This favourable effect of a normal LDH is similar to that reported by Albain et al. [6].

A particular advantage of LDH is that this laboratory test is inexpensive and readily available. In patients staged as having limited disease, the assessment of LDH may define disease burden or activity and obviate the necessity of more complex and invasive staging investigations. Consequently, the requirements for the assessment of prognosis and treatment planning could be simplified, patient discomfort minimized and health care costs might be reduced. These results, however, await confirmation in a large prospective study in which lymph node involvement as well as performance status should be included.

References