Original Articles

Expression of Carcinoembryonic Antigen in Peripheral- or Central-located Small Cell Lung Cancer: Its Clinical Significance

Shuji Bandoh1, Jiro Fujita1, Yutaka Ueda1, Yoko Fukunaga1, Kazutaka Dohmoto1, Satoko Hojo1, Yu Yang1, Yasufumi Yamaji2, Jiro Takahara1 and Toshihiko Ishida1

1First Department of Internal Medicine, Kagawa Medical University, Kagawa and 2Mitoyo General Hospital, Kagawa, Japan

Received December 15, 2000; accepted March 22, 2001

Background: Small cell lung cancer (SCLC) has a higher percentage of hilar masses than other histological types of lung cancer. The primary site is usually adjacent to the hilum, but we often observe primary sites in the peripheral lung field. In this study, our objectives were to elucidate whether peripheral-located small cell lung cancer (PSCLC) is an independent entity and whether it differs clinically from central-located small cell lung cancer (CSCLC).

Methods: We reviewed the clinical and pathological features of 52 patients treated at Kagawa Medical University Hospital between 1987 and 1996 with a diagnosis of SCLC. We defined CSCLC as a tumor whose primary site is located in the segmental bronchi or more proximally and PSCLC as a tumor located distal to the subsegmental bronchi. Twenty-one PSCLC patients and 31 CSCLC patients were identified. Kaplan–Meier survival curves were constructed and comparisons were made between PSCLC and CSCLC by the log-rank test. The carcinoembryonic antigen (CEA) level was also evaluated in each group.

Results: Although the percentage of limited disease (LD) in the patients with PSCLC was higher than that in the patients with CSCLC, the 3-year survival rate of PSCLC tended to be worse than that of CSCLC (9% for patients with PSCLC and 29% for those with CSCLC). Survival curves of patients with PSCLC also tended to be worse than those of patients with CSCLC, not only in the limited disease group but also in the extensive disease (ED) group. In addition, the mean CEA value in patients with PSCLC was higher than that in patients with CSCLC (p < 0.001), whereas the neuron specific enolase (NSE) level was not significantly different between PSCLC and CSCLC. The median survival of patients with pretherapeutic CEA titers of ≥5 ng/ml was significantly shorter than that in patients with CEA levels <5 ng/ml.

Conclusion: These findings suggest that the survival of SCLC patients with a high CEA level was significantly shorter than that of patients with a low CEA level. In addition, CEA levels in PSCLC patients were significantly higher than those in CSCLC patients. However, the survivals of LD or ED patients with PSCLC and CSCLC were not statistically different.

Key words: lung cancer – small cell carcinoma – peripheral – central – carcinoembryonic antigen

INTRODUCTION

A number of studies have been carried out to establish the frequency of various radiographic abnormalities associated with bronchogenic carcinoma, according to the individual cell types (1–4). A mass or prominence in or about the hilum is characteristic of the radiographic pattern of small cell carcinoma, occurring in 52–78% of cases (1,4,5). In most of these cases, the hilar mass probably represented a primary lesion and its metastasis. It has been pointed out in pathological studies that hilar nodes in small cell lung cancer (SCLC) tend to be involved early and massively when the primary lesion is in the parenchyma. Hilar or perihilar masses are seen much less frequently with tumors of other cell types. On the other hand, a peripheral mass on a chest radiograph occurs most often in

© 2001 Foundation for Promotion of Cancer Research
association with adenocarcinoma, being present in 72% of cases (3). In contrast, peripheral masses are much less frequently seen in cases of squamous cell and small cell carcinoma, occurring in 31 and 32% of cases, respectively (1,2,4).

Certainly, SCLC could be more successfully managed if a good tumor marker was determined. The ideal tumor marker would be useful in the screening of high-risk populations, in the diagnosis of symptomatic patients and as a prognostic indicator. It would correlate with the tumor burden and vary with the clinical course. To our knowledge, no single marker has all of these properties. Based on the neuroendocrine activity and aminoprecursor uptake and decarboxylation characteristics of SCLC, different components of blood such as creatine kinase-BB (6), neurophysins (7) and bombesin (8) have been evaluated as tumor markers for SCLC. However, none of these markers have been widely applied in clinical practice. Some other substances are probably more useful as markers for SCLC. Neuron-specific enolase (NSE) is a protein that is selectively expressed in SCLC. This protein is used clinically as both a serum and an immunocytochemical diagnostic marker of SCLC (9,10). It has been reported that pre-gastrin-releasing peptide (pro-GRP) is helpful as a diagnostic aid and as a marker for therapeutic effect and relapse in patients with SCLC, supplemented with serum NSE (11,12). Another useful marker is serum thymidine kinase, which reflects the degree of cell proliferation.

Carcinoembryonic antigen (CEA), which is often elevated in the patients with adenocarcinoma, has been shown to increase mainly in patients with extensive disease and thus correlates with the tumor burden; however, because it can also be increased in patients with limited disease, it is of no use as a staging test. Very high levels of CEA have been correlated with liver metastasis (13). Prognostic values have been found for different levels of CEA, but not all of the studies have taken into account other prognostic variables (14,15). CEA also has been correlated with the clinical course of SCLC and thus found to be an adjunct to clinical evaluation (14,16).

Based on the clinical observation that a significant proportion of patients with relapsing SCLC show an elevated serum CEA concentration whereas the serum NSE concentration remains normal, the aim of this study was to investigate, in a larger population of SCLC patients, correlations between CEA levels and the outcome of therapy and prognosis. In addition, our aim was also to determine whether patients with peripheral-located small cell lung cancer (PSCLC) differed clinically from those with central-located small cell lung cancer (CSCLC).

**PATIENTS AND METHODS**

**PATIENTS AND CLINICAL EXAMINATION**

From 1987 to 1996, 56 consecutive patients with histologically or cytologically proven SCLC were analyzed in this retrospective study. Patients had to be aged 18–75 years with a WHO performance status of 0–2. The population included 10 (19%) female patients. The age range was 39–75 years with a median of 67 years.

The initial chest radiographs of all cases were available and these formed the basis of our analysis. We also grouped our own cases according to the radiographic sites of origin. Peripheral origin included parenchymal and apical masses, whereas central origin consisted of both central masses (including lymph nodes) and obstructive findings without peripheral masses. Cases defined as peripheral in origin showed a small peripheral mass with a large central mass. We also defined central tumors as being located in the segmental bronchi or more proximally and peripheral tumors as being located distal to the subsegmental bronchi. The original radiologists’ reports for all patients were examined for cases that met these criteria. These radiographs were then reviewed by one of the authors to ensure conformity with these criteria. Four cases could not be classified according to the site of origin because of massive pleural effusion or obstructive pneumonitis. Therefore, these cases were excluded from our study.

Pretreatment evaluation consisted of a complete blood count (including an estimation of platelet number and a leukocyte differential count), chemistry profile, serum electrolytes, CEA, NSE, chest roentgenogram, computed tomography (CT) scans of the abdomen and brain, bone scintigraphy, bronchoscopy, electrocardiogram and urinalysis.

Patients were considered to have limited disease (LD) if all demonstrable tumors were encompassed within a tolerable radiation port. Extensive disease (ED) refers to metastatic disease outside the chest. Patients with mediastinal or contralateral adenopathy or ipsilateral pleural effusion were included in the limited-stage category.

**TREATMENT**

Most patients (17 patients with PSCLC and 26 patients with CSCLC) were treated by combination chemotherapy with cisplatin and etoposide (cisplatin 80 mg/m² on day 1 and etoposide 100 mg/m² on days 1–3, repeated every 3 weeks). Four patients with PSCLC and five patients with CSCLC were treated with cyclophosphamide, adriamycin and vincristine (cyclophosphamide 800 mg/m², adriamycin 50 mg/m² and vincristine 1.4 mg/m² on day 1, repeated every 3 weeks). Chest irradiation was performed in all patients with LD, sequentially (two patients with PSCLC and three patients with CSCLC) or concurrently (eight patients with PSCLC and eight patients with CSCLC). Prophylactic cranial irradiation was not performed on any patient.

The treatment response was evaluated by the same methods as used for pretreatment evaluation. Response categories included complete response (CR), partial response (PR), and no response. A complete response was defined as the disappearance of all clinical evidence of active tumors for a minimum of 4 weeks. A partial response was a ≥50% decrease in the sum of the products of the two longest perpendicular diameters of measured lesions, without increase in the size of any other lesion or the appearance of a new lesion. Any case that
did not qualify as complete or partial response was considered to be a no response.

PATHOLOGICAL DIAGNOSIS

New paraffin sections of tumor tissue blocks (including primary tumor tissue obtained by bronchial biopsy or regional lymph nodes containing a metastatic tumor) were cut and stained with hematoxylin and eosin and categorized into one of three WHO (World Health Organization) (1981) subtypes of SCLC (oat cell carcinoma, intermediate cell type and combined oat cell carcinoma).

CARCINOEMBRYONIC ANTIGEN AND NEURON-SPECIFIC ENOLASE ASSAY

Serum CEA values were determined by a direct competitive binding radioimmunoassay. In the current study, the upper normal limit (x ± 2SD) was 2.5 ng/ml.

NSE in serum from the 52 patients in the series was determined by radioimmunoassay (RIA). The normal level of serum NSE based on the investigation of healthy individuals is 10 ng/ml.

STATISTICAL ANALYSIS

Mean comparisons of samples were performed by the Mann–Whitney–Wilcoxon test. The survival curves were computed by the Kaplan–Meier method. To test for equality of survival curves, Mantel’s log-rank test was employed.

RESULTS

A total of 52 patients were analyzed in this study (Table 1). These patients consisted of 21 (40.4%) with PSCLC and 31 (59.6%) with CSCLC. There were no differences in age, sex or smoking history between those patients with PSCLC and CSCLC. Ten (47.6%) had LD and 11 (52.4%) had ED among PSCLC patients and 11 (35.5%) had LD and 20 (64.5%) had ED among CSCLC patients. Nine (42.9%) had oat cell carcinoma and 12 (57.1%) had intermediate cell carcinoma in PSCLC patients and 19 (61.3%) had oat cell carcinoma and 12 (38.7%) had intermediate cell carcinoma in CSCLC patients. There were no cases diagnosed as combined oat cell type in our series.

The total response rate was 88%. Of the 21 patients with PSCLC, five (23.8%) showed a complete response and 13 (61.9%) a partial response. There were 10 (32.3%) complete responses and 18 (58.1%) partial responses in the 31 patients with CSCLC. The 3-year survivals of patients with PSCLC and CSCLC were 9 and 23%, respectively, whereas overall survival was 21%. Treatment failure was local and systemic in 19 patients (90%) with PSCLC and 22 patients (71%) with CSCLC. Systemic failure included 14 patients (74%) with PSCLC and 18 patients (82%) with CSCLC. Local failure included five patients (26%) with PSCLC and four patients (18%) with CSCLC, respectively.

Survival curves from the date of diagnosis for patients with PSCLC or CSCLC are shown in Fig. 1. Although the survival curves for PSCLC tended to be worse than those for CSCLC, the difference was not significant in Mantel’s log-rank test. In addition, survival curves of patients with PSCLC tended to be worse than those of patients with CSCLC in both the LD and ED groups (Fig. 2).
Plasma CEA was measured at the time of diagnosis in all patients. The distribution of the initial CEA levels by location of the tumor is shown in Fig. 3A. Fifteen (71.4%) of the patients with PSCLC had an abnormal level of CEA (>2.5 ng/ml), compared with eight patients (25.8%) with CSCLC. The median CEA levels were significantly higher ($p < 0.001$) in patients with PSCLC than in those CSCLC (8.78 and 1.88 ng/ml, respectively), whereas NSE levels were similar in PSCLC and CSCLC patients (Fig. 3B).

In order to assess the prognostic significance of a given level
of pretreatment plasma CEA, a cut-off point was evaluated. It was found that those patients who did poorly in the course of the disease had shown a pretreatment CEA level >5 ng/ml. Two CEA groups were thus defined. Group I comprised patients with a pretreatment CEA level ≤5 ng/ml and Group II patients with a CEA level ≥5 ng/ml. As shown in Fig. 4, the survival of the patients in Group II was significantly worse than that of patients in Group I (p = 0.02960). However, there was no significant difference in response rate between Group I (87.5%) and Group II (91.6%). Increased CEA levels tended to correspond with a higher proportion of patients with PSCLC.

DISCUSSION

Textbook and review articles state that SCLC continues to have the highest relative frequency of central mass at presentation. Usually, it has neuroendocrine activity and amino precursor uptake and decarboxylation characteristics. In addition, most SCLCs are sensitive to chemotherapeutic agents. On the other hand, adenocarcinoma of the lung is primarily a peripheral tumor (17). Since adenocarcinoma of the lung often produces CEA and is resistant to chemotherapeutic agents, the prognosis is known to be poor.

In our study, the apparent sites of origin (peripheral 40.3% vs central 59.6%) for SCLC were the same as in earlier reports (1,4,5). In addition, the survivals of PSCLC and CSCLC patients were not statistically different between LD and ED patients. However, the CEA levels were significantly higher in PSCLC than in CSCLC patients. Such a high expression of CEA in patients with PSCLC has several possible explanations. One such factor may be that PSCLC represents a fundamentally different neoplasm than the more common CSCLC. That is, PSCLC may share characteristics with adenocarcinoma.

Several studies have shown that there is a pathological subgroup of pulmonary neoplasms categorized as small cell by light microscopic examination which shows ultrastructural features more consistent with adenocarcinoma. Nomori et al. (18) reported that there are different types of subgroups in SCLC such as very poorly differentiated adenocarcinoma of the small cell type, small cell carcinoma with a large cell component and very poorly differentiated squamous cell carcinoma of the small cell type. In addition, they stated that undifferentiated carcinoma of the small cell type (but not intermediate subtype) belong to these criteria (18). These trend to be peripheral tumors, classified as the intermediate subtype, and have a poor prognosis. In one review of 45 patients who underwent surgery for SCLC, 37 (82%) were of the intermediate cell type whereas in the non-surgical group of 481 patients fewer than 50% were of this subtype (19). Most of the resected intermediate cell type lesions were small peripheral carcinomas. The predominance of subtypes other than oat cell was also found in a study by Gephart et al. (20). In our series, however, statistical significance was not obvious; there were more cases diagnosed as intermediate cell type in patients with PSCLC than in those with CSCLC.

Histological heterogeneity of lung cancer is also important. Although recent ultrastructural, cytological and immunohistochemical observations have contributed substantially to our understanding of the histological features and histogenesis of lung cancer, the concept of lung cancer heterogeneity is not novel. In 1955, Olcott (21) reported the results of a light microscopic autopsy study of 234 lung cancers: 65% of the tumors, with an average of 3.7 blocks per case, were homogeneous, whereas 35%, with an average of 4.3 blocks per case, appeared to be heterogeneous. Reid and Carr (22) found an even higher percentage of lung cancer heterogeneity in a study of 138 lung cancer specimens obtained at surgery and autopsy, with only 37% of the tumors appearing to be homogeneous on light microscopic examination.

The heterogeneity of SCLC is also of particular interest and several studies have addressed this issue (23–26). Brereton et al. (24) reported that in four cases of SCLC that had been diagnosed by biopsy, features of mixed small cell and squamous cell carcinoma were seen at autopsy. Abeloff et al. (25), in a light microscopic study of 40 biopsy and autopsy specimens from patients with SCLC, found that 28% of the tumors were heterogeneous. Roggli et al. (26) reported that a pattern of SCLC was found in association with any of the three histological patterns of non-SCLC.

McDowell and Trump (27) described a small cell carcinoma with tripartite differentiation of individual cells within the tumor. Hess et al. (28) reported that cytological examination of tumor cells stained by the Papanicolaou technique often demonstrates heterogeneity within lung cancer, with up to half of the tumors showing adenomatous differentiation. Immunoperoxidase studies of lung cancer for the presence of CEA have demonstrated variable staining for this antigen among different histological types as well as local variability within individual tumors, indicative of heterogeneity for the production of CEA (29).

Waalkes et al. (14) found that a CEA level of 15 ng/ml is adequate for a prognosis in extensive disease. On the other hand, Lokich (30) reported no relation between survival and
plasma CEA. Sculier et al. (15) found that a CEA level ≥50 ng/ml is associated with shorter survival; median survivals were 7.5 months in the high CEA group and 11.5 months in the low CEA group (p < 0.001). They also reported that this level of CEA was an independent prognostic factor when adjustment was made for extent of disease and performance status (15). Krischke et al. (31) also reported that a CEA level ≥5 ng/ml at the time of diagnosis serves as an independent prognostic factor by its ability to identify a subgroup of SCLC patients with a poor prognosis. From the above investigations, the majority of the authors came to the conclusion that serum CEA determinations improve diagnosis and control of therapy in patients with SCLC. The data also suggest that high serum CEA levels are an adverse prognostic factor.

It is unknown whether the biological behavior or treatment response of homogeneous tumors is different from that of heterogeneous tumors. Radice et al. (32) reported differences in behaviors and treatment responses for mixed large cell/small cell carcinomas compared with oat cell or intermediate small cell carcinomas. Further studies are clearly required to elucidate this problem.

If it is true that PSCLC shares some characteristics with adenocarcinoma, we should introduce surgery at some point of the treatment in order to improve prognosis. Adjuvant surgical resection after chemotherapy has been found to result in long-term survival and cure for a significant proportion of patients with pathological stage I disease. A significant improvement in survival could not be documented for patients in stages II and III (33). We believe that surgical therapy contributed significantly to improved survival for patients with PSCLC of mixed histological types and, for that reason, we emphasize the importance of the location of the primary site and the serum CEA level in patients with SCLC. As a result, surgery is again being evaluated as a possible treatment for PSCLC. Although rare, patients with a radiologically defined PSCLC would theoretically be among the most appropriate candidates for resection. Further prospective studies are clearly required in this area.

References