CD117 (c-KIT) overexpression in patients with extensive-stage small-cell lung carcinoma

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Background: The aim of this study was to determine the incidence and role of CD117 (c-KIT) overexpression as a predictive/prognostic marker in extensive-stage small-cell lung carcinoma (ESSCLC). We performed a retrospective study on subjects with a biopsy-proven diagnosis of ESSCLC.

Patients and methods: A chart review for demographic and clinical data was performed on patients with ESSCLC diagnosed between 1991 and 2001. CD117 overexpression was evaluated using immunohistochemistry (A4052 polyclonal antibody) performed on archival paraffin-embedded specimens.

Results: Two hundred and twenty-three patients with ESSCLC were identified, of whom 193 (84 females, 109 males) with a mean age of 68.5 years (range 42–90) had adequate tissue specimens available for CD117 testing. The most commonly presenting symptom was weight loss, seen in 61 patients (31.6%). Of the 193 specimens, 54 (27.9%) showed CD117 overexpression. The median length of survival for CD117-positive patients was 9 months as compared with the CD117-negative population, in whom the survival was 6 months (P = 0.025, Cox proportional hazard method).

Conclusions: CD117 overexpression detected using immunohistochemistry is observed in about a third of patients with ESSCLC and does not have statistically significant prognostic value. However, CD117 may be a potential target for site-specific immunotherapy in ESSCLC. Our findings suggest a role for clinical trials assessing the role of selective tyrosine kinase inhibitor STI-571 (alone or in combination with conventional therapy) in patients with ESSCLC.

Key words: c-kit, extensive stage, small-cell lung carcinoma, survival

Introduction

Lung cancer remains the leading cause of death from cancer in the United States and its overall incidence is increasing [1]. Carcinoma of the lung is divided into two broad categories: small-cell lung cancer (SCLC) and non-small-cell lung cancer, which have significant differences in clinical and biological behavior [2]. SCLC, which accounts for 15–20% of all lung cancers [3], is a distinct clinicopathological entity among lung cancers, with a highly aggressive clinical course and neuroendocrine properties [4]. Despite recent advances in therapy, because SCLC has metastasized outside the chest in two-thirds of patients at the time of clinical presentation, only 7% of these patients are alive at 5 years from the start of treatment [3]. Median survival of extensive-stage SCLC (ESSCLC) is only 10.1 months [5].

To understand the biological basis for the rapid progression of SCLC, biochemical, serological, cytogenetic and molecular studies have been conducted and the understanding of carcinogenesis of SCLC has rapidly evolved [6, 7]. Growth deregulation in human SCLC has been attributed to many genetic abnormalities, including mutation/deletion of tumor suppressor genes, the existence of multiple autocrine growth loops, and the amplification and overexpression of various proto-oncogenes.

The proto-oncogene c-kit encodes a transmembrane tyrosine kinase receptor (c-KIT/CD117) related to the platelet-derived growth factor (PDGF)/colony-stimulating factor 1 (CSF-1) (c-fms) receptor subfamily [8]. CD117 is thought to play an important role in hematopoiesis, spermatogenesis, melanogenesis and, more recently, in carcinogenesis [9–11]. Overexpression of CD117 has previously been documented in myeloid leukemia, neuroblastoma, breast cancer, colon tumors, gynecological tumors, testicular germ cell tumors and SCLC [12–15]. However, few studies have addressed the prognostic implication of CD117 overexpression in the select population of patients with ESSCLC. To determine the incidence and role of CD117 overexpression as a predictive/prognostic marker in ESSCLC, we performed a retrospective study on subjects with a biopsy-proven diagnosis of ESSCLC.

Patients and methods

The records of all patients with a diagnosis of ESSCLC from January 1991 to April 2001 were reviewed. An extensive chart review was performed to collect
relevant patient demographic and clinical data that included information regarding gender, age at diagnosis, mean age at death, performance status and presenting symptoms. In addition, detection of CD117 overexpression was assayed using an immunohistochemical (IHC) technique on archival paraffin-embedded tissue specimens.

CD117 testing performed using IHC was recorded on a semi-quantitative scale to record the number of positive cells (10%, 10–50% and >50%) and the intensity of reaction. CD117 status was reported as positive if it was >10% and negative if it was ≤10%. Immunohistochemical staining for c-KIT (CD117) was performed using a 1:250 dilution of the rabbit polyclonal antibody A4502 (IMPATH, Los Angeles, CA, USA) with the EnVision detection system (IMPATH). An antigen retrieval method was not utilized. Appropriate positive and negative controls were used throughout the testing process. We used the A4502 antibody because it has shown consistent performance with a low background, because it seems to be the most widely used Kit antibody, and because it is the antibody specified for CD117 testing in the large cooperative clinical trials of selective tyrosine kinase inhibitor STI-571. All interpretation of CD117 testing was performed by a single pathologist who was blinded from the clinical data of patients in our study population.

Two hundred and twenty-three patients with a biopsy-proven diagnosis of ESSCLC were identified from our database. Overall survival was calculated by the Kaplan–Meier product limit method from the date of diagnosis of lung carcinoma. After adjusting for age, smoking history, performance scores, presence of weight loss and therapy, a multivariate analysis using the Cox proportional hazard method was performed to analyze the prognostic impact of CD117 overexpression. Statistical analysis and survival curves were obtained using SPSS-10 for Windows.

**Results**

Between 1991 and 2001, 223 patients with ESSCLC were identified, of whom 193 (84 females, 109 males) with a mean age of 68.5 years (range 42–90) had adequate tissue specimens available for CD117 testing. The common symptoms at initial presentation included weight loss in 61 patients (31.6%), cough in 53 (27.5%) and dyspnea in 39 (20.2%). A total of 32 patients (16.6%) were asymptomatic while 29 (15%) had other symptoms including hoarseness, lymphadenopathy and neurological complaints. In our study population, 81 patients (41.9%) had an Eastern Cooperative Oncology Group performance score >2. The most common first-line chemotherapy regimen used was a combination of cisplatin/carboplatin with etoposide (86%). The most common second-line agent was docetaxel. Of the 193 specimens, 54 (27.9%) showed CD117 overexpression [35 males (64.8%) and 19 females (27.9%)]. The average age at diagnosis of a CD117-positive patient was 66 years while the average age of a CD117-negative patient was 64 years. Forty-one patients (76%) in the CD117-positive population had an initial clinical and radiological response to treatment, as opposed to 99 (71.2%) in the CD117-negative group. In patients with CD117 overexpression, the median length of survival was 16.5 months as compared with the CD117-negative population, in whom survival was only 14 months ($P = 0.025$; Figure 1). The most common presenting complaint in CD117-negative patients was weight loss (28.1%), while cough was the most likely symptom (46.3%) in the CD117-positive population. The most common site of metastatic disease was the brain (82 patients, 42%) followed by the adrenal glands (55 patients, 28.2%). There was no significant difference in the proportionate rate of CD117 expression seen based on the site of metastasis (23 of 54 positive for CD117 had brain metastases and 19 of 54 CD117-positive subjects had adrenal metastasis). Additional demographic and clinical data of the CD117-positive and -negative subgroups are given in Table 1.

![Image](Figure 1. Kaplan–Meier survival analysis by CD117 (c-KIT) overexpression (determined by immunohistochemistry) in patients with extensive-stage small-cell lung carcinoma.)

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>CD117-negative (n = 139) (%)</th>
<th>CD117-positive (n = 54) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age at diagnosis (years)</td>
<td>64</td>
<td>66</td>
</tr>
<tr>
<td>Mean age at death (years)</td>
<td>66</td>
<td>67</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male (n = 109)</td>
<td>74</td>
<td>35</td>
</tr>
<tr>
<td>Female (n = 84)</td>
<td>65</td>
<td>19</td>
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<tr>
<td>ECOG performance score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–2 (n = 112)</td>
<td>85</td>
<td>27</td>
</tr>
<tr>
<td>3–4 (n = 81)</td>
<td>50</td>
<td>31</td>
</tr>
<tr>
<td>Symptoms</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>128 (20.1)</td>
<td>4 (7.4)</td>
</tr>
<tr>
<td>Cough</td>
<td>28 (20.1)</td>
<td>25 (46.3)</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>28 (20.1)</td>
<td>11 (20.4)</td>
</tr>
<tr>
<td>Weight loss</td>
<td>39 (28.1)</td>
<td>22 (40.7)</td>
</tr>
<tr>
<td>Lymphadenopathy</td>
<td>3 (2.2)</td>
<td>2 (3.7)</td>
</tr>
<tr>
<td>Hoarseness</td>
<td>3 (2.2)</td>
<td>1 (1.8)</td>
</tr>
<tr>
<td>Chest pain</td>
<td>12 (8.6)</td>
<td>3 (5.6)</td>
</tr>
<tr>
<td>Neurological symptoms</td>
<td>4 (2.9)</td>
<td>7 (13.0)</td>
</tr>
<tr>
<td>Other</td>
<td>2 (1.4)</td>
<td>7 (13.0)</td>
</tr>
<tr>
<td>Median survival (months)*</td>
<td>14</td>
<td>16.5</td>
</tr>
</tbody>
</table>

* $P = 0.025$; Cox proportional hazards method.

ECOG, Eastern Cooperative Oncology Group.
**Discussion**

SCLC, despite recent advances, continues to have a poor long-term survival. This is especially true for ESSCLC, where the prognosis is even worse. This has led to numerous studies in an effort to understand the cytogenetic and molecular biology of SCLC. Some of those studies demonstrated R3 and p53 genes to be the targets of mutation in SCLC, which inactivates their properties as anti- oncogenes [16]. In addition, SCLC has been studied as a model for autocrine and paracrine growth of tumor, since bombesin/gastrin-releasing peptide has been shown to have mitotic activity in SCLC cells in vitro [17].

Transmembrane protein-tyrosine kinases play an important role in the regulation of cell growth as receptors for growth factors [18]. CD117 encodes a transmembrane tyrosine kinase receptor that is structurally similar to the receptors for CSF-1 and PDGF [8, 15]. Previously, several small studies have indicated a preferential expression of CD117 proto-oncogene in SCLC [19–27], but none describes the prognostic implication of CD117 overexpression in ESSCLC. In an attempt to elucidate the predictive role of IHC determination of CD117 overexpression in patients with ESSCLC, we assessed CD117 status on pathological lung specimens in the largest reported cohort of patients with biopsy-proven ESSCLC.

Of the 193 specimens in our study, 54 (27.9%) showed CD117 overexpression by IHC. The incidence of overexpression in our population was lower than previously reported. Hibi et al. [28] reported that over 60% of SCLCs overexpress CD117. In another series, Sekido et al. [21] reported a higher incidence of CD117 overexpression (81%) in SCLC. The reason for the difference in our findings and the previous reports may be attributable to the fact that our large study included only patients with ESSCLC. Thus, although the presence of CD117 does not carry definite prognostic value, it is possible that overexpression may be preferentially observed in patients with limited-stage SCLC, in whom the biology of lung carcinoma is different compared with ESSCLC. But, more importantly, the earlier reports used northern or western blotting techniques for assessing CD117 expression; both northern and western blotting are more sensitive but less specific than IHC techniques [29, 30].

The median survival in patients with CD117 overexpression was 16.5 months as compared with the CD117-negative population, in whom survival was only 14 months. After adjusting for age, performance status, smoking history, presence of weight loss as a symptom and therapy, the survival difference was not statistically significant (P = 0.025, Cox proportional hazard multivariate analysis). Also, interestingly, men were more likely to have CD117 overexpression than women. This intriguing finding will need to be validated in future trials. Thus, CD117 may play a role as a target for site-specific therapy; however, it lacks definitive prognostic value in patients with ESSCLC.

**Conclusion**

IHC identification of CD117 overexpression is seen in about a third of patients with ESSCLC, but it lacks prognostic value. However, CD117 can also be used as potential target for site-specific immunotherapy in ESSCLC. Our findings suggest a role for randomized clinical trials assessing the role of STI-571 (alone or in combination with conventional therapy) in patients with ESSCLC.

**Acknowledgements**

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**References**