Original
Article

Platinum-Based Adjuvant Chemotherapy for Stage II and Stage III Squamous Cell Carcinoma of the Lung

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Introduction: The efficacy of platinum-based adjuvant chemotherapy (PBAC) for pathological stage II and stage III squamous cell carcinoma (SCC) of the lung was analyzed retrospectively. **Materials and Methods:** The prognoses of 94 patients with stage II and stage III SCC with or without PBAC (more than three courses of cisplatin-, carboplatin-, and nedaplatin-based adjuvant chemotherapy) were compared.

Results: The mean observation period was 46.1 months. PBAC was not administered for the following reasons: 39 (55.7%) patients had comorbidities, 25 (35.7%) were older than 75 years, 19 (27.1%) patients underwent surgery before the approval of PBAC, and 3 (4.3%) patients could not continue PBAC (≤ 2 cycles) because of adverse events. PBAC patients ($n = 24$) were significantly younger than non-PBAC patients ($n = 70$; 66.3 vs 69.6 years old, respectively; $p = 0.043$). Disease-free survival (DFS) did not differ between PBAC and non-PBAC patients (55.0% and 67.1%, respectively; $p = 0.266$). PBAC patients tended to have worse overall survival (OS) than non-PBAC patients (56.1% and 70.2%, respectively; $p = 0.138$). PBAC was not prognostic for OS (hazard ratio (HR), 2.11; 95% confidence interval (CI), 0.82%–5.40%; $p = 0.120$).

Conclusion: PBAC did not improve the prognoses of patients with pathological stage II or stage III SCC in the single institution experience.

Keywords: platinum-based adjuvant chemotherapy, squamous cell carcinoma of the lung, disease-free survival, overall survival

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Introduction

Squamous cell carcinoma (SCC) of the lung accounts for 20%–30% of primary lung cancers and is the second most common histopathological type after pulmonary adenocarcinoma in Japan.^{1,2)} The prognoses of SCC and pulmonary adenocarcinoma differ according to lung cancer progression after complete resection. In stage I lung cancer, disease-free survival (DFS) and overall survival (OS) of patients with SCC are poorer than those of patients with pulmonary adenocarcinoma because adenocarcinoma in situ or minimally invasive adenocarcinoma confers good prognoses after curative resection.³⁾ Moreover, SCC is more frequent among elderly men who smoke, which might be related to non-cancer

deaths.^{3,4)} However, the prognosis of resectable advanced SCC of stage II or higher after complete resection is better than that of pulmonary adenocarcinoma of the same stage.^{5,6)} Platinum-based doublet chemotherapy is commonly used for recurrent SCC, while various types of therapy, including molecular targeted drugs, are used for recurrent pulmonary adenocarcinoma.^{7–11)} Whether the favorable prognosis of patients with resectable advanced SCC is due to the less aggressive nature of the SCC tumor or the therapeutic effect of the chemotherapy on SCC remains unclear.

Based on several studies in unresectable advanced SCC, cisplatin + docetaxel is considered the standard first-line chemotherapy.^{11–13)} However, evidence for adjuvant chemotherapy to treat SCC remains unclear. Based on several clinical trials and the lung adjuvant cisplatin evaluation (LACE) pooled analysis, cisplatin-based chemotherapy improves OS for patients with non-small-cell lung cancer^{14–19)} although its efficacy for patients with SCC was not evident. Thus, in clinical practice, a cisplatin + vinorelbine regimen is used as adjuvant chemotherapy for SCC patients,²⁰⁾ and carboplatin- or nedaplatin-based regimens are used for those who cannot tolerate cisplatin toxicity. This retrospective study aimed to examine the efficacy of platinum-based adjuvant chemotherapy (PBAC) for completely resected pathological stage II and stage III SCC.

Materials and Methods

Patients

From April 2002 to June 2015, 94 patients were treated with complete resection (pneumonectomy, lobectomy, or segmentectomy with negative surgical margin and lymph node dissection) for pathological stage II or stage III SCC. Patients who received neoadjuvant therapy and those who died within 3 months of surgery were excluded (one patient died of acute exacerbation of interstitial pneumonia). A pneumonectomy was performed depending on the location and expanse of the tumor. A segmentectomy was performed for high-risk patients who were considered intolerable to lobectomy. All other patients underwent lobectomy. Staging was based on the 7th Edition of the TNM Classification for Lung and Pleural Tumors.

Definition of postoperative adjuvant chemotherapy and regimen

Patients who received platinum doublet chemotherapy including cisplatin (60–80 mg/m²), carboplatin (an area

Table 1 Platinum-based adjuvant chemotherapy regimens

Platinum-based adjuvant chemotherapy regimen	24
Cisplatin + vinorelbine	7
Cisplatin + docetaxel	1
Cisplatin + TS-1 (tegafur, gimeracil, and oteracil potassium)	1
Carboplatin + paclitaxel	4
Carboplatin + vinorelbine	1
Carboplatin + TS-1 (tegafur, gimeracil, and oteracil potassium)	1
Nedaplatin + irinotecan	9
Discontinuation of adjuvant chemotherapy due to side effects	3
Carboplatin + paclitaxel	2
Cisplatin + vinorelbine	1

under the curve dose of 5–6 mg/ml per minute), and nedaplatin (100 mg/m²) regimens every 4 weeks for at least three cycles were included in the PBAC group. Concomitant drugs used along with platinating agents were vinorelbine (25 mg/m² on days 1 and 8), paclitaxel (200 mg/m² on day 1), docetaxel (60 mg/m² on day 1), irinotecan (50–60 mg/m² on days 1 and 8), and TS-1 (tegafur, gimeracil, and oteracil potassium; 40 mg/m² twice per day). Patients who ceased treatment within two cycles of PBAC due to adverse events were included in the non-PBAC group. PBAC regimens used for the patients enrolled in the study are shown in **Table 1**. All patients who underwent surgery before 2006 were included in the non-PBAC group because PBAC was not approved for SCC at stage II and stage III at our hospital before 2006.

Postoperative follow-up and recurrence pattern

Patients received medical examinations every 3–6 months for the first to third years and every 6–12 months for fourth and fifth years after surgery. Computed tomography or positron emission tomography - computed tomography was performed at least once a year. When patients presented with recurrent cancer, cranial bone magnetic resonance imaging and positron emission tomography - computed tomography or bone scintigraphy were also conducted to determine the recurrence pattern (locoregional or distant). Locoregional recurrence was defined as a recurrence in the ipsilateral chest including dissemination at the mediastinum, supraclavicular, or cervical lymph nodes. Distant metastasis was defined as all recurrences other than locoregional recurrence, such as recurrence in the contralateral lung, brain, liver, adrenals, or bone.

Table 2 Comparison of clinicopathological features between PBAC and non-PBAC patients

	PBAC (+) (n = 24)	PBAC (–) (n = 70)	p values ^a
Mean age (range)	66.3 (50–74)	69.6 (51–82)	0.043 ^b
Male (%)	22 (91.7)	62 (88.6)	0.967
Current ex-smoker (%)	24 (100)	69 (98.6)	0.573
Comorbidity incidence (%)	11 (45.8)	39 (55.7)	0.403
Cardiac diseases	0	7 (10.0)	0.246
Other cancers	5 (20.8)	13 (18.6)	0.954
Chronic hepatitis	0	4 (5.7)	0.541
Respiratory dysfunctions	7 (29.2)	26 (37.1)	0.480
Tumor size (mm)	49.2	39.1	0.008 ^b
Surgical procedures (%)			
Lobectomy	23 (95.8)	61 (87.1)	
Pneumonectomy	1 (4.2)	6 (8.6)	
Segmentectomy	0	3 (4.3)	0.352
Pathological stage (%)			
p Stage IIA	12 (50.0)	38 (54.3)	
p Stage IIB	5 (20.8)	15 (21.4)	
p Stage IIIA	7 (29.2)	17 (24.3)	0.891
Lymphatic invasion (%)	6 (25.0)	27 (38.6)	0.229
Vascular invasion (%)	20 (83.3)	53 (75.7)	0.625
Pleural invasion	9 (37.5)	23 (32.9)	0.679
Pathological N status (%)			
pN0	1 (4.2)	8 (11.4)	
pN1	18 (75.0)	47 (67.1)	
pN2	5 (20.8)	15 (21.4)	0.564
Recurrent (%)	6 (25.0)	15 (21.4)	0.717
Distant metastasis	1 (16.7)	4 (26.7)	
Locoregional	6 (100)	11 (73.3)	0.921

PBAC: platinum-based adjuvant chemotherapy. ^aFisher's exact test; ^bStudent's t-test.

Pathological examination

Pathological diagnoses were made by pathological experts according to the 2004 World Health Organization classification. Tumor sections were routinely stained with hematoxylin and eosin as well as p40 or p63 to confirm SCC. Thyroid transcription factor 1 and napsin A or synaptophysin, CD56, and chromogranin A were stained to distinguish SCC from adenocarcinoma or neuroendocrine tumors, respectively, when necessary. Elastica-van Gieson or D2-40 staining was performed to evaluate vascular and pleural invasion or lymphatic invasion, respectively, when necessary.

Statistical analysis

Student's t-tests and Fisher's exact tests were used to analyze the continuous and categorical variables between PBAC and non-PBAC patients, respectively. Five-year DFS and OS were analyzed using the Kaplan–Meier method and compared between PBAC and non-PBAC patients using log-rank tests. The Cox proportional hazard regression model was used for multivariate analysis. A p value <0.05 was considered statistically significant.

This study was approved by the Institutional Review Board at Kanagawa Cancer Center and was performed in accordance with the Declaration of Helsinki.

Results

The mean observation period for all patients was 46.1 months. Five-year DFS and OS of all patients were 64.2% and 67.2%, respectively. Five-year OS of pathological stage IIA (n = 50), IIB (n = 20), and stage IIIA (n = 24) was 76.6%, 44.5%, and 64.1%, respectively.

In total, 24 (25.5%) and 70 (74.5%) patients were included in PBAC and non-PBAC groups, respectively. PBAC was not given for the following reasons: 39 (55.7%) patients had comorbidities, 25 (35.7%) patients were older than 75 years, 19 (27.1%) patients were treated before 2006, and 3 (4.3%) patients discontinued PBAC (≤ 2 cycles) because of adverse events (some patients were not administered PBAC for multiple reasons). The regimens used for the three patients who discontinued PBAC within two cycles are also shown in **Table 1**.

Fig. 1 DFS and OS for patients treated with or without PBAC. (A) DFS did not differ between PBAC and non-PBAC patients (55.0% vs 67.1%; $p = 0.266$). (B) PBAC patients tended to have worse 5-year OS than non-PBAC patients (56.1% vs 70.2%; $p = 0.138$). DFS: disease-free survival; OS: overall survival; PBAC: platinum-based adjuvant chemotherapy

The clinicopathological backgrounds of PBAC and non-PBAC patients are shown in **Table 2**. PBAC patients were significantly younger than non-PBAC patients ($p = 0.043$). Tumors in PBAC patients were significantly larger than in non-PBAC patients ($p = 0.008$). However, other clinicopathological backgrounds did not differ between PBAC and non-PBAC patients. The most common SCC recurrence pattern was local (81.0% of patients with relapse), and the recurrence pattern did not differ between PBAC and non-PBAC patients.

DFS did not differ between PBAC and non-PBAC patients (55.0% vs 67.1%; $p = 0.266$; **Fig. 1A**). PBAC patients tended to have worse OS as compared to non-PBAC patients (56.1% vs 70.2%; $p = 0.138$; **Fig. 1B**). PBAC was not a prognostic factor for DFS by multivariate analysis (hazard ratio (HR), 1.42; 95% confidence interval (CI), 0.60–3.35; $p = 0.429$), and OS (HR, 2.11; 95% CI, 0.82–5.40; $p = 0.120$; **Table 3**). OS did not differ between each platinum (cisplatin, carboplatin, or nedaplatin)-based regimen ($p = 0.284$; **Fig. 2**).

Discussion

This retrospective study did not demonstrate any positive effect of PBAC for patients after curative resection of stage II or stage III SCC. Because PBAC patients were

younger and were considered more tolerant of chemotherapy, they were hypothesized to have better prognoses than non-PBAC patients. Indeed, there were no deaths in the PBAC group, whereas five deaths were observed in the non-PBAC group within 1 year of surgery (data not shown). However, as shown in **Fig. 1B**, OS curves intersected approximately 15 months after surgery, and the OS curve of the PBAC group fell below that of the non-PBAC group, suggesting a possible negative effect of PBAC on OS after a certain period of time. Moreover, the HR of the PBAC group was 2.11 ($p = 0.120$) by multivariable analysis, which suggests that PBAC did not improve the prognoses of these patients, rather, it may have a negative impact on OS.

LACE meta-analysis has shown a significant OS benefit of postoperative cisplatin-based chemotherapy as compared to surgery alone (HR, 0.89; 95% CI, 0.82–0.96; $p = 0.005$), and the absolute benefit of chemotherapy after 5 years was 5.4%.¹⁹⁾ Moreover, the CALGB9633 study has demonstrated a survival benefit of postoperative carboplatin + paclitaxel for stage IB non-small-cell lung cancer for patients with tumor size of 4 cm or more (HR, 0.69; 95% CI, 0.48–0.99; $p = 0.043$).²¹⁾ The reason that PBAC was not beneficial in patients with stage II and stage III SCC remains unclear; however, the survival benefit of PBAC might be reduced by its detrimental effects on SCC patients.

Table 3 Multivariate Cox proportional hazard regression model for DFS and OS

Variable	Multivariate analysis for DFS			Multivariate analysis for OS		
	HR	95% CI	p value	HR	95% CI	p value
Age (>65)	0.72	0.34–1.50	0.379	1.41	0.60–3.33	0.437
Sex (male)	1.82	0.41–7.98	0.428	1.49	0.34–6.63	0.600
Tumor size (>50 mm)	1.36	0.53–3.49	0.524	0.70	0.26–1.91	0.487
Pathological stage (II and III)	1.32	0.62–2.78	0.473	1.91	0.95–3.88	0.070
Differentiation (well, moderate, and poor)	1.00	0.58–1.72	0.990	0.86	0.46–1.61	0.635
Lymphatic invasion (+)	0.96	0.46–2.03	0.915	0.85	0.37–1.92	0.695
Pleural invasion (+)	1.30	0.58–2.88	0.526	1.68	0.68–4.17	0.264
PBAC (+)	1.42	0.60–3.35	0.429	2.11	0.82–5.40	0.120

DFS: disease-free survival; OS: overall survival; HR: hazard ratio; CI: confidence interval; PBAC: platinum-based adjuvant chemotherapy

A higher HRs of adjuvant chemotherapy were observed in SCC than in adenocarcinoma patients in a subgroup analysis of the International Adjuvant Lung Cancer Trial and in a LACE pooled analysis although they were not statistically significant.^{14,19)} The majority of studies have analyzed the efficacy of postoperative adjuvant chemotherapy for non-small-cell lung cancer in heterogeneous populations. Because patients with resectable advanced SCC inherently have more favorable prognoses than those with resectable advanced pulmonary adenocarcinoma,^{5,6)} adjuvant chemotherapy for SCC patients might be omissible.

There are various toxicities experienced in response to platinating agents. Renal and cardiovascular adverse events that are often life-threatening occur after cisplatin administration.^{22–25)} Although carboplatin-based chemotherapy is considered less toxic than cisplatin-based chemotherapy, thrombocytopenia, neutropenia, and nephrotoxicity often become problematic for patients during the course of chemotherapy.^{22,26)} Nedaplatin is a cisplatin derivative designed to reduce cisplatin toxicity and has potential antitumor effects against SCC in various organs.^{10,27)} Its use in combination with irinotecan confers a prognostic benefit for patients with SCC.¹¹⁾ However, hematological adverse events are problematic in nedaplatin-based chemotherapy.¹⁰⁾ Because SCC frequently occurs in smoking elderly men who might have complicating respiratory disorders, vascular disorders, or other cancers,²⁸⁾ these toxicities might negatively influence patient prognosis.

Long-term survival (beyond 5 years) benefits of adjuvant chemotherapy have not been shown;^{21,29)} however, patients who did not smoke after adjuvant chemotherapy and had fewer comorbidities received a survival benefit from adjuvant chemotherapy.³⁰⁾ Because 11 patients

Fig. 2 Survival curves of patients receiving cisplatin-, carboplatin-, and nedaplatin-based regimens. All patients who received cisplatin-based chemotherapy remained alive for the duration of the observation period although no significant differences were detected in OS between patients who received carboplatin- and nedaplatin-based chemotherapy ($p = 0.284$). OS: overall survival

(45.8%) had comorbidities in this study, these patients might not have received a survival benefit from PBAC. Moreover, it is uncertain whether patients in this study discontinued cigarette use.

There were some limitations in this study because it was a retrospective analysis with a small number of patients performed at a single institution. Patient backgrounds were not strictly matched between PBAC and non-PBAC groups, and various platinum-based chemotherapy regimens were included in this study. All of the patients who received cisplatin-based chemotherapy remained alive for the observation period; however, this study did not come to a definitive conclusion on

whether cisplatin-based chemotherapy was superior to carboplatin- or nedaplatin-based chemotherapy because the number of the patients was too small (**Fig. 2**). A prospective study that includes a large patient population using a single platinum-based regimen is necessary to evaluate the efficacy and toxicity of PBAC for stage II and stage III SCC.

Conclusion

PBAC did not improve the prognoses of patients with pathological stage II or stage III SCC after curative resection of the lung, rather, it might have a negative impact on OS. A prospective study was required to evaluate whether PBAC was omissible for the patients with pathological stage II or stage III SCC.

Disclosure Statement

Tetsuya Isaka and other co-authors have no conflict of interest.

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