Cyfra 21-1 as a Biologic Marker of Non-small Cell Lung Cancer*

Evaluation of Sensitivity, Specificity, and Prognostic Role

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Background: Cytokeratins are epithelial markers whose expression is not lost during malignant transformation. Cyfra 21-1 is a cytokeratin-19 fragment that is soluble in serum and may be a useful circulating tumor marker.

Study objective: The aims of this study were (1) to confirm sensitivity and specificity of Cyfra 21-1 in detecting non-small cell lung cancer (NSCLC) and especially the squamous cell subtype, (2) to assess the potential relationship between Cyfra 21-1 and disease stage of the disease in NSCLC, and (3) to evaluate prognostic effect of Cyfra 21-1 in NSCLC.

Methods: An immunoradiometric assay of serum Cyfra 21-1 was performed in 161 patients with lung cancers and 71 others with benign lung diseases. The ability of Cyfra 21-1 to detect different histologic subtypes of lung cancer vs benign lung diseases was assessed through receiver operating characteristic (ROC) curves and comparisons with other tumor markers such as carcinoembryonic antigen, neuron-specific enolase, and squamous cell carcinoma antigen. Comparisons of Cyfra 21-1 levels according to histologic subtype and disease stage were done using Kruskal-Wallis test. Independent prognostic value of Cyfra 21-1 was studied with a multivariate analysis of survival (Cox’s model).

Results: Using a threshold of 3.3 ng/mL for Cyfra 21-1, sensitivity and specificity were, respectively, 0.59 and 0.94 in NSCLC, 0.68 and 0.94 in the subgroup of the squamous cell carcinoma, and 0.19 and 0.94 in small cell lung cancer. Cyfra 21-1 levels were significantly higher in advanced NSCLC than in early-stage disease. All 29 patients with serum concentrations >32 ng/mL had stage IIIB-IV and only one of 14 patients with stage I-II disease had Cyfra 21-1 level >18 ng/mL. In the multivariate analysis of survival, Cyfra 21-1 was an independent prognostic factor along with performance status and disease stage in NSCLC.

Conclusions: Cyfra 21-1 is a sensitive and specific tumor marker of NSCLC, especially of squamous cell subtype. It also reflects the extent of the disease and has an independent prognostic role along with performance status and disease stage in NSCLC.

Implications: A high level of Cyfra 21-1 in apparently early-stage NSCLC should be an indication for more extensive workup before thoracotomy. The independent prognostic role of Cyfra 21-1 level may be useful in stratifying populations with advanced NSCLC or early-stage resected NSCLC as elevated Cyfra 21-1 levels might identify those patients at high risk for treatment failure.

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Key words: Cyfra 21-1; non-small cell lung cancer; prognostic factor; squamous cell lung cancer; tumor markers

Formerly relatively rare, lung cancer is now the most common fatal malignancy in both men and women. There are over 150,000 new cases diagnosed every year in the United States.1

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The four most important histologic categories in terms of both frequency and clinical significance are squamous cell carcinoma, small cell carcinoma, adenocarcinoma, and large cell carcinoma. Approximately 90% of all lung carcinomas are included in these four main categories.2

The prognosis of lung cancer is generally poor and only slight improvement in survival has been obtained during the last decades. In non-small cell lung cancer (NSCLC), 5-year survival varies from 50% in resected stage I disease to 5% in stage IIIB and virtually 0% in stage IV.3 In small cell lung cancer (SCLC), median survival is 10 to 18 months in the limited disease stage and 7 to 12 months in extensive
disease. Some of the prognostic factors common to NSCLC and SCLC are the stage and performance status.

Tumor markers, including carcinoembryonic antigen (CEA), neuron-specific enolase (NSE), and squamous cell carcinoma (SCC) antigen have been investigated for putative diagnostic and prognostic value. Many lung adenocarcinomas contain immunoreactive CEA, but there is no specificity at all for lung origin. NSE, a neural form of a glycolytic enzyme present in all human cells, is found to be elevated in a majority of patients with SCLC. Serial NSE levels tend to mirror the patient’s clinical course, falling with remission, rising with relapse. Unfortunately, NSE lacks specificity and like CEA, occasionally is elevated in nonmalignant conditions. SCC is a tumor antigen purified from a cervical squamous cell carcinoma and has a sensitivity between 33 and 61%.

Cytokeratin 19 is an acidic protein of 40 kD that is part of the cytoskeleton of epithelial cells. The distribution of the intermediate filament is exclusive to cells of simple and pseudostratified epithelium (such as the bronchial epithelium). Cytokeratin 19 is specifically recognized by two monoclonal antibodies (mAbs), KS 19-1 and BM 19-21.

Serum levels of Cyfra 21-1 have been determined in healthy individuals and those with benign lung disease. Of 71 healthy blood donors, 99.8% had a Cyfra 21-1 level below 1.2 ng/mL. In a group of 546 patients with benign lung diseases, 96% had levels below 3.3 ng/mL. Recent results suggest that Cyfra 21-1 has a good sensitivity and specificity for the diagnosis of squamous cell carcinoma as well as prognostic value.

The aims of the current study are to (1) investigate the sensitivity and specificity of Cyfra 21-1 for squamous cell carcinoma and other subtypes of NSCLC, (2) identify any relationships between elevated Cyfra 21-1 levels and other tumor markers, and (3) evaluate the putative independent prognostic value of Cyfra 21-1 in NSCLC.

METHODS

Patients

One hundred sixty-one patients with lung cancer admitted to the Department of Chest Disease (University Hospital, Strasbourg, France) between March 1989 and June 1993 were prospectively entered in the study (Table 1). All had histologically and/or cytologically confirmed lung cancer. There were 72 with squamous cell carcinomas, 29 with adenocarcinomas, 15 with large cell carcinomas, and 45 with SCLC. Karnofsky performance status was noted and staging of NSCLC was done by clinical examination; chest radiography; bronchoscopy; computed tomographic scan of chest, upper abdomen, and brain; abdominal ultrasonography; and bone scan. Following identical staging for SCLC, limited disease was defined as any disease limited to the hemithorax, including mediastinal and/or ipsilateral supraclavicular lymph nodes. Extensive disease was defined as any disease extending beyond the hemithorax by invasion or metastasis. In addition to Cyfra 21-1, CEA, NSE, and total lactate dehydrogenase (LDH) serum levels were performed. SCC levels were determined only in patients with squamous cell carcinoma.

Control Subjects

The serum Cyfra 21-1 was measured in 71 control subjects with nonmalignant pulmonary disease (sarcoidosis, COPD, asthma). CEA, NSE, and SCC levels were performed in 38 of the 71 nonmalignant controls.

Cyfra 21-1 Immunoradiometric Assay

A special kit (ELSA-Cyfra 21-1) is used for the immunoradiometric assay of Cyfra 21-1 in human serum. Serum samples were separated and stored at −30°C until tested. Cyfra 21-1 (CIS Biointernational; GIF/Yvette, France) is a solid-phase “sandwich” immunoradiometric assay. The cytokeratin 19 was recognized by two mouse mAbs, KS 19-1 and BM 19-21, directed against two different epitopes present on the soluble fragment of the cytokeratin, namely serum Cyfra 21-1. These mAbs had been obtained by immunization against the MCF-7 cell line.

KS 19-1 coated ELSA tubes were incubated with 100 μL of the patient’s serum, a control serum, and a standard curve (composed of the following concentrations of cytokeratin 19: 0, 2.1, 11.5, 34, and 65 ng/mL) and 300 μL of iodine-125 labeled BM 19-21 (18.5 kBq/mL) for 20 h at 8°C. Afterwards, the ELSA tubes were washed with a solution of 9 mL of polysorbate 20 (Tween 20) in 3 L of distilled water.

Radioactivity was counted in a gamma scintillation counter calibrated for iodine-125 (1 KB counter) and expressed in nanograms per milliliter. The amount of radioactivity bound to the ELSA is proportional to the amount of Cyfra 21-1 present at the beginning of the assay.

The CEA, SCC, and NSE assays were performed, respectively, with different analyzers (Boehringer ES 600 [ELISA assay], IMx Abbot [MEIA assay], and Pharmacia kit [double-antibody

Table 1—Characteristics of the Patients with NSCLC and SCLC

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>M/F</th>
<th>Mean age, yr (range)</th>
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<td></td>
<td></td>
<td>116</td>
<td>45</td>
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<td></td>
</tr>
<tr>
<td>&gt;70</td>
<td>74</td>
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<td>IIIb</td>
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<tr>
<td>&gt;70</td>
<td>39</td>
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</tr>
<tr>
<td>≤70</td>
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<tr>
<td>Unknown</td>
<td>3</td>
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</tbody>
</table>
radioimmunoassay]. Upper limit of normal values are 5 ng/mL for CEA, 1.5 ng/mL for SCC, and 12.5 ng/mL for NSE.\textsuperscript{16-18}

Statistics

Sensitivity and specificity of Cyfra 21-1 as a serologic marker were determined. Sensitivity is defined as the probability of testing positive if the disease is truly present, whereas, specificity is the probability of screening negative if the disease is truly absent. Sensitivity = TP/TP+FN and specificity = TN/TN+FP where TP is true-positive, TN is true-negative, FP is false-positive, and FN is false-negative.\textsuperscript{19} To evaluate the ability of tumor markers to predict the histologic type, receiver operating characteristic (ROC) curves were plotted. As an example, in squamous cell carcinoma for different cutoffs of Cyfra 21-1 levels, the ROC curve shows the proportion of patients with a TP test (i.e., patients with squamous cell carcinoma and a serum Cyfra 21-1 above a given level) as compared with the proportion with a FP test (i.e., patients with benign lung disease and a serum Cyfra 21-1 above the given level).

If a test is of no use, then both proportions are roughly equal for all values and the ROC curve is a straight line with a slope of 1. A useful test is indicated by a ROC curve that rises rapidly then reaches a plateau; the point of inflection represents the value of the test giving the best compromise between the TP and FP.\textsuperscript{20}

Results of the serum markers were expressed in each subset of patients as median and variation as interquartile range.

To compare quantitative variables, nonparametric statistical analysis was used. Differences between more than two groups were evaluated by means of the Kruskal-Wallis one-way analysis of variance. Correlation between quantitative variables was established through Spearman’s coefficient.

Survival analysis was performed for NSCLC. Survival was defined as the time from the date of serum sampling to the date of death or to the date of analysis, on October 31, 1993. Probability of survival was estimated through the Kaplan-Meier method. Univariate comparisons of survival curves were done by means of the log rank test and multivariate analysis of survival was performed using the Cox model.\textsuperscript{21} Before inclusion in the model, quantitative variables were categorized to allow a baseline hazard ratio (Karnofsky performance score $\leq$ 70 or $>70$, LDH $\leq$ upper limit of normal or $>$ upper limit of normal, Cyfra 21-1 $\leq$ 3.3 ng/mL or $>$ 3.3 ng/mL, and ACE $\leq$ 5 ng/mL or $>$ 5 ng/mL).

All statistical calculations were performed using a software package (BMDP, Statistical Graphics System).

**RESULTS**

Reproductibility of Cyfra 21-1 Radiometric Assay

Reproductibility of determination of serum con-

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**FIGURE 1.** ROC curves of all NSCLC vs benign lung diseases. The areas under the ROC curve for Cyfra 21-1, NSE, and CEA were 0.85, 0.78, and 0.66, respectively.
centrations was examined by measuring a control serum control in 13 different assays (interassay). The mean ± standard deviation and coefficient of variation was 3.67 ng/mL ± 0.41 and 4.6%, respectively.

**Cyfra 21-1 and Histology**

The median (interquartile) serum Cyfra 21-1 in all NSCLC, squamous cell carcinoma, NSCLC other than squamous cell, and SCLC were 4.3 (2.05 to 16), 6.0 (2.55 to 19), 2.6 (1.25 to 9.75), and 1.7 (0.98 to 2.4) ng/mL, respectively. The median (interquartile) serum Cyfra 21-1 in nonmalignant control subjects was 1.0 (0.87 to 1.4). The Cyfra 21-1 level was found to vary significantly with respect to the different histologic groups (\(p=1.5\times10^{-15}\)).

**ROC Curves for Serum Cyfra 21-1 and Other Tumor Markers**

A ROC curve with various cutoff levels of Cyfra 21-1 was first constructed to study the ability of this marker to predict NSCLC (Fig 1). For all 116 NSCLC, the best compromise between TP (80.5%) and FP (19.5%) was given by the threshold of 1.5 ng/mL. At the threshold of 3.3 ng/mL, TP rate was 59% and FP rate was only 5.6%. For squamous cell carcinoma, the best compromise between TP (83.1%) and FP (16.9%) was given by the threshold of 1.5 ng/mL (Fig 2). At the threshold of 3.3 ng/mL, specificity was greater (94.4%) at the expense of a loss of sensitivity (68.1%). For other NSCLC, the best compromise was also given by the threshold of 1.5 ng/mL with a sensitivity of 70.2% and a FP rate of 14%.

At the threshold of 3.3 ng/mL, sensitivity was 40.9% and specificity was 94.4%. CEA and NSE had a limited ability to predict either NSCLC (Fig 1) or squamous cell carcinoma (Fig 2) or other NSCLC. For squamous cell carcinoma, SCC with a threshold of 1.5 ng/mL was a less sensitive marker than Cyfra 21-1 (sensitivity=51%;specificity=87.5%). There was a moderate but significant correlation between SCC and Cyfra 21-1 (Spearman’s coefficient=0.35,
p=0.007). In SCLC, Cyfra 21-1 was not as good as NSE in predicting SCLC (area under ROC curve 0.68 for Cyfra 21-1 vs 0.94 for NSE). At the threshold of 3.3 ng/mL, sensitivity of Cyfra 21-1 was 19% and specificity was 94.4%.

**Cyfra 21-1 and TNM Stage**

The Cyfra 21-1 level differed significantly according to stage both in all patients with NSCLC and in those with squamous subtype (p=9×10^-4 and 0.006, respectively). Among all NSCLC, the median (interquartile range) serum Cyfra 21-1 of stage I-II, IIIa, IIIb, and IV was 1.1 (0.75 to 2), 5.8 (2.3 to 12), 5.7 (1.8 to 16), and 5.35 (2.7 to 25), respectively (Fig 3). Among squamous cell carcinomas, the median (interquartile range) serum Cyfra 21-1 of stage I-II, IIIa, IIIb, and IV was 1.05 (0.75 to 1.80), 4.15 (1.10 to 10.4), 5.70 (1.8 to 11.0), and 12.4 (4 to 34.5), respectively. All 29 patients with a Cyfra 21-1 serum concentration above 32 ng/mL had stage IIIB or IV. Only one patient with stage I-II disease had a Cyfra 21-1 serum concentration above 18 ng/mL.

**Prognostic Role of Cyfra 21-1 in NSCLC**

Univariate analysis of survival of all patients with NSCLC showed a significant difference according to performance status (≤70 vs >70), stage, Cyfra 21-1 level (≤3.3 or >3.3 ng/mL), CEA level (≤5 vs >5 ng/mL), and LDH (below or more than the upper normal limit). There was no significant difference in survival according to age (≤60 years vs >60 years), sex, and histologic subtype.

All variables with significant prognostic impact in univariate analysis were included in Cox’s model. In addition, sex and age were forced into the model. Proportionality of hazards hypothesis was verified for each of the variables. Performance status, stage, and Cyfra 21-1 serum concentration were the only independent prognostic factors (Table 2).

**Discussion**

Our study confirms that Cyfra 21-1 is a both sensitive and specific tumor marker for NSCLC and especially for squamous cell carcinoma. It appears more sensitive and more specific than other tumor markers such as CEA, NSE, and slightly better than...
Table 2—Cox’s Regression Analysis: Estimated Relative Risks (n=105)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Relative Risk (95% Confidence Interval)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Performance status</td>
<td>5.25 (2.9-9.5)</td>
<td>&lt;10^-4</td>
</tr>
<tr>
<td>Cyfra 21-1</td>
<td>2.8 (1.5-5)</td>
<td>0.0004</td>
</tr>
<tr>
<td>Stage</td>
<td>1.5 (1.1-2)</td>
<td>0.0054</td>
</tr>
</tbody>
</table>

SCC in squamous cell carcinoma. The inability of Cyfra 21-1 to detect SCLC was also confirmed. The Cyfra 21-1 level in NSCLC correlates with the stage and, moreover, it appears as an independent prognostic factor along with performance status and stage.

Cytokeratins are not randomly distributed in different epithelia, but they appear to be characteristic for certain types of epithelial differentiation. Their expression is not lost by malignant transformation of epithelial cells. Therefore, subtypes of lung cancer demonstrate characteristic cytokeratin profiles that can be evaluated immunohistochemically to assist with tumor classification. Although the normal role of the cytokeratin as a component of cytoskeleton is unknown, necrosis and cell lysis are likely to be the events preceding the release of the cytokeratin 19 fragment into the blood.

Cell type heterogeneity may explain some differences between the published studies with respect to sensitivity of Cyfra 21-1 in the various histologic subtypes of lung cancer. Table 3 shows that the magnitude of these differences is very small for NSCLC and rather large for SCLC. Elevated Cyfra levels in SCLC could be either due to tumor heterogeneity with subpopulations of squamous cell differentiation or due to cytokeratin expression by the SCLC tumor cells.

<table>
<thead>
<tr>
<th>Source</th>
<th>Cut-off Level of Cyfra 21-1, ng/mL</th>
<th>Histologic Subtype</th>
<th>Se</th>
<th>Sp</th>
<th>AUROCC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pujol et al^13</td>
<td>3.6</td>
<td>NSCLC</td>
<td>0.56</td>
<td>0.89</td>
<td>0.80</td>
</tr>
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<td></td>
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<td>SQC</td>
<td>0.63</td>
<td>0.91</td>
<td>0.83</td>
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<td>0.46</td>
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<td>0.74</td>
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<tr>
<td>Ebert et al^25</td>
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<td>NSCLC</td>
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<tr>
<td></td>
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<td>0.67</td>
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<tr>
<td>Stieber et al^24</td>
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<td>0.95</td>
<td>—</td>
</tr>
<tr>
<td></td>
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<td>SQC</td>
<td>0.60</td>
<td>0.95</td>
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<tr>
<td></td>
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<td>SCLC</td>
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<tr>
<td>Present Study</td>
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<tr>
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<td>SCLC</td>
<td>0.19</td>
<td>0.944</td>
<td>0.68</td>
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</table>

*SQC=squamous cell carcinoma subtype; ND=not done; Se=sensitivity; Sp=specificity; AUROCC=area under ROC curve.

There is a strong relationship between serologic Cyfra 21-1 levels and staging of NSCLC. Elevated Cyfra 21-1 levels were usually indicative of extensive disease, findings that are very consistent with those of the previous published studies. A primary objective of oncology health-care workers is to determine those patients with NSCLC who would benefit from surgical resection, i.e., patients with stage I and II and some with stage IIIA. Accurate determination of the stage is strongly related first to the extent of the staging procedures and second to their sensitivity and specificity. In this setting, biologic variables that would be able to predict extensive disease are potentially very useful. In this study, serum concentrations >32 ng/mL were associated with stage IIIB or IV disease. Careful staging to rule out advanced disease is indicated in patients having Cyfra 21-1 levels of this magnitude.

Even though Cyfra 21-1 level was correlated with stage of disease in NSCLC, it nevertheless was an independent prognostic factor in our study. Pujol et al^13 found that Cyfra 21-1 was an independent prognostic factor in their entire population of lung cancers (NSCLC and SCLC) along with performance status and disease stage (relative risk [95% confidence interval], respectively, 1.64 [1.1 to 2.5], 2.81 [1.8 to 4.3], and 2.47 [1.4 to 4.3]). The importance of Cyfra 21-1 as a prognostic factor in their study was inferior to that found by us, as they included patients with SCLC in their analysis.

The characterization of prognostic factors in a population with NSCLC is of primary importance in assessing the efficacy of a new treatment, whether it be chemotherapy for advanced disease or adjuvant therapy for resected early-stage disease. For instance, it is known that performance status will impact as much as chemotherapy on the prognosis of stage IV NSCLC. Also, recent studies have emphasized the prognostic significance of K-ras mutations and ploidy
in resected NSCLC, especially adenocarcinomas.\(^{26}\) Another independent prognostic factor such as serum Cyfra 21-1 may serve to explain some of the differences in survival between different populations with advanced NSCLC who were given the same chemotherapy. Hypothetically, in resected early-stage NSCLC, elevated Cyfra 21-1 level might identify those patients at high risk for recurrence and thus select a population for trials of adjuvant therapy.

We conclude that Cyfra 21-1, a soluble fragment of cytokeratin 19, is more sensitive and specific than other markers in NSCLC. Its level correlates with disease stage in NSCLC. Cyfra 21-1 performance status and disease stage are independent prognostic factors in NSCLC.

ACKNOWLEDGMENTS: We are grateful to Yolande Ledermann for excellent technical assistance.

REFERENCES