ABSTRACT

CYP1A1 is responsible for the metabolic activation of benzo(a)pyrene in cigarette smoke, and high susceptibility to smoking-related lung cancer has been associated with theMspI polymorphism of theCYP1A1 gene. Individuals with a susceptible CYP1A1 genotype have been found to be at remarkably high risk when the genotype is combined with a deficient Mu-class glutathione S-transferase (GSTM1) genotype. In this study, we investigated the relationship between germ line polymorphisms of these genes and clinical characteristics or survival rates in 232 patients with non-small cell lung cancer (NSCLC). Statistical analysis revealed a significant association (P < 0.05) of the MspI polymorphism of the CYP1A1 gene with histological type, performance status (general conditions of patients), and the extent of the primary tumor (T-factor). On the other hand, the GSTM1 polymorphism was significantly associated with performance status, the extent of regional lymph node metastasis (N-factor), and the extent of distant metastasis (M-factor). NSCLC patients with at least one susceptible allele of theMspI polymorphism of theCYP1A1 gene [heterozygous genotype B or a rare homozygous genotype C; n = 131; median survival time (MST) = 24.2 months] were associated with a shortened survival compared with those with nonsusceptible homozygous alleles (genotype A; n = 101; MST = 65.2 months; P = 0.005 by log-rank test). Smokers with susceptible genotypes (n = 104; MST = 18.2 months) were markedly associated with a shortened survival compared with those with genotype A (n = 76; MST = 69.2 months; P = 0.024); such an association was not found among nonsmokers by genotypes. Genotype-dependent survival was also observed in patients at an advanced stage of disease (P = 0.010), but not in those at an early stage of disease (P = 0.382). Patients with the susceptible CYP1A1 genotype had remarkably shortened survival compared to those with the deficient genotype GSTM1(-) (P = 0.017; degree of freedom = 3). Multivariate analysis by the Cox proportional hazards model also revealed that the CYP1A1 polymorphism was an independent prognostic factor in patients at a non-resectable advanced stage of NSCLC (P = 0.005; hazard ratio = 1.98; 95% confidence interval, 1.24-3.17).

INTRODUCTION

Human lung carcinogenesis usually requires exposure to the pro-carcinogens that are contained mainly in cigarette smoke, and many aromatic hydrocarbons, such as benzo(a)pyrene, first require metabolic activation by CYP1A1 to their ultimate DNA-binding, mutagenic, or carcinogenic forms (1). Activated metabolites of benzo(a)pyrene are subjected in part to metabolic detoxication by GSTM1 (2). Thus, the expression and catalytic activity of these carcinogen-metabolizing enzymes in the lung and their metabolic balance may be important determinant host factors underlying lung cancer (3, 4). We have shown previously that two mutually linked CYP1A1 gene polymorphisms, the MspI polymorphism located in the 3'-flanking region of the gene and the Ile-Val polymorphism at amino acid residue 462 in the heme binding region of CYP1A1 protein, are associated with high susceptibility to smoking-associated lung cancer (5-7). Genotype C in theMspI polymorphism and genotype Val/Val in the Ile-Val polymorphism among patients with squamous cell carcinoma were more than twice as common relative to their frequency among the controls. Patients with genotype C or Val/Val contracted carcinoma after smoking fewer cigarettes than those with genotypes A or Ile/Ile, respectively (8, 9). Relative risks were estimated at cigarette dose levels by case-control studies, revealing that individuals with these genotypes were at an especially high risk of carcinoma at a low dose level of cigarette smoking. Furthermore, individuals with the susceptible CYP1A1 genotype were shown to be at a remarkably high risk when the genotype was combined with a deficient GSTM1 genotype, GSTM1(−) (10). The functional significance of the polymorphic human CYP1A1 gene may be an association with inducible expression or difference in the catalytic activity of the CYP1A1 enzyme (7, 11, 12). The GSTM1(−) genotype was associated completely with deficient GSTM1 enzyme activity (13).

Lung cancers are characterized by multiple genetic changes, which include the activation of proto-oncogenes and the inactivation of tumor suppressor genes (14, 15). Among the genetic alterations identified in NSCLC, mutations in the p53 gene (16-18) and an allelic deletion of chromosome 3p (19-21) seem to be the most frequent targets in the process of lung carcinogenesis. Furthermore, it has been reported recently that p53 (22, 23) or ras (24-26) mutations as well as 3p deletions (23) in patients with NSCLC were found to be associated not only with the genes and progression of lung cancer but also with shortened survival as predictors of poor prognosis, although this notion remains controversial (27). In this regard, it is interesting to note that mutation frequencies of the two target genes in lung cancer, the p53 and Ki-Ras genes, were significantly affected by the CYP1A1 and GSTM1 genotypes that are predisposing factors (28). In addition, Okada et al. (29) demonstrated that lymph node or distant metastasis was more frequently observed among patients with squamous cell carcinoma with genotype C of the CYP1A1 gene. Therefore, in this study, we investigated the relationship between various clinical characteristics or survival rates in 232 patients with NSCLC and germ line polymorphisms of the CYP1A1 and GSTM1 genes. We report here that the patients with genotypes susceptible to lung cancer are associated with a shortened overall survival.

PATIENTS AND METHODS

Patients. We studied 232 Japanese patients (166 males and 66 females) with histologically primary NSCLC who received treatment between 1988 and 1993 at the Saitama Cancer Center Hospital. None of the patients had received previous treatment by chemotherapy, radiotherapy, or surgery. Histological classification of tumors was conducted according to the
CYP1A1 POLYMORPHISMS AND PROGNOSIS IN NSCLC

According to the criteria, the cases consisted of 124 adenocarcinomas, 93 squamous cell carcinomas, and 15 large cell carcinomas. PS was documented according to classification by the Eastern Cooperative Oncology Group (31). We used the American Joint Committee Staging system to stage the disease or to classify the tumors-nodes-metastasis factors (32). Stages I-II were considered to be early stage, and stages IIIa-IV were considered to be advanced stage of the disease. We found that 65 patients had stage I disease, 20 had stage II, 46 had stage IIIa, 42 had stage IIIb, and 59 had stage IV disease. A systematical review of pathological or clinical diagnoses was conducted. Of the group, 129 patients had been treated by surgery as a routine therapeutic operation, whereas the remaining 103 patients had been treated by chemotherapy and/or radiotherapy. Smoking habits for cases were reviewed from medical records, in which routine questions were asked of all outpatients at the time of the first visit to the hospital. The study was approved by the medical ethical review committee in this hospital (Institutional Review Board).

Identification of the CYP1A1 and GSTM1 Genotypes in Patients with NSCLC. Blood samples (5–10 ml) were obtained from the 232 patients with NSCLC from whom we could obtain appropriate informed consent, and genomic DNAs were isolated from the peripheral lymphocytes of the samples using standard procedures with proteinase K digestion and phenol-chloroform extraction. The CYP1A1 genotypes ascribed to the presence (CCGG) or absence (CTGG) of the Msp1 site at the 264th base from the polyadenylate additional signal in the 3'-flanking region were identified by the PCR-restriction enzyme digest genotyping method as described previously (6). GSTM1 genotyping was conducted by the presence or absence of a PCR product according to the methods of Comstock et al. (33) and Groppi et al. (34).

Statistical Analysis. The Pearson χ² test was used to compare the association between the CYP1A1 or GSTM1 genotype and several clinical and pathological parameters. The Kaplan-Meier method (35) was used to estimate the probability of survival as a function of time, and survival differences were analyzed using the log-rank test (36). The Cox proportional hazards modeling technique was used to identify which independent factors had a jointly significant influence on overall survival (37).

RESULTS

Overall Survival Rate in Patients with NSCLC in Relation to the CYP1A1 or GSTM1 Polymorphisms. The clinical characteristics of the 232 NSCLC patients examined are summarized in Table 1 in relation to the genotypes of the CYP1A1 or GSTM1 gene. The Msp1 polymorphism of the CYP1A1 gene was associated with histological type, PS, T-factor, and the ratio of subjects who had surgery:subjects who did not have surgery with statistical significance (P < 0.05) and was associated with N- and M-factors with borderline significance (0.05 < P < 0.1). On the other hand, the GSTM1 polymorphism was associated with PS, N- and M-factors, clinical stages, and the rate of operation (P < 0.05). Namely, patients with susceptible genotypes B + C or GSTM1(−) had characteristics of more clinically advanced disease compared to those with genotype A or GSTM1(+) when diagnosed with NSCLC. It is suggested from these observations that the CYP1A1 and GSTM1 genotypes, which are predisposing factors to smoking-related lung cancer, may be associated with survival rates in patients with NSCLC.

We first analyzed the association between CYP1A1 genotypes and overall survival in all patients with NSCLC (Table 2). The MST of 24.2 months among patients with genotypes B + C (n = 131) was significantly shorter than that of 65.2 months for patients with genotypes A (n = 101) and GSTM1(+) (n = 62). The survival differences were analyzed using the log-rank test (36). The Cox proportional hazards modeling technique was used to identify which independent factors had a jointly significant influence on overall survival (37).

### Table 1 Characteristics of patients with NSCLC in relation to polymorphisms of the CYP1A1 and GSTM1 genes

<table>
<thead>
<tr>
<th>Variables</th>
<th>No. of patients</th>
<th>CYP1A1 polymorphism</th>
<th>GSTM1 polymorphism</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Msp1 genotypes</td>
<td>GSTM1 genotypes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>A        B + C</td>
<td>(+)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>P        (−)</td>
<td>P</td>
</tr>
<tr>
<td>Case</td>
<td>232</td>
<td>101      61.6 ± 9.5</td>
<td>61.3 ± 10.3</td>
</tr>
<tr>
<td>Age (mean ± SD)</td>
<td></td>
<td>131      62.8 ± 9.3</td>
<td>63.1 ± 8.5</td>
</tr>
<tr>
<td>&lt;65</td>
<td>122</td>
<td>56       66</td>
<td>52</td>
</tr>
<tr>
<td>≥65</td>
<td>110</td>
<td>45       65</td>
<td>49</td>
</tr>
<tr>
<td>Sex</td>
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<tr>
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<td>66</td>
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a P was calculated by χ² test.
b P calculated for adenocarcina versus squamous cell carcinoma and large cell carcinoma.

P calculated for M0 (stage I–IIIb) versus M1 (stage IV).

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Table 2 Overall survival in patients with NSCLC in relation to CYP1A1 and GSTM1 polymorphisms

<table>
<thead>
<tr>
<th>CYP1A1 polymorphism</th>
<th>Cases</th>
<th>MST (mo)</th>
<th>3-yr survival rate (%)</th>
<th>P*</th>
<th>GSTM1 genotypes</th>
<th>Cases</th>
<th>MST (mo)</th>
<th>3-yr survival rate (%)</th>
<th>P*</th>
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<tr>
<td>A</td>
<td>101</td>
<td>65.2</td>
<td>59.8</td>
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<tr>
<td>A</td>
<td>76</td>
<td>69.2</td>
<td>56.0</td>
<td></td>
<td>(+)</td>
<td>83</td>
<td>42.6</td>
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<td>18.2</td>
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<td>(+)</td>
<td>97</td>
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<tr>
<td>A</td>
<td>24</td>
<td>65.2</td>
<td>70.8</td>
<td></td>
<td>(+)</td>
<td>18</td>
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<tr>
<td>B+C</td>
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<td>29.0</td>
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<td>0.102</td>
<td>(+)</td>
<td>33</td>
<td>38.1</td>
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<td></td>
</tr>
<tr>
<td>A</td>
<td>62</td>
<td>44.6</td>
<td>54.6</td>
<td></td>
<td>(+)</td>
<td>58</td>
<td>38.4</td>
<td>50.9</td>
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<tr>
<td>B+C</td>
<td>62</td>
<td>18.0</td>
<td>36.5</td>
<td>0.033</td>
<td>(+)</td>
<td>66</td>
<td>23.6</td>
<td>40.7</td>
<td>0.143</td>
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<td>Squamous cell carcinoma</td>
<td>34</td>
<td>NR</td>
<td>69.8</td>
<td></td>
<td>(+)</td>
<td>38</td>
<td>NR</td>
<td>60.4</td>
<td></td>
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<tr>
<td>B+C</td>
<td>59</td>
<td>34.2</td>
<td>45.7</td>
<td>0.025</td>
<td>(+)</td>
<td>55</td>
<td>41.8</td>
<td>50.7</td>
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<tr>
<td>A</td>
<td>43</td>
<td>NR</td>
<td>88.3</td>
<td></td>
<td>(+)</td>
<td>39</td>
<td>NR</td>
<td>84.6</td>
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<tr>
<td>B+C</td>
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<td>80.7</td>
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<td>46</td>
<td>137.8</td>
<td>84.2</td>
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<td>Advanced stages (III–IV)</td>
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<td>23.6</td>
<td>38.5</td>
<td></td>
<td>(+)</td>
<td>62</td>
<td>21.7</td>
<td>35.4</td>
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<tr>
<td>B+C</td>
<td>89</td>
<td>10.4</td>
<td>20.2</td>
<td>0.010</td>
<td>(+)</td>
<td>85</td>
<td>12.4</td>
<td>22.2</td>
<td>0.061</td>
</tr>
</tbody>
</table>

* P is calculated by log-rank test.

NR: median survival not reached.

Next, we divided all the NSCLC patients into two groups: early stage or advanced stage of the disease (Table 2). When a comparison was made within the group with early stage disease, the effect of the CYP1A1 genotypes on survival was not statistically significant (P = 0.382). This could be due to the longer overall survival among patients with early stage disease compared to those with advanced-stage disease, and our follow-up study may not have been long enough to find a survival difference in terms of genotype. By contrast, when a comparison was made within the group with advanced-stage disease, the difference in survival times between patients with genotypes B + C (n = 89; MST = 10.4 months) and those with genotype A (n = 58; MST = 23.6 months) was highly significant (P = 0.010). The differences in survival time between patients with genotypes B + C and those with genotype A with advanced-stage adenocarcinoma or squamous cell carcinoma were also statistically significant, but were not statistically significant in patients with early stage disease (data not shown).

We also analyzed the association between the GSTM1 polymorphism and overall survival. The survival in NSCLC patients with genotype GSTM1(−) (MST = 29.0 months; n = 131) was shorter than that in patients with genotype GSTM1(+) (MST = 50.1 months; n = 101), with borderline significance (P = 0.092 in Table 2). When we compared this relationship by taking the stage or histological type of the disease into account, we found a poorer prognosis among patients with GSTM1(−) (MST = 12.4; n = 85) than among those

Table 3 Overall survival in patients with NSCLC based on combined genotypes of the CYP1A1 and GSTM1 genes

<table>
<thead>
<tr>
<th>Combined genotypes</th>
<th>No. of patients</th>
<th>No. of deaths</th>
<th>MST (mo)</th>
<th>3-yr survival rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP1A1</td>
<td>GSTM1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>(+)</td>
<td>45</td>
<td>21</td>
<td>100.0</td>
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<tr>
<td>A</td>
<td>(−)</td>
<td>56</td>
<td>31</td>
<td>41.8</td>
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<tr>
<td>B + C</td>
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<td>56</td>
<td>32</td>
<td>22.8</td>
</tr>
<tr>
<td>B + C</td>
<td>(−)</td>
<td>75</td>
<td>51</td>
<td>24.2</td>
</tr>
</tbody>
</table>

* P = 0.017 by log-rank test; df = 3.
CYPIA1 POLYMORPHISMS AND PROGNOSIS IN NSCLC

Fig. 2. Kaplan-Meier survival curve for all patients with nonresectable advanced-stage NSCLC (stage IIIa-IV) with respect to the Mspl polymorphism of the CYPIA1 gene. Genotype A (□), n = 34; genotypes B + C (○), n = 64; P = 0.003.

with GSTM1(+) (MST = 21.7; n = 62) at the advanced stage of NSCLC (P = 0.061 by log-rank test; Table 2). In addition, we examined the effect of combined genotyping of genes for the carcinogen-metabolizing enzymes on prognosis. The Kaplan-Meier survival curve for patients with NSCLC in relation to the combined genotypes of CYPIA1 and GSTM1 genes is shown in Fig. 1. As shown in Table 3, the shortest survival time was observed in patients with the combination of B + C and GSTM1(−) (n = 75; MST = 24.2 months; 3-year survival rate was 36.6%), whereas the longest survival was obtained in patients with combination genotypes of A and GSTM1(+) (n = 45; MST = 100 months; 3-year survival rate was 66.4%). The difference in overall survival among the four groups of patients with different combined genotypes was found at the statistically significant level of P = 0.017 (log-rank test; df = 3). A similar survival profile was obtained when a comparison was made within the group with advanced-stage NSCLC in relation to the combined genotypes (P = 0.013; df = 3; data not shown).

CYPIA1 Genotypes as an Independent Prognostic Factor for Patients at a Nonresectable Advanced Stage of NSCLC. As mentioned, the Mspl polymorphism of the CYPIA1 gene was significantly associated with several potential prognostic factors and overall survival rates in patients with NSCLC. To investigate the prognostic significance of the germ line polymorphism of the CYPIA1 gene, we analyzed the association between CYPIA1 genotypes and MST in patients with nonresectable advanced NSCLC (n = 98) in terms of several prognostic factors. The Kaplan-Meier survival curves for all patients with nonresectable advanced-stage (IIIa-IV) NSCLC in relation to the CYPIA1 genotypes are shown in Fig. 2. As shown in Table 4, the MST of patients with genotypes B + C was shorter than that of patients with genotype A at the level of significance or borderline significance when a comparison was made within each category (including age, sex, smoking status, histological type, PS, clinical stages, and GSTM1 genotypes). In addition, the MST of 8.0 months for genotypes B + C (n = 40) was significantly shorter than that of 21.7 months for genotype A (n = 12) in patients with T4 (P = 0.008). Similarly, the log-rank test revealed that patients with genotypes B + C (n = 52) with N2-N3 had a significantly poorer prognosis of MST than patients with genotype A (n = 24; P = 0.014).

Table 5 shows the result of univariate or multivariate analyses using CYPIA1 genotypes and covariables including age, sex, smoking status, histology, PS, clinical stages, and GSTM1 genotypes. The Mspl polymorphism of the CYPIA1 gene was shown to be an independent prognostic indicator in patients with nonresectable advanced-stage NSCLC. Specifically, patients with genotypes B + C of the CYPIA1 gene survived for a significantly shorter period of time than those with genotype A (hazard ratio from 1-1.98; 95% CI, 1.24–3.17; P = 0.005). A similar result was obtained when multivariate analysis

Table 4. Characteristics of patients with nonresectable advanced-stage NSCLC in relation to polymorphisms of the CYPIA1 genes

<table>
<thead>
<tr>
<th>Variables</th>
<th>No. of patients</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All A B + C</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>98</td>
<td>34</td>
<td>64</td>
<td></td>
</tr>
<tr>
<td>Age (≤65)</td>
<td>47</td>
<td>15</td>
<td>32</td>
<td>21.9</td>
</tr>
<tr>
<td>Age (≥65)</td>
<td>51</td>
<td>19</td>
<td>32</td>
<td>14.7</td>
</tr>
<tr>
<td>Sex Male</td>
<td>73</td>
<td>26</td>
<td>47</td>
<td></td>
</tr>
<tr>
<td>Sex Female</td>
<td>25</td>
<td>8</td>
<td>17</td>
<td>15.6</td>
</tr>
<tr>
<td>Smoking status</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smokers</td>
<td>79</td>
<td>29</td>
<td>50</td>
<td>20.0</td>
</tr>
<tr>
<td>Never smoked</td>
<td>18</td>
<td>4</td>
<td>14</td>
<td>10.0</td>
</tr>
<tr>
<td>Histology</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Squamous cell carcinoma</td>
<td>32</td>
<td>7</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>Non-sq</td>
<td>66</td>
<td>37</td>
<td>39</td>
<td>17.5</td>
</tr>
<tr>
<td>PS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–1</td>
<td>56</td>
<td>21</td>
<td>35</td>
<td></td>
</tr>
<tr>
<td>2–4</td>
<td>41</td>
<td>12</td>
<td>29</td>
<td>18.8</td>
</tr>
<tr>
<td>Clinical stage</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IIIa</td>
<td>10</td>
<td>3</td>
<td>7</td>
<td>32.6</td>
</tr>
<tr>
<td>IIIb</td>
<td>30</td>
<td>12</td>
<td>18</td>
<td>21.7</td>
</tr>
<tr>
<td>IV</td>
<td>58</td>
<td>19</td>
<td>39</td>
<td>13.9</td>
</tr>
<tr>
<td>GSTM1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(+)</td>
<td>36</td>
<td>12</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td>(−)</td>
<td>62</td>
<td>22</td>
<td>40</td>
<td>21.9</td>
</tr>
</tbody>
</table>

a P was calculated by χ² test for genotype A vs. B + C.
b P was calculated by log-rank test for genotype A vs. B + C.
c P was calculated by log-rank test for each category.
d NR, median survival not reached.
e Non-sq, adenocarcinoma and large cell carcinoma.
CYP1A1 POLYMORPHISMS AND PROGNOSIS IN NSCLC

<table>
<thead>
<tr>
<th>Variables</th>
<th>Hazard ratio</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Univariate analysis</td>
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<td></td>
</tr>
<tr>
<td>Age ≤65 vs. &gt;65</td>
<td>1.30</td>
<td>0.85-1.99</td>
<td>0.223</td>
</tr>
<tr>
<td>Sex (female vs. male)</td>
<td>1.07</td>
<td>0.66-1.72</td>
<td>0.784</td>
</tr>
<tr>
<td>Smoking (smokers vs. never smoked)</td>
<td>1.08</td>
<td>0.636-1.85</td>
<td>0.767</td>
</tr>
<tr>
<td>Histology (Sq. vs. non-sq.)</td>
<td>0.94</td>
<td>0.59-1.49</td>
<td>0.786</td>
</tr>
<tr>
<td>PS (0-1 vs. 2-4)</td>
<td>2.15</td>
<td>1.39-3.34</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Stage (IIIa vs. IIb vs. IV)</td>
<td>1.45</td>
<td>0.96-1.87</td>
<td>0.086</td>
</tr>
<tr>
<td>GSTM1 [(+] vs. [-])</td>
<td>1.31</td>
<td>0.840-2.04</td>
<td>0.235</td>
</tr>
<tr>
<td>CYP1A1 (A vs. B + C)</td>
<td>2.02</td>
<td>1.27-3.21</td>
<td>0.003</td>
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<tr>
<td>Multivariate analysis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PS (0-1 vs. 2-4)</td>
<td>2.18</td>
<td>1.40-3.39</td>
<td>0.001</td>
</tr>
<tr>
<td>CYP1A1 (A vs. B + C)</td>
<td>1.98</td>
<td>1.24-3.17</td>
<td>0.005</td>
</tr>
</tbody>
</table>

*a*SQ, squamous; non-sq., adenocarcinoma and large cell carcinoma.

The longer overall survival among patients with early stage disease compared to those with advanced-stage disease was dependent mainly on whether or not the patients had received surgical treatment. Of the patients with early stage NSCLC, 80 of 85 (94%) had been treated with curative surgery, whereas only 49 of 147 (33%) with advanced-stage disease had been treated surgically. When a comparison was made in the group without surgical treatment (n = 103), the MTS of 8.0 months among patients with genotypes B + C (n = 66) was significantly shorter than that of 18.8 months among patients with genotype A (n = 37; P = 0.0002 by log-rank test). On the other hand, no significant survival difference was observed among surgically treated patients in relation to CYP1A1 genotypes (P = 0.740).

In this regard, it is interesting to mention that the proportion of surgically treated cases among patients with NSCLC differed in accordance with the genotypes of the CYP1A1 gene. Among 101 NSCLC patients with genotype A, 64 and 37 individuals had been treated with or without curative surgery, respectively. By contrast, among 131 patients with genotypes B + C, 65 and 66 individuals had been treated with or without surgery, respectively. The difference can be explained by the association of CYP1A1 genotypes with T-, N-, and M-factors (Table 1).

The CYP1A1 and GSTM1 polymorphisms, which are heritable predisposing factors to smoking-related lung cancer, are also related to the prognosis for lung cancer. Individuals with combination genotypes with a high risk of lung cancer may have an increased probability of mutations in target genes, resulting in a shortened overall survival. In clinical trials among patients with nonresectable advanced NSCLC, easy and precise identification of CYP1A1 genotypes using lymphocyte DNA may have to be considered to evaluate the effect of treatment on overall survival.

REFERENCES


Prognostic Significance of Germ Line Polymorphisms of the CYP1A1 and Glutathione S-Transferase Genes in Patients with Non-Small Cell Lung Cancer

Isao Goto, Shuichi Yoneda, Mitsunobu Yamamoto, et al.


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