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Adjuvant Chemotherapy of Gemcitabine plus Carboplatin versus Paclitaxel plus Carboplatin in Patients with Resected Non-Small Cell Lung Cancer

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ABSTRACT

Background: This retrospective study was to evaluate the efficacy and toxicity of gemcitabine plus carboplatin (GC regimen) and paclitaxel plus carboplatin (PC regimen) combination chemotherapy administered as an adjuvant therapy after complete resection of non-small cell lung cancer. **Methods:** Forty-four patients (GC regimen, n = 29; PC regimen, n = 15) received gemcitabine at a dose of 1000 mg/m^2 on days 1 and 8, and carboplatin with the target dose of area under the curve (AUC) of 4 on day 8 every 28 days and paclitaxel at a dose of 70 mg/m^2 on days 1, 8 and 15, and carboplatin with the target dose of AUC of 5 on day 1 every 28 days. **Results:** A total of 130 cycles of the treatment were administered (averaged, 3.1 in GC arm and 2.7 cycles in PC arm). Forty-three patients (97.7%) completed the scheduled cycles. One patient (2.3%) was discontinued due to grade 4 pneumonia. The dose was reduced in 2 patients (4.5%) due to grade 4 thrombocytopenia. Grade 3/4 neutropenia was significantly observed in the PC group (GC: 12/29, 41.4%; PC: 11/15, 73.3%, p = 0.0443). The nonhematological toxicities were mild. Grade 1/2 alanine aminotransferase and aspartate aminotransferase in the GC group was significantly observed higher compared to those of the PC group (GC: 20/29, 69.0%; PC: 4/15, 26.7%, p = 0.0076). Grade 1/2 alopecia was significantly observed in the PC group (GC: 0/25, 0.0%; PC: 13/15, 86.7%, p < 0.0001). There was no treatment-related death. The median survival time (MST) of the entire GC group was 784 days, the 3-year overall survival (OS) was 75.9%, and 3-year recurrence-free survival (RFS) was 65.5%. The MST of the entire PC group was 963 days, the 3-year OS was 80.0%, and the 3-year RFS was 60.0%. **Conclusion:** These results demonstrate that the GC and PC combination chemotherapies are efficacious and feasible regimens, which should be considered as one of the standard therapies for adjuvant therapy.

Keywords: Non-Small Cell Lung Cancer; Gemcitabine; Paclitaxel; Carboplatin; Combination Chemotherapy; Adjuvant Therapy

1. Introduction

Non-small cell lung cancer (NSCLC) is currently the leading cause of death related to cancer [1,2]. The most effective treatment for the early stages (IA-IIIA) NSCLC is surgical resection. However, up to 60% of patients with IB to IIIA NSCLC relapse after surgery and die [2,3]. Adjuvant therapy for early-stage NSCLC has been the focus of much study in the hope of reducing the relapse risk and improving survival from the 40% to 60% achieved with surgery alone [2]. The presence of micrometastatic disease at the time of resection is the most likely cause of recurrence occurring even after complete resection of all the macroscopically recognizable lesions. If micrometastases are indeed responsible for the disease recurrence, adjuvant chemotherapy would be a rational treatment, and this hypothesis has led to the attempt to reduce the risk of relapse and death from lung cancer by giving adjuvant chemotherapy to patients with complete surgical resection [4].

More recent randomized trials of adjuvant cisplatin-based chemotherapy have shown only marginally better compliance despite considerable improvements in the supportive care medications available over the past decade. North American [5], Japanese [6], and European [7-9] intergroup trials reported that only 58% - 69% of patients received all of the planned cycles of chemotherapy.

A meta-analysis of small randomized trials of patients

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with early stage NSCLC in the preceeding 30 years was performed in 1995 [4]. This analysis revealed a 5% survival advantage at 5 years for patients with surgically resected early stage NSCLC treated with cisplatin-based chemotherapy compared to those patients only followed up after resection.

It is not yet clear whether platinum-based chemotherapy is feasible or available in an adjuvant setting for Japanese patients. Adjuvant chemotherapy is the standard of therapy for some patients with stage I, II, and III breast cancers. The therapeutic efficacy of adjuvant chemotherapy following surgical resection of early stage NSCLC has been less clear. In clinical practice, we conducted trials to assess the efficacy and safety of two regimens in Japanese patients with NSCLC in a single institution. This retrospective study was to evaluate the efficacy and toxicity of gemcitabine plus carboplatin (GC regimen) and paclitaxel plus carboplatin (PC regimen) combination chemotherapy administered as an adjuvant therapy after complete resection of non-small cell lung cancer.

2. Patients and Methods

2.1. Patients

From December 2004 to July 2009, a total of 44 patients who had undergone surgical resection received adjuvant chemotherapy of the gemcitabine plus carboplatin or paclitaxel plus carboplatin doublet combinations. The characteristics of the 44 patients entered in this study are summarized in **Tables 1** and **2**. TNM classification is based on the Union for International Cancer Control (UICC) [10]. The histological analysis of the tumor was based on the World Health Organization classification for cell types [11]. Patients with histologically documented NSCLC and pathologically staged were eligible to receive adjuvant chemotherapy after complete resection of the primary tumor and mediastinal lymph nodes in our department.

2.2. Each Patient Had to Meet the Following Eligibility Criteria

Pathological stage from IB to IV diagnosed with complete resection, Eastern Cooperative Oncology Group Performance Status of 0, 1 or 2, adequate bone marrow function (total leukocyte count $\geq 4.0 \times 10^9$/l, hemoglobin concentration ≥ 10.0 g/dl, platelet count $\geq 100 \times 10^9$/l), adequate liver and renal function (serum transaminase ≤ 2 times normal value; serum creatinine ≤ 1.5 times normal value), partial pressure of arterial oxygen (paO_2) ≥ 60 torr,

Table 1. Patient characteristics.

		GEM + CBDCA group (n = 29)		PTX + CBDCA group (n = 15)		Overall (n = 44)	
		No. of patients	(%)	No. of patients	(%)	No. of patients	(%)
Age (years)	Mean ± SD	64.0 ± 9.2		61.2 ± 12.5		62.8 ± 10.6	
	range	45 - 78		35 - 77		35 - 78	
Gender	Male	18	62.1	13	86.7	31	70.5
	Female	11	37.9	2	13.3	13	29.5
ECOG-PS	0	27	93.1	14	93.3	41	93.2
	1	2	6.9	1	6.7	3	6.8
Surgery	Lobectomy	27	93.1	14	93.3	41	93.2
	Pneumonectomy	2	6.9	1	6.7	3	6.8
Histology	Adenocarcinoma	26	89.7	13	86.7	39	88.6
	Squamous cell carcinoma	2	6.9	1	6.7	3	6.8
	Adenosquamous cell carcinoma	1	3.4	1	6.7	2	4.6
Clinical stage	IB	1	3.4	1	6.7	2	4.6
	IIA	5	17.2	4	26.7	9	20.4
	IIB	4	13.8	1	6.7	5	11.4
	IIIA	14	48.3	8	53.3	22	50
	IIIB	2	6.9	1	6.7	3	6.8
	IV	3	10.3			3	6.8

ECOG-PS: Eastern Cooperative Oncology Group Performance Status.

Table 2. Treatment background.

		GEM + CBDCA group (n = 29)	PTX + CBDCA group (n = 15)
Planned cycles	1/2/3/4/5/6 cycles	0/11/5/13/0/0	0/9/0/5/0/1
Received cycles	1/2/3/4/5/6 cycles	0/11/5/13/0/0	1/9/0/4/0/1
Compliance	Total cycles	89	41
	mean	3.1	2.7
	Completed	29 (100.0%)	14 (93.3%)
	Discontinued	0 (0.0%)	1* (6.7%)
	Dose reduction	1 (2.2%)	1 (6.7%)
	Delayed	3 (6.7%)	0 (0.0%)
Toxicities	≥ Grade 3/4	12 (41.4%)	10 (66.7%)

*Grade 4 pneumonia.

past history of severe allergic reaction to drugs, interstitial pneumonia identified by computed-tomography of chest, cirrhosis, or other serious complications, such as uncontrolled angina pectoris, myocardial infarction within 3 months, heart failure, uncontrolled diabetes mellitus or hypertension, and uncontrolled massive pleural effusion or ascites, no postoperative complications, able to undergo first course treatment in an inpatients setting within 4 to 8 weeks after surgery, and written informed consent. All patients provided written informed consent before the treatment.

2.3. Treatment Schedule

All patients received one of the two treatment groups by attending doctors' direction and/or patients' favorable selection depending on their toxicities. The body surface area was calculated using the DuBois equation. Carboplatin dosage calculation was based on glomerular filtration rate according to the Calvert formula [12], and evaluated with the Cockcroft-Gault equation [13]. The administration of carboplatin dosage was adjusted prior to each cycle through re-determination of the glomerular filtration rate.

2.3.1. Gemcitabine plus Carboplatin Regimen (GC Group)

Gemcitabine (Gemzar, Eli Lilly Japan K.K., Kobe, Japan) was adminstered at a dose of 1000 mg/m^2 on days 1 and 8, and carboplatin (Paraplatin, Bristol-Myers K.K., Tokyo, Japan) with the target dose of area under the curve (AUC) of 4 on day 8 every 28 days. Premedication was intravenously performed with drip infusion of 100 ml of isotonic sodium chloride solution containing of 8 mg dexamethasone sodium phosphate and 3 mg of granisetron hydrochloride. An infusion pump was used to ensure the exact infusion time. On days 1 and 8, the intravenous administration of 1000 mg/m^2 gemcitabine mixed in 100 ml of isotonic sodium chloride solution was performed with drip infusion for 30 minutes. On the day 8, carboplatin with the calculated dose of the AUC mixed in 250 ml of a 5% glucose solution was administered for 1 hour, following the drip infusion of gemcitabine.

2.3.2. Paclitaxel plus Carboplatin Regimen (PC Group)

Paclitaxel (Paclitaxel, Bristol-Myers K.K., Tokyo, Japan) was administered at of 70 mg/m^2 on days 1, 8 and 15, and carboplatin (Paraplatin, Bristol-Myers K.K., Tokyo, Japan) with the target dose of AUC of 5 on day 1 every 28 days. As a premedication, 50 mg of diphenhydramine hydrochloride was intravenously infused. The drip infusion of 50 ml of an isotonic sodium chloride solution containing 8 mg of dexamethasone sodium phosphate, 50 mg of ranitidine hydrochloride and 10 mg of azasetron hydrochloride were performed. After the administration of 70 mg/m^2 of paclitaxel in 250 ml of a 5% glucose solution for over 1 hour, carboplatin with the calculated dose of the AUC mixed in 250 ml of a 5% glucose solution was intravenously infused for 1 hour.

Each treatment was recommended for four cycles as a standard course. Patients could plan their scheduled cycle number between 1 to 6 and also refuse the treatment unless they met the criteria for experienced unacceptable toxicity. Full supportive therapy, corticosteroids, anticonvulsants and antibiotics were given as needed. No routine use of heatopoietic growth factors was planned. No prophylactic antibiotics were used. All patients were treated on an inpatient basis.

2.3.3. The Exclusion Criteria

The exclusion criteria included serious infection, fever (≥38˚C), impairments of the organ function (bone marrow, central nervous and cardiovascular system, liver, kidneys, interstitial pneumonia, DIC), patient's refusal

and attending doctor's decision.

2.4. Dose Modification

Dose adjustments during the treatment were based on the judgement of the respective physicians-in-charge, but, as a rule, when Grade 3 or more severe nonhematotoxicity or Grade 4 hematotoxicity appeared, the doses of the anticancer drugs were reduced. The complete blood count and biochemistry were usually examined at least once or twice per week.

On the scheduled day-1 treatment, if the total leukocyte count and absolute neutrophil count (ANC) was $\leq 3.0 \times 10^9$/l and $\leq 1.5 \times 10^9$/l and/or platelet count $\leq 100 \times 10^9$/l, respectively, the chemotherapy doses were either delayed (for up to 2 weeks) or reduced by 20% - 25% (gemcitabine: from 1,000 mg/m^2 to 800 mg/m^2, AUC of carboplatin from 4 to 3; paclitaxel: from 70 mg/m^2 to 60 mg/m^2, AUC of carboplatin from 5 to 4) to allow recovery from hematological toxicity.

On the scheduled day-8 treatment, if the total leukocyte count and ANC was $\leq 1.0 \times 10^9$/l and $\leq 0.5 \times 10^9$/l and/or platelet count $\leq 75 \times 10^9$/l, and if these parameter did not improve sufficiently, then the day-8 administrations of drugs were postponed and omitted. A 2-week delay in initiating the subsequent course was allowed. Patients, who cannot recover from the hematological toxicity (ANC $\geq 1.0 \times 10^9$/l and/or platelet count $\geq 75 \times 10^9$/l) within 2 weeks were withdrawn from the treatment. For patients of the delayed day-8 and/or of the no recovery within 2 weeks for any ≥grade 2 impairments of the organ function (hepatic, renal, cardiovascular, pulmonary, nervous system) and/or ≥grade 3 nonhematological toxicities (excluding nausea, vomiting, anorexia, fatigue, and alopecia), the doses of the next cycle were reduced by 20% - 25%.

If these toxicities persisted after 6 weeks from day-1 of the previous cycle, then the treatment regimen was discontinued.

The next cycle was discontinued in the case of ≥Grade 3 impairments on the organ function (hepatic, renal, cardiovascular, pulmonary, nervous system) and/or ≥grade 4 nonhematological toxicities (nausea, vomiting, anorexia, fatigue, and alopecia). The subsequent course of chemotherapy was begun if patients had a total leukocyte count at $\geq 3.0 \times 10^9$/l, ANC $\geq 1.5 \times 10^9$/l, platelet count $\geq 100 \times 10^9$/l, creatinine ≥1.5 mg/dl, alanine aminotransferase and aspartate aminotransferase (AST/ALT) levels ≤2.5 times the normal upper limit, and total bilirubin ≤1.5 times the normal upper limit, respectively. Both regimens were repeated every 4 weeks.

Regarding the use of the granulocyte colony-stimulating factor (G-CSF), patients were not to receive prophylactic G-CSF during any cycle. The use of G-CSF (100 μg/day, subcutaneous injection) was allowed only for patients who had the total leukocyte count $\leq 1.0 \times 10^9$/l, ANC $\leq 0.5 \times 10^9$/l, neutropenic fever, or documented infections with febrile neutropenia.

2.5. Toxicity and Treatment Evaluation

Prior to the adjuvant chemotherapy after surgery, all patients provided a complete medical history and underwent a physical examination. Patients were monitored weekly throughout treatment by physical examination, recording of toxic effects, complete blood cell counts, and blood chemistry. These patients were examined for the patient background characteristics, adverse events, treatment compliance and relapse-free survival. Adverse events were evaluated until 4 weeks after the completion of the chemotherapy according to the Common Terminology Criteria for Adverse Events Version. 3.0. The recurrence-free survival (RFS) was measured from the date of the first administration of surgery to the date of recognition of the local recurrence or distant metastasis. Overall survival (OS) was measured from the date of the first administration of surgery to the date of death or the last follow-up. The Kaplan-Meier technique [14] was used for the RFS and OS analysis. The accrual period and period of follow-up after accrual closure were 6 years and 4 months, respectively.

2.6. Statistical Analysis

Statistical differences in the toxicities between the two regimens were calculated using the Chi-square (χ^2) test. A p value less than 0.05 was considered to be statistically significant.

3. Results

3.1. Patient Characteristics.

A total of 44 patients (29 patients in GC regimen and 15 in PC regimen) were completely resected in our department and summarized in **Table 1**. The majority of patients were males (31/44, 70.5%), with a median age of 64.0 years (range 45 - 78) in the GC arm and 61.2 years (range 35 - 77) in the PC arm. The Eastern Cooperative Oncology Group Performance Status was 0 in 41 patients (41/44, 93.3%) and 1 in 3 patients (3/44, 6.8%). A lobectomy was performed in 41 patients (41/44, 93.2%) and a pneumonectomy was done in 3 patients (3/44, 6.8%). Tumor histology included 39 patients with adenocarcinoma (88.6%), 3 patients with squamous cell carcinoma (6.8%) and 2 patients with adenosquamous cell carcinoma (4.5%). There were 2 patient with stage IB (4.5%), 9 patients with stage IIA (20.5%), 5 patients with stage IIB (11.4%), 22 patients with stage IIIA (50.0%), 3

patients with stage IIIB (6.8%), and 3 patients with stage IV disease (6.8%).

3.2. Treatment Administration

A total of 130 chemotherapy cycles were administered (89 cycles in the GC regimen: median, 3.1; range, 2 - 4, and 41 cycles in the PC regimen: median, 2.7; range, 1 - 6) as listed in **Table 2**. On compliance, forty-three of 44 patients (97.7%) completed the planned cycles, the remaining 1 patient did not complete the course due to grade 4 pneumonia. Two patients (4.5%) received a dose reduction in the next course, and 3 patients (6.8%) delayed the course.

3.3. Toxicity

For the grade 3/4 toxicities (**Table 2**), the PC regimen had 10 patients (10/15, 66.7%) and showed a higher incidence compared to twelve patients of the GC regimen (12/29, 41.4%) in **Table 2**. Overall, twenty-two patients in both regimens showed grade 3/4 toxicities (22/44, 50.0%). The hematological toxicities are shown in **Table 3**. The grade 3/4 neutropenia was significantly observed in the PC regimen (GC regimen: 12/29, 41.4%; PC regimen: 11/15, 73.3%, $p = 0.0443$). The grade 3/4 thrombocytopenia was more frequently seen in 6 patients (20.7%) of the GC regimen compared to 1 patient (6.7%) of the PC regimen ($p = 0.2280$). The grade 3/4 febrile neutropenia was seen in 2 patients (6.9%) of the GC regimen compared to 0 patient (0%) of the PC regimen ($p = 0.2979$).

The nonhematological toxicities are mild except for infection as shown in **Table 4**. However, grade 4 pneumonia was more frequently observed in 1 patient (1/15, 6.7%) of the PC regimen compared to none in the GC regimen ($p = 0.1596$). Grade 1/2 anorexia was observed in the GC arm (GC arm: 18/29, 62.1%; PC arm: 13/15, 86.7%, $p = 0.0900$). Grade 1/2 alanine aminotransferase and aspartate aminotransferase (ALT/AST) in the GC regimen were more significantly observed compared to those of the PC arm (GC arm: 20/29, 69.0%; PC arm: 4/15, 26.7%, $p = 0.0076$). Grade 1/2 alopecia was significantly observed in PC arm (GC arm: 0/25, 0.0%; PC arm: 13/15, 86.7%, $p < 0.0001$). For the other toxicities, they were observed in 3 patients with headache were observed in the GC regimen. In the PC regimen, grade 4 pneumonia, headache, and hematuria in 1 patient. The overall grade 1/2 non-hematologic toxicities were mild. There was no treatment-related death.

3.4. Survival

A survival analysis was performed in April 2011. Ten patients had been followed for less than 1 year. The median survival time (MST) of the entire GC regimen group was 784 days; 1-year overall survival (OS) was 89.7%, 2-year OS was 79.3%, and 3-year OS was 75.9%, respectively (**Table 5**). The median recurrence-free survival (RFS) at 1-year, 2-year, and 3-year, was 65.5%. The MST of the entire PC regimen group was 963 days; 1-year OS was 93.3%, 2-year OS was 86.7%, and 3-year OS was 80.0%, respectively. The median recurrence-free survival (RFS) at 1-year, 2-year, and 3-year, was 80.0%, 66.7% and 60.0%, respectively.

4. Discussion

Five-year survival rate after surgical treatment in the United States and Japan in each pathological stage of NSCLC was reported as follows: IA, 67%; IB, 27%; IIA, 55%; IIB, 39%; IIIA, 38%; IIIB, 3% - 7%; IV, 1% in the United States, and IA, 79.5%; IB, 60.1%; IIA, 59.9%; IIB, 42.2%; IIIA, 29.8%; IIIB, 19.3%; IV, 20.0% in Japan [2,3]. However, up to 60% of patients with IB to IIIA NSCLC relapse after surgery and die. [2,3].

Meta-analysis of the randomized trials of adjuvant therapy of NSCLC in 1995 suggested the survival benefit of cisplatin-based chemotherapy after surgery [4]. From the meta-analysis using 9387 patients (7151 deaths) from 52 randomized clinical trials, trials comparing surgery with surgery plus chemotherapy gave a hazard ratio of

Table 3. Summary of hematological toxicities.

	GEM + CBDCA group (n = 29)					PTX + CBDCA group (n = 15)					G3/4
	n (% of patients)					n (% of patients)					
Toxicity	G1	G2	G3	G4	G3/4 (%)	G1	G2	G3	G4	G3/4 (%)	*p* value
Leukopenia	18	4	3	0	10.3	5	7	1	0	6.7	0.6875
Neutropenia	8	7	6	6	41.4	1	1	7	4	73.3	0.0443
Anemia	2	8	1	0	3.4	4	0	1	0	6.7	0.6271
Thrombocytopenia	2	7	6	0	20.7	2	0	0	1	6.7	0.228
Febrile neutropenia	4	0	2	0	6.9	0	0	0	0	0	0.2979

Table 4. Summary of nonhematological toxicities.

	GEM + CBDCA group (n = 29)				PTX + CBDCA group (n = 15)				G1/2	G3/4
	n (% of patients)				n (% of patients)					
Toxicity	G1/2	G3/4	G1/2 (%)	G3/4 (%)	G1/2	G3/4	G1/2 (%)	G3/4(%)	*p* value	*p* value
Nausea	16	0	55.2	0	7	0	46.7	0	0.5923	-
Vomiting	2	0	6.9	0	2	0	13.3	0	0.4814	-
Anorexia	18	0	62.1	0	13	0	86.7	0	0.09	-
Fatigue	20	0	69	0	13	0	86.7	0	0.1987	-
Diarrhea	3	0	10.3	0	1	0	6.7	0	0.6875	-
Constipation	12	0	41.4	0	5	0	33.3	0	0.6034	-
ALT/AST	20	0	69	0	4	0	26.7	0	0.0076	-
Creatinine	2	0	6.9	0	1	0	6.7	0	0.6271	-
Neuropathy	0	0	0	0	0	0	0	0	-	-
Pain, joint	2	0	6.9	0	1	0	6.7	0	0.6271	-
Pain, muscle	1	0	3.4	0	1	0	6.7	0	0.6271	-
Skin rash	2	0	6.9	0	3	0	20	0	0.1942	-
Alopecia	0	0	0	0	13	0	86.7	0	<0.0001	-
Infection	0	0	0	0	1**	1*	6.7	6.7	0.1596	0.1596
Fever	4	0	13.8	0	1	0	6.7	0	0.4802	-
Others (hearing)	1	0	3.4	0	0	0	0	0	-	-
	GC group: headache (n = 3)				PC group: headache (n = 1), hematuria (n = 1)					

ALT/AST: alanine aminotransferase and aspartate aminotransferase; *G4 pneumonia, **G1 prostatitis.

Table 5. Recurrence-free and overall survivals.

		GEM + CBDCA group (n = 29)	PTX + CBDCA group (n = 15)
Median survival time (days)		784	963
Recurrence-free survival (%)	1-year	65.5	80
	2-year	65.5	66.7
	3-year	65.5	60
Overall survival (%)	1-year	89.7	93.3
	2-year	79.3	86.7
	3-year	75.9	80

0.87 (13% reduction in the risk of death, equivalent to an absolute benefit of 5% at five years). However, there are no statistical differences between the postoperative adjuvant group and surgery alone [4], and this includes a number of small trials and trials with the following disability criteria and chemotherapy regimens.

After the above-mentioned meta-analysis by the Non-small Cell Lung Cancer Collaborative Group, several clinical trials examining the adjuvant chemotherapy were performed, but the efficacy of adjuvant chemotherapy remained a matter of controversy. However, useful evidence was reported after 2003. The International Adjuvant Lung Cancer Collaborative Group Trial (IALT) [15] demonstrated a 4.1% improvement in survival for patients with stage I to III NSCLC. The JBR.10 trial [16] demonstrated a 15% improvement in the 5-year survival

for the adjuvant chemotherapy arm in stage IB or II patients. The Adjuvant Navelbine International Trialist Association (ANITA) trial [17] reported that the overall survival at 5 years improved by 8.6% in the chemotherapy arm and that this survival rate was maintained at 7 years (8.4%) in stage II and IIIA patients. A meta-analysis based on collected and pooled individual patient data from the 5 largest randomized trials was conducted by the Lung Adjuvant Cisplatin Evaluation (LACE) [18]. This analysis demonstrated that cisplatin-based adjuvant chemotherapy improved survival in patients with stage II or III cancer. Alternatively, uracil-tegafur has been developed and tested in Japan. The Japan Lung Cancer Research Group (JLCRG) [19] on Postsurgical Adjuvant Chemotherapy reported a 5-year overall survival advantage of 11% in the uracil-tegafur (UFT) group patients with stage IB cancer. The benefit of adjuvant chemotherapy for resected stage IB, II, or IIIA NSCLC has been shown based on the results of phase III trials, such as the IALT, JBR.10, ANITA and JLCRG studies. In clinical practice, however, the 5-year survival benefit was only 5% to 10%, and severe adverse reactions were seen in patients receiving cisplatin.

In 2010, the NSCLC Meta-analysis Collaborative Group [20] showed a benefit of adjuvant chemotherapy after surgery by the results that the meta-analysis of surgery plus chemotherapy versus surgery alone was based on 34 trial comparisons and 8447 patients (3323 deaths). NSCLC Meta-analyses Collaborative Group [20] recorded a benefit of adding chemotherapy after surgery (hazard ratio [HR] 0.86, 95%CI 0.81 - 0.92, $p < 0.0001$) with an absolute increase in survival of 4% (95%CI 3 - 6) at 5 years (from 60% to 64%).

There were phase III trials using four cycles of vi- norelbine and cisplatin, namely the JBR.10 [16] and ANITA trials [17]. In the JBR.10 trial, 77% of patients required at least a one-dose reduction [16]. In the ANITA trial, the median percentage of the planned doses of vinorelbine and cisplatin were 56.3% and 76.1%, respectively, because of adverse events [17]. Treatment compliance has thus to date been low in the platinum-based adjuvant chemotherapy in oversea postsurgical resection patients. In the Japanese patients, the UFT trial has only been phase III trial to demonstrate survival benefits for patients whose NSCLCs were completely resected.

It is not clear whether platinum-based chemotherapy is feasible or available in an adjuvant setting for the Japanese population. A four-arm cooperative study (FACS) including the doublet of paclitaxel plus carboplatin, gemcitabine plus cisplatin, vinorelbine plus cisplatin, and irinotecan plus cisplain for Japanese patients with advanced NSCLC has been reported [21]. Based on the above results, the four regimens have similar efficacy and different toxicity profiles, and they can be used to treat advanced NSCLC patients.

The evidence report on the carboplatin plus gemcitabine regimen in Japan was few compared to those of carboplatin plus paclitaxel, almost all being reported from overseas [22,23]. The gemcitabine plus carboplatin regimen was allowed to administer in an outpatients setting due to the short time of drip infusion and mild nonhematological toxicities such as alopecia and gastroenterological symptoms, however, thrombocytopenia should require attention. On the other hand, carboplatin plus paclitaxel was one of the standard treatments based on much evidence reported around the world, and was appropriate to administer in an outpatients setting due to the mild toxicities. However, during the long-term administration, its neuropathy was frequently recognized [24]. For these reasons and the inconvenience of prolonged infusion, weekly administration of paclitaxel was evaluated in various cancer patients, yielding a beneficial activity and reduced toxicity [25].

The above two regimens are frequently selected for inoperable advanced lung cancer in clinical practice. In our adjuvant chemotherapy setting for the resected non-small cell lung cancer, on the grade 3/4 toxicities, the PC regimen showed a higher incidence compared to the GC regimen. Grade 3/4 leukopenia was significantly observed in the PC regimen, and grade 3/4 thrombocytopenia was more frequently seen in the GC regimen compared to those in the PC regimen. Grade 3/4 febrile neutropenia was seen in the GC regimen compared to none in the PC regimen. The nonhematological toxicities were mild. However, grade 4 pneumonia was more frequently observed in the PC regimen compared to none in the GC regimen.

Based on the results of the above-mentioned our clinical outcomes, the toxicities of the GEM + CBDCA and PTX + CBDCA groups for the resected non-small lung cancer were different, however, as adjuvant chemotherapy, both regimens were feasible and safely performed in the postoperative period. The adjuvant GEM + CBDCA and PTX + CBDCA treatments were well tolerated, and there were no chemotherapy-related deaths. Accordingly, the GEM + CBDCA and PTX+CBDCA regimens could be considered as a treatment option for Japanese surgical patients.

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