

CD117 expression is a predictive marker for poor prognosis in patients with non-small cell lung cancer

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Abstract. Non-small cell lung cancer (NSCLC) accounts for >85% of incidences of lung cancer, for which the predicted 5-year survival rates are low and recurrence rates remain high. Although it has been reported that the patients with SCLC cells that possess the cluster of differentiation (CD) 117 marker exhibited poor prognosis and poor response to chemotherapy, no studies concerning the association of CD117 expression with prognosis of the patients with NSCLC have been reported. An *in vitro* study reportedly revealed that CD117-positive cell populations in NSCLC cell lines exhibited cancer stem cell (CSC) phenotypes including self-renewal and chemoresistance. Therefore, the present study hypothesized that if CD117-positive cells are CSC-like cells, CD117 positivity may be associated with the prognosis of patients with NSCLC. To confirm this hypothesis, the association between CD117 expression in patients with NSCLC and clinicopathological characteristics was investigated. CD117 expression was examined by immunohistochemistry in 99 patients with NSCLC who underwent curative surgical resection. Tumor samples in the present study included 73 samples of adenocarcinoma and 26 of squamous carcinoma. The associations of CD117 expression with clinicopathological features and prognosis were examined. The lymph node metastasis and rates of recurrence were significantly associated with overall survival rates through multivariate analysis

($P < 0.001$ and $P < 0.001$), respectively. A Kaplan-Meier analysis for relapse-free survival and the log-rank test revealed that the patients with CD117-positive cell populations exhibited shorter relapse-free survival rates compared with patients whose cells were CD117-negative ($P = 0.014$). The multivariate analysis demonstrated that venous invasion, pathological stage, and CD117 expression were independent prognostic parameters for relapse-free survival in patients with NSCLC ($P = 0.001$, $P = 0.001$ and $P = 0.002$), respectively. In conclusion, these data suggest that CD117 expression in NSCLC may serve as a useful marker for predicting the prognosis of patients with NSCLC.

Introduction

The occurrence of cancer is increasing in association with the prevalence of established risk factors such as smoking, obesity and life style (1). In 2012, ~14.1 million incident cancer cases and 8.2 million mortalities occurred worldwide (1). Lung cancer is the leading cause of cancer mortality in developed countries. In 2015, 221,200 incident cases of lung and bronchial cancer were estimated to be diagnosed and 158,040 mortalities were estimated to occur in the United States (2). Non-small cell lung cancer (NSCLC) is currently defined by pathological characteristics (3,4). NSCLC represents >85% incidences of lung cancer, for which the predicted 5-year survival rate is 15.9% and recurrence rates remain high at 30-50% (5). NSCLC is classified into two major histological phenotypes: Adenocarcinoma (ADC; ~50%) and squamous cell carcinoma (SCC; ~40%). ADCs generally arise in the distal airways, whereas SCCs arise in the proximal airways. Conversely, SCCs are more closely associated with cigarette smoking and chronic inflammation compared with ADCs (3,4). A number of complex somatic alterations that extend beyond protein kinase activity to include transcription factors, epigenetic modifiers, and splicing variants were recently reported in NSCLCs (5-8). When somatic point mutations were analyzed using whole-exome sequence across 21 different tumor types, the mutation frequency in lung SCC and ADC ranked second and third highest, respectively (9). Additionally, heterogeneity of tumor microenvironments, such as tumor-associated macrophages and neutrophils, are associated with poor prognosis

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Abbreviations: NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer; CSC, cancer stem cell; ADC, adenocarcinoma; SCC, squamous carcinoma; SCF, stem cell factor; GISTs, gastrointestinal stromal tumors; IgG, immunoglobulin G; K14, keratin 14

Key words: non-small cell lung cancer, immunohistochemistry, CD117, relapse-free survival, prognostic marker

in NSCLC (10-12). Therefore, tumor heterogeneity provides explanation for poor responses to treatment of NSCLC.

The CD117 gene, termed c-Kit, encodes a tyrosine kinase growth factor receptor for stem cell factor (SCF), and has been extensively examined in hematopoietic stem cells (13). CD117 reportedly serves an important oncogenic role in solid tumors including gastrointestinal stromal tumors (GISTs) (14). Notably, it has been reported that CD117 expression was observed in small cell lung cancer (SCLC), and this molecule is associated with therapeutic and prognostic consequences in patients with SCLC (15,16). Based on these findings, STI-571 (imatinib), which blocks the phosphorylation of the CD117 tyrosine kinase, has been developed and used for patients with GISTs. Additionally, it has been demonstrated that STI-571 demonstrates inhibitory effects on SCLC cell lines (17,18). The overexpression of CD117 has been observed in NSCLC tumors (19,20), suggesting that CD117 may be a therapeutic target in a subset of NSCLCs. In addition, CD117-positive NSCLC cells reportedly exhibit cancer stem cell (CSC) characteristics including self-renewal and chemoresistance (19). Previous experimental evidence suggests that the presence of CSCs may be associated with the prognosis of the patient in various types of tumor (21,22). In the present study, it was hypothesized that if CD117 possesses prognostic significance in the patients with NSCLC, it may be used as a therapeutic target and prognostic marker for patients with NSCLC. To confirm this hypothesis, the association of CD117 expression with the clinicopathological characteristics of NSCLC was examined.

Materials and methods

Patients and clinical specimens. Formalin-fixed paraffin embedded tissue samples of NSCLC were obtained from 99 patients who were admitted to Tottori University Hospital (Yonago, Japan) between January 2005 and December 2007 and underwent curative surgical resection subsequent to informed consent. Detailed clinicopathological characteristics for these patients are summarized in Table I. The present study followed the principles of the Declaration of Helsinki and was approved by the ethics committees of Tottori University Faculty of Medicine (Yonago, Japan; approval no. 1830).

Immunohistochemical analysis. All specimens from 99 patients with NSCLC were fixed in 10% neutrally buffered formalin and embedded in paraffin. The fixed tissue sections of 3- μ m thickness were deparaffinized and treated with 3% hydrogen peroxide solution to block endogenous peroxidase activity. Subsequently, the sections were treated in sodium citrate buffer (pH 6.0) using a 500-watt microwave oven for 12 min to improve the antigen retrieval. Subsequent to cooling to room temperature, the specimens were incubated for 1 h at 37°C with anti-CD117 monoclonal antibody (cat. no. ab32363; clone YR145; dilution, 1:250; Abcam, Cambridge, MA, USA). The sections were treated for 30 min at room temperature with biotinylated anti-rabbit immunoglobulin G (IgG) antibody (cat. no. BA-1000; dilution, 1:200; Vector Laboratories, Inc., Burlingame, CA, USA) and then incubated for 30 min at 37°C with streptavidin-biotinylated horseradish peroxidase complex (cat. no. SA-5004; dilution, 1:500;

Table I. Clinicopathological factors of patients with lung cancer.

Characteristics	n
No. of patients	99
Age (year)	69 (26-81)
Gender	
Male/female	59/40
Maximum tumor size (mm)	26 (11-82)
Lymph node metastasis	
Negative/positive	77/22
Pleural invasion	
Negative/positive	73/26
Lymphatic invasion	
Negative/positive	26/73
Venous invasion	
Negative/positive	51/48
Pathological stage	
Stage I/Stage II/Stage III	73/14/12
Differentiation	
Well/moderate/poor	21/69/9
Histological type	
Ad/Sq	73/26
Recurrence	
Negative/positive	85/14
Overall survival (month)	72 (2-104)
Relapse-free survival (month)	66 (2-104)

Ad, adenocarcinoma; Sq, squamous carcinoma. Values of age, maximum tumor size, overall survival, and relapse-free survival were provided as median and parenthetical values showed range.

Vector Laboratories, Inc.). Color development was achieved by the treatment with ImmPACT DAB Substrate (Vector Laboratories, Inc.) and counterstained with hematoxylin. Images were acquired using a Nikon Eclipse E800 upright microscope (Nikon Corporation, Tokyo, Japan). The results were evaluated by a pathologist who was blinded with respect to the clinicopathological characteristics. The stained samples were classified into the following two groups: The positive group, which was defined as the samples with the cell membrane expression of CD117; and the negative group, which was defined as the samples with no expression or cytoplasmic expression of CD117.

Statistical analysis. Microsoft Excel 2013 (Microsoft Corporation, Redmond, WA) and SPSS statics (version 22.0; SPSS, Inc., Chicago, IL, USA) were used for the statistical calculations. A χ^2 test was performed to calculate the association between CD117 expression and the clinicopathological factors in patients with lung cancer. A univariable analysis using the log-rank test was performed to compare the overall survival ratio and disease free survival ratio in patients with lung cancer. A Cox regression model was used for the

Table II. χ^2 test of clinicopathological factors and CD117 expression.

Characteristics	Sample size (%)		P-value
	CD117-	CD117+	
Age (years)			0.957
≤69	44 (44.4)	9 (9.1)	
>69	38 (38.4)	8 (8.1)	
Gender			0.036
Male	45 (45.5)	14 (14.1)	
Female	37 (37.4)	3 (3.0)	
Maximum tumor size			0.897
≤26	42 (42.4)	9 (9.1)	
>26	40 (40.4)	8 (8.1)	
Lymph node metastasis			0.254
Negative	62 (62.6)	15 (15.2)	
Positive	20 (20.2)	2 (2.0)	
Pleural invasion			0.746
Negative	61 (61.6)	12 (12.1)	
Positive	21 (21.2)	5 (5.1)	
Lymphatic invasion			0.778
Negative	22 (22.2)	4 (4.0)	
Positive	60 (60.6)	13 (13.1)	
Venous invasion			0.349
Negative	44 (44.4)	7 (7.1)	
Positive	38 (38.4)	10 (10.1)	
Pathological stage			0.375
Stage I	59 (59.6)	14 (14.1)	
Stage II/III	23 (23.2)	3 (3.0)	
Histological type			0.352
Ad	62 (62.6)	11 (11.1)	
Sq	20 (20.2)	6 (6.1)	
Differentiation			0.693
Well	18 (18.2)	3 (3.0)	
Moderately/poorly	64 (64.6)	14 (14.1)	
Recurrence			<0.001
Absence	75 (75.8)	10 (10.1)	
Presence	7 (7.1)	7 (7.1)	

Ad, adenocarcinoma; Sq, squamous carcinoma; CD, cluster of differentiation. Age and maximum tumor size were divided into two categories according to the median line.

multivariable analysis. $P < 0.05$ were considered to indicate a statistically significant difference.

Results

Clinicopathological features. The clinicopathological features of 99 patients enrolled in the present study are summarized in Table I. All patients were classified into two groups based on histology: ADC, 73 patients, and SCC,

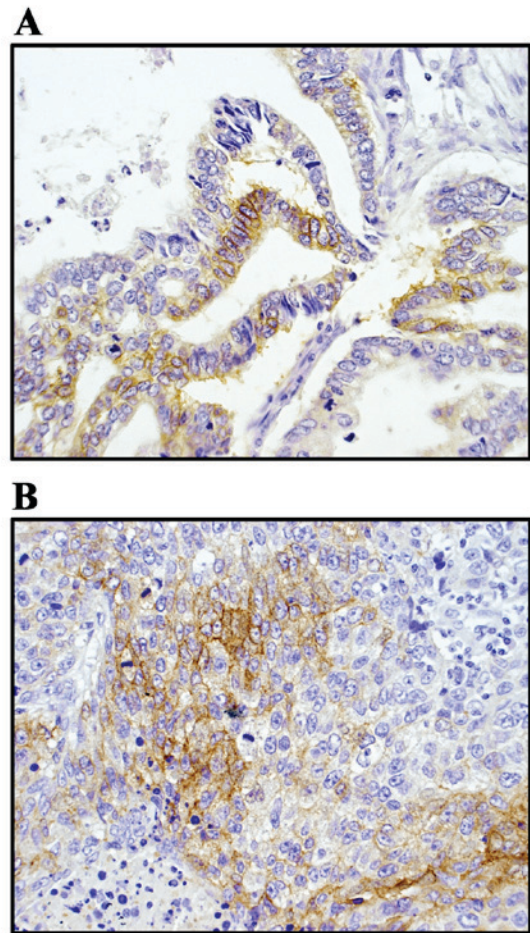


Figure 1. Immunohistochemical staining of CD117 expressions in patients with non-small cell lung cancer. Representative images of CD117 expression in FFPE non-small cell lung cancer tissues. Positive expression of CD117 in FFPE lung (A) adenocarcinoma tissues and FFPE lung (B) squamous cell carcinoma tissues. The expression of CD117 was demonstrated using the avidin-biotin complex staining method. All images were captured using a Nikon Eclipse E800 upright microscope (x400 magnification). FFPE, formalin-fixed paraffin-embedded; CD, cluster of differentiation.

26 patients. Of those patients, 14 patients relapsed. The median overall survival and relapse-free survival were 72 (range 2-104) months and 66 (range 2-104) months in patients with ADC and SCC, respectively.

Expression of CD117 in NSCLC patients. Immunohistochemical staining of CD117 expressions in 99 patients with NSCLC was performed. The representative images of CD117 expression in formalin-fixed paraffin-embedded sections are demonstrated in Fig. 1. Positive expression of CD117 in lung ADC and SCC tissues are illustrated in Fig. 1A and B, respectively. CD117 was expressed mainly on the cell membrane and occasionally in the cytoplasm of cancer cells.

Association of CD117 expression with clinicopathological features. The CD117 protein expression was positive in 17 cases, whereas it was negative in 82 cases, as summarized in Table II. The result from clinicopathological analysis revealed that CD117 positivity is significantly associated with gender and recurrence rate. The positivity of CD117 expression was higher in males compared with females ($P < 0.05$) and was

Table III. Univariate and multivariate analysis of clinical variables associated with overall survival in patients with lung cancer.

Characteristics	Category	Univariate	Multivariate univariate	
		P-value	HR (95% CI)	P-value
Age	≤69 vs. >69	0.172		
Gender	Male vs. Female	0.596		
Maximum tumor size	≤26 vs. >26	0.003		
Lymph node metastasis	Negative vs. Positive	<0.001	4.055 (2.004-8.205)	<0.001
Pleural invasion	Negative vs. Positive	0.015		
Venous invasion	Negative vs. Positive	0.001		
Pathological stage	Stage I vs. Stage II/III	<0.001		
Differentiation	Well vs. Moderate/Poor	0.005		
Recurrence	Negative vs. Positive	<0.001	4.672 (2.264-9.638)	<0.001
CD117 expression	Negative vs. Positive	0.113		

HR, hazard ratio; CI, confidence interval; CD, cluster of differentiation.

Table IV. Univariate and multivariate analysis of clinical variables associated with relapse-free survival in patients with lung cancer.

Characteristics	Category	Univariate	Multivariate univariate	
		P-value	HR (95% CI)	P-value
Age	≤69 vs. >69	0.213		
Gender	Male vs. Female	0.458		
Maximum tumor size	≤26 vs. >26	<0.001		
Lymph node metastasis	Negative vs. Positive	<0.001		
Pleural invasion	Negative vs. Positive	0.002		
Venous invasion	Negative vs. Positive	<0.001	4.596 (2.053-10.289)	<0.001
Pathological stage	Stage I vs. Stage II/III	<0.001	3.347 (1.685-6.651)	0.001
Differentiation	Well vs. Moderate/Poor	<0.001		
CD117 expression	Negative vs. Positive	0.014	3.352 (1.583-7.096)	0.002

HR, hazard ratio; CI, confidence interval; CD, cluster of differentiation.

also higher in recurrent patients compared with non-recurrent patients ($P<0.001$). Notably, 50% of recurrent patients exhibited CD117 positivity. Meanwhile, CD117 positivity was not associated with age, tumor size, pleural effusion, venous invasion, pathological stage, histological type or differentiation.

Prognostic significance of CD117 expression in NSCLC patients. To investigate the association between clinicopathological variables, including CD117 expression, and prognosis of patients with NSCLC, a Kaplan-Meier analysis was performed. As demonstrated in Table III, the univariate analysis identified that overall survival was associated with maximum tumor size ($P=0.003$), lymph node metastasis ($P<0.001$), pleural effusion ($P=0.015$), venous invasion ($P=0.001$), pathological stage ($P<0.001$), differentiation ($P=0.005$) and recurrence ($P<0.001$). However, overall survival was not associated with age, gender or CD117 expression. Additionally, the multivariate analysis

showed that only lymph node metastasis and recurrence were significantly associated with overall survival ($P<0.001$, each), as illustrated in Table III. When patients were classified into CD117-negative and CD117-positive groups, the Kaplan-Meier analysis for overall survival demonstrated that patients with CD117-positive cell populations tended to exhibit shorter overall survival rates compared with patients with CD117-negative cell populations ($P=0.113$; Fig. 2). Additionally, the Kaplan-Meier analysis for relapse-free survival was performed according to the expression of CD117 and revealed that patients with CD117-positive cell populations exhibited significantly shorter survival rates compared with patients with CD117-negative cell populations ($P=0.014$; Fig. 3). In addition to CD117 expression, the following clinicopathological variables were associated with relapse-free survival: Maximum tumor size ($P<0.001$), lymph node metastasis ($P<0.001$), pleural effusion ($P=0.002$), venous invasion ($P<0.001$), pathological stage

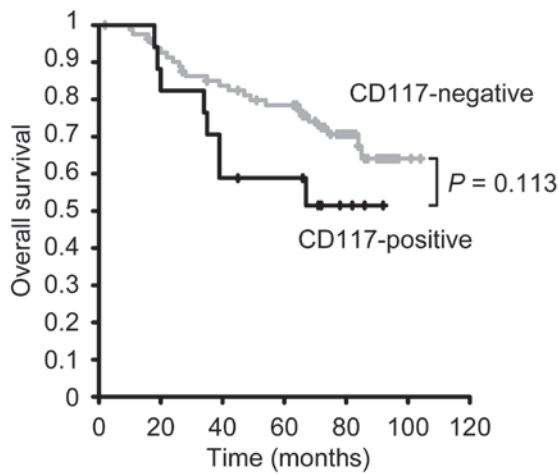


Figure 2. Kaplan-Meier analysis for overall survival rate in 99 non-small lung cancer cell patients. Patients were classified into negative (82 cases) and positive groups (17 cases) according to the expression of CD117. Data analysis was performed using the log-rank test. CD, cluster of differentiation, gray curve, CD117-negative group; black curve, CD117-positive group.

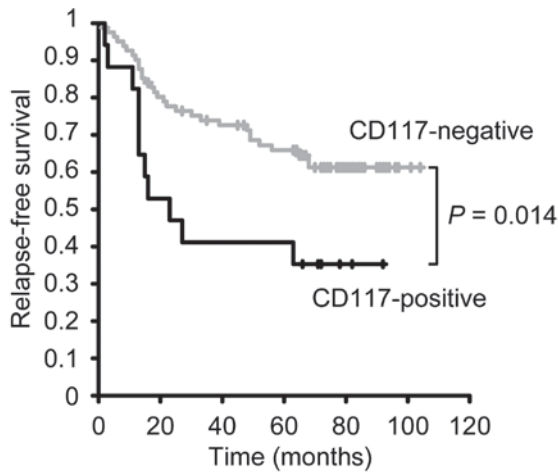


Figure 3. Kaplan-Meier analysis for relapse-free survival in 99 non-small lung cancer cell patients. Patients were classified into negative (82 cases) and positive groups (17 cases) according to the expression of CD117. Data analysis was performed using the log-rank test. CD, cluster of differentiation, gray curve, CD117-negative group; black curve, CD117-positive group.

($P < 0.001$) and differentiation ($P < 0.001$), as summarized in Table IV. The multivariable analysis revealed that relapse-free survival was significantly associated with venous invasion ($P < 0.001$), pathological stage ($P = 0.001$) and CD117 expression ($P = 0.002$). These findings suggest that CD117 expression is an independent factor for predicting relapse-free survival and may serve as a prognostic marker for tumor recurrence and survival in patients with NSCLC.

Discussion

In the present study, the patients with CD117-positive expression in NSCLC tissues exhibited significantly shorter relapse-free survival compared with patients with CD117-negative expression. This is the first report that CD117 expression may be a predictive marker for poor prognosis in the patients

with NSCLC. CD117 expression in a subset of patients with NSCLC was not predictive of overall survival (20), which is in agreement with the present study due to the small number of patients enrolled. However, the present study demonstrates that CD117 expression is associated with the relapse-free survival. Additionally, the combined treatment of cisplatin with imatinib or anti-SCF antibody reportedly inhibits the growth of NSCLC cells (19). These findings are similar to the reports that CD117 expression is associated with poor prognosis in SCLC (15,16). Taken together, these data suggest that the SCF/CD117 axis is a therapeutic target of a subset of lung cancer cells, and the inhibition of this signaling pathway may improve the efficacy of chemotherapy in lung cancer.

The majority of solid tumors are composed of a heterogeneous population including cells characterized by capacity for differentiation, self-renewal and resistance to chemotherapy, and radiotherapy (23,24). Although ~20% of patients with NSCLC exhibited surgically-correctable tumors at presentation, the recurrence rates following surgery remain high at 30-50% (25). This indicates that there is minimal residual disease, which contains a population that possesses a high proliferative potential and self-renewal capacity. To delay or prevent tumor recurrence in lung cancer, there should be a focus on the stem-like cells present. Some CSC markers have been identified in lung cancer, including a subset of keratin 14-expressing progenitor epithelial cells, which are involved in airway epithelial repair subsequent to injury, were reported to be tumor-initiating cells in the subgroup of smokers with NSCLC (26). Additionally, CD133-positive lung cancer cells exhibited CSC-like features, such as increased tumorigenic potential and higher sphere-forming ability (27,28). CD133 expression in NSCLC represents an anticancer drug resistance phenotype and evidence of metastatic cells, but does not correlate with the survival of patients with NSCLC (29). Conversely, another study suggests that CD133 expression is a temporary marker of CSCs in SCLC but not in NSCLC (30). CSC populations isolated from NSCLC cell lines were reported to express SCF and CD117 in an autocrine fashion (19). Although cisplatin treatment did not eliminate CSCs from NSCLC cells, inhibition of the SCF-CD117 axis by imatinib or anti-SCF antibody suppressed CSC proliferation (19), which suggests that this signaling pathway serves an important role in lung CSCs maintenance and survival. In the present study, CD117-positivity was associated with relapse-free survival, but not with overall survival, suggesting that CD117-positive cells may exhibit some CSC characteristics. Additional research is required to demonstrate that the acquisition of cancer stemness in NSCLC cells is associated with poor prognosis in patients with NSCLC.

In conclusion, the present study demonstrated that the positive expression of CD117 is significantly associated with a shorter relapse-free survival rate in patients with NSCLC. This observation suggests that CD117 may serve as a prognostic marker for predicting poor prognoses and a novel therapeutic target for patients with NSCLC.

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