Adjuvant Chemotherapy Improves the Probability of Freedom From Recurrence in Patients With Resected Stage IB Lung Adenocarcinoma

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Background. **The benefit of adjuvant chemotherapy remains controversial for patients with stage IB non–small-cell lung cancer (NSCLC). This study investigated the effect of adjuvant chemotherapy and the predictors of benefit from adjuvant chemotherapy in patients with stage IB lung adenocarcinoma.**

Methods. **A total of 243 patients with completely resected pathologic stage IB lung adenocarcinoma were included in the study. Predictors of the benefits of improved overall survival (OS) or probability of freedom from recurrence (FFR) from platinum-based adjuvant chemotherapy in patients with resected stage IB lung adenocarcinoma were investigated.**

Results. **Among the 243 patients, 70 (28.8%) had received platinum-based doublet adjuvant chemotherapy. A micropapillary/solid–predominant pattern (versus an acinar/papillary–predominant pattern) was a significantly worse prognostic factor for probability of FFR ($p = 0.033$). Although adjuvant chemotherapy (versus surgical intervention alone) was not a significant prognostic factor for OS ($p = 0.303$), it was a significant prognostic factor for a better probability of FFR ($p = 0.029$) on multivariate analysis. In propensity-score–matched pairs, there was no significant difference in OS between patients who received adjuvant chemotherapy and those who did not ($p = 0.386$). Patients who received adjuvant chemotherapy had a significantly better probability of FFR than those who did not ($p = 0.043$). For patients with a predominantly micropapillary/solid pattern, adjuvant chemotherapy ($p = 0.033$) was a significant prognostic factor for a better probability of FFR on multivariate analysis.**

Conclusions. **Adjuvant chemotherapy is a favorable prognostic factor for the probability of FFR in patients with stage IB lung adenocarcinoma, particularly in those with a micropapillary/solid–predominant pattern.**

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Lung cancer is the leading cause of cancer death worldwide [1]. Surgical resection is the treatment of choice for early-stage non–small cell lung cancer (NSCLC) [2, 3]. Tumor recurrence is the major cause of treatment failure after resection [4, 5]. Several meta-analyses and randomized controlled trials have reported that adjuvant chemotherapy substantially improved survival in patients with resected NSCLC [6–8]. However, the benefit of adjuvant chemotherapy remains controversial for patients with resected stage IB NSCLC [9].

In 2011, the International Association for the Study of Lung Cancer (IASLC), The American Thoracic Society (ATS), and the European Respiratory Society (ERS) proposed a new classification system for lung adenocarcinoma [10]. Several studies have reported the impact of the new classification on death and recurrence [11–17]. In our previous reports [18, 19], we have shown that micropapillary- and solid-predominant subtypes were significant prognostic factors for death and recurrence [18, 19]. However, the predictive value of the new classification for benefit from adjuvant chemotherapy remains unknown. The present study aimed to determine whether the IASLC/ATS/ERS classification of lung adenocarcinoma is predictive for a benefit of adjuvant chemotherapy in patients with completely resected stage IB lung adenocarcinoma.

Patients and Methods

Patients

This study was approved by the Institutional Review Board of Taipei Veterans General Hospital. From January

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2004 to December 2012, all patients who underwent complete resection for stage IB (T2aN0M0) lung adenocarcinoma at Taipei Veterans General Hospital were retrospectively reviewed. Patients undergoing neoadjuvant chemotherapy were excluded. A total of 359 patients with pathologic stage IB lung adenocarcinoma were identified. Among them, 21 patients were classified as having a predominantly lepidic pattern. These 21 patients were excluded from analysis because of their small number and the fact that none of them had received adjuvant chemotherapy. One hundred thirty-eight (40.8%) of the remaining 338 patients received adjuvant therapy. To demonstrate the factors predicting benefits from adjuvant platinum-based doublet chemotherapy, patients received oral tegafur-uracil (n = 58) and epidermal growth factor receptor [*EGFR*] tyrosine kinase inhibitor (n = 6) for adjuvant therapy were excluded from analysis. The remaining 274 patients underwent operation alone or received platinum-based adjuvant chemotherapy. Thirty-one of the 274 patients underwent sublobar resection and were also excluded. The remaining 243 patients were eligible and were included in the study. The preoperative staging workup—including chest and upper abdomen computed tomographic (CT) scans, bronchoscopic examination, CT scanning or magnetic resonance imaging of the brain, nuclear medicine survey of bone—was done as previously described [18, 19] (see Supplemental Patients for details). All patients underwent complete resection of lung cancer with mediastinal lymph node dissection/sampling as previously described [18, 19].

The indication for platinum-based adjuvant chemotherapy in our institution is pathologic stage II-IV disease after surgical resection. According to our previous report [18] regarding death and recurrence in stage I lung adenocarcinoma, visceral pleural invasion and a micropapillary/solid–predominant pattern were significant predictors for recurrence. Although the use of adjuvant chemotherapy and the regimens used for adjuvant chemotherapy in patients with stage IB disease were not randomized but took place according to physician preference in the current study, patients with a predominantly micropapillary/solid pattern were more likely to be offered adjuvant chemotherapy (Table 1). Four cycles were typically administered in the adjuvant setting.

Clinicopathologic Characteristics and Patient Follow-Up

All resected specimens were formalin fixed and stained with hematoxylin and eosin and were reevaluated microscopically as previously described [19]. The criteria

Table 1. Relationship Between Adjuvant Chemotherapy (Surgical Intervention Alone or With Adjuvant Chemotherapy) and Clinicopathologic Variables in 243 Patients With Stage IB Lung Adenocarcinoma

Variable	All Patients	Surgical Intervention Alone (n = 173)	With Adjuvant Therapy (n = 70)	*p* Value
Age, y (mean ± SD)	63.8 ± 10.3	64.9 ± 10.3	61.1 ± 10.0	0.010
Sex, no. (%)				
Male	126 (51.9)	99 (57.2)	27 (38.6)	0.008
Female	117 (48.1)	74 (42.8)	43 (61.4)	
Invasive tumor size, no. (%)				
≤3 cm	168 (69.1)	120 (69.4)	48 (68.6)	0.904
>3 cm	75 (30.9)	53 (30.6)	22 (31.4)	
Visceral pleural invasion, n (%)[a]				
Absent	22 (9.1)	17 (9.9)	5 (7.1)	0.501
Present	220 (90.5)	155 (90.1)	65 (92.9)	
Unknown	1 (0.4)	. . .	. . .	
Predominant pattern, n (%)				
Acinar	104 (42.8)	77 (44.5)	27 (38.6)	0.016
Papillary	76 (31.3)	59 (34.1)	17 (24.3)	
Micropapillary	38 (15.6)	19 (11.0)	19 (27.1)	
Solid	25 (10.3)	18 (10.4)	7 (10.0)	
Predominant pattern group, n (%)				
Acinar/papillary	180 (74.1)	136 (78.6)	44 (62.9)	0.011
Micropapillary/solid	63 (25.9)	37 (21.4)	26 (37.1)	
FEV_1 (% predicted) (mean)	96.4	95.7	98.0	0.299
DLCO (% predicted) (mean)	73.2	72.9	74.0	0.627
Comorbidity, n (%)				
No	131 (53.9)	87 (50.3)	44 (62.9)	0.075
Yes	112 (46.1)	86 (49.7)	26 (37.1)	

[a] Patients with unknown status were excluded from the analysis.

DLCO = diffusing capacity of the lungs for carbon monoxide; FEV_1 = forced expiratory volume in 1 second; SD = standard deviation.