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Renal Toxicity Caused by Brand-name Versus Generic Cisplatin: A Comparative Analysis

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Objective: A generic cisplatin formulation has replaced the brand-name formulation since November 2003 in our hospital. We retrospectively assessed the renal toxicity caused by the brand-name and generic cisplatin formulations.

Methods: The medical records of patients with thoracic malignancy who were treated at our hospital between November 2000 and April 2008 were reviewed. In total, 1296 eligible patients received 80 mg/m^2 of cisplatin: 499 patients were treated with the brand-name cisplatin formulation before November 2003 (Group 1) and 797 patients were treated with the generic formulation after November 2003 (Group 2). We compared the maximum serum creatinine level after chemotherapy in the two groups.

Results: The patient characteristics, including age, sex and performance status, and pretreatment serum creatinine levels were well balanced between the two groups. More patients received four cycles of chemotherapy in Group 2 ($P < 0.0001$). The median (range) of the maximum serum creatinine levels during all the chemotherapy cycles were 1.1 (0.5–4.1) mg/dl and 1.1 (0.5–4.4) mg/dl in Groups 1 and 2, respectively ($P = 0.0237$). The incidence of grade 0 serum creatinine elevations decreased from 47% to 39%, while that of grade 1 serum creatinine elevations increased from 32% to 41% ($P = 0.0094$). The incidence rates of grade 2 or 3 serum creatinine elevations were similar (21 vs. 20%). The time to serum creatinine elevation was also similar in Groups 1 and 2 ($P = 0.161$).

Conclusion: Although grade 1 maximum serum creatinine level was more common in the generic cisplatin formulation group, this was attributed to the larger number of patients receiving four cycles of chemotherapy in this group.

Key words: cisplatin – generic – brand name – renal toxicity

INTRODUCTION

Cisplatin-based chemotherapy is curative for testicular cancer and is active against gynecologic, gastrointestinal, genitourinary, head and neck, and lung cancers as well as other malignant diseases. Carboplatin has the same range of clinical activity as cisplatin but is less nephrotoxic and less emetogenic. Therefore, carboplatin has essentially replaced cisplatin for the treatment of ovarian cancer, lung cancer and a range of other malignancies (1). In some diseases, such as germ cell tumors (2), head and neck cancer (3), and non-small-cell lung cancer (4,5), however, cisplatin is more effective clinically in terms of the response rate and survival.

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Cisplatin can cause dose-dependent renal toxicity. Large infusion amounts are needed to prevent cisplatin-induced renal toxicity. Patients are usually prehydrated and posthydrated with at least 2 l of IV fluid to maintain good urine flow. Risk factors for cisplatin nephrotoxicity include the dose and frequency of administration and the cumulative dose of cisplatin, older age, female sex, smoking and hypoalbuminemia (6).

Generic drugs are believed to be bioequivalent to brand-name drugs in terms of dosage form, safety, quality, performance and intended use. They are usually sold at substantial discounts from the branded price. The spread of generic drugs relieves the financial burden of patients' and improves the financial affairs of medical insurance providers (7). Recently, a retrospective analysis from the National Cancer Center Hospital (NCCH) in Tokyo, Japan, demonstrated that renal toxicity was more severe in patients treated with a generic cisplatin formulation than in those treated with the brand-name formulation, especially among male patients (8). To validate these findings, we conducted the same analysis in another patient cohort from the NCCH East, since the same generic cisplatin formulation had been introduced at our hospital, replacing the brand-name formulation, in November 2003.

PATIENTS AND METHODS

Patients were retrospectively selected for this study according to the following criteria, which were identical to those used in the previous analysis (8): (i) a histological or cytological diagnosis of thoracic malignancy; (ii) no prior chemotherapy; (iii) chemotherapy with a regimen that included 80 mg/m^2 of cisplatin; and (iv) receiving treatment as an inpatient at the NCCH East between November 2000 and April 2008. During this period the brand-name cisplatin formulation was administered between November 2000 and October 2003, and CISPLATIN for I.V. infusion (MARUKO), a generic cisplatin formulation, was administered thereafter. Patients with an abnormally elevated serum creatinine (CRN) level prior to the initiation of chemotherapy were excluded from this study. Serum CRN was measured using an enzymatic assay throughout the study period. The upper limit of normal for serum CRN was 1.1 mg/dl for men and 0.9 mg/dl for women.

After 750 ml of intravenous infusion fluids, cisplatin (80 mg/m^2) and 300 ml of fluids were intravenously infused over a 60-min period on day 1 in combination with other chemotherapeutic agents, followed by 40 g of mannitol and 1450 ml of hydration. A total of 2500 ml of hydration fluids, which consisted of 1000 ml of normal saline and 1500 ml of hypotonic crystalloid solution (Solita-T3®), were infused at a rate of 300 ml/h. Twenty milligrams of furosemide was intravenously administered at the end of hydration. One thousand milliliters of intravenous infusion fluids were administered on days 2 and 3 and 500 ml was administered on days 4 and 5 at a rate of 300 ml/h. Antiemetic prophylaxis consisted of a 5HT3 antagonist and 16 mg of dexamethasone on day 1, followed by 8 mg of dexamethasone on days 2 and 3 and 4 mg on days 4 and 5. This sequence of administration was consistently maintained during the study period.

The patients' baseline characteristics including age, sex, performance status (PS), pretreatment CRN level (CRN_{pre}), chemotherapy regimen, number of chemotherapy cycles and maximum CRN level (CRN_{max}) during the first cycle and during all chemotherapy cycles were retrospectively obtained from the patients' medical records. The median CRN_{max} and the Common Toxicity Criteria-Adverse Event (CTC-AE version 3.0) grades of the CRN_{max} were compared in patients treated with the brand-name cisplatin formulation (Group 1) and those treated with the generic formulation (Group 2). The time to serum CRN elevation was defined as the interval between the start of chemotherapy and the development of serum CRN elevation grade 1 or worse. Patients who did not develop serum CRN elevation grade 1 or worse were censored at the end of the cisplatin-based chemotherapy. The time to serum CRN elevation was estimated using the Kaplan–Meier analysis method (9) and was compared between groups using a log-rank test. Mann–Whitney tests were used to evaluate continuous variables and χ^2 tests were used for categorical variables. Multivariate analyses were performed using Cox proportional hazards models to determine the risk factors for the time until serum CRN elevation. Group 1 or 2 and the presence of significant risk factors in the univariate analyses were evaluated using a multivariate analysis. All the reported *P* values were two-sided. GraphPad InStat version 3.10 for Windows (GraphPad Software, San Diego, USA) and PASW Statistics 18 for Windows (SPSS Inc., Chicago, USA) were used for the statistical analyses. The present study was approved by an institutional review board.

RESULTS

Out of 1341 patients assessed for eligibility in this study, 1310 patients met the inclusion criteria; 31 patients were subsequently excluded because of an abnormal CRN_{pre} level. An additional 14 patients were excluded because they were treated with the brand-name cisplatin formulation during the first cycle of chemotherapy but received the generic formulation in subsequent cycles. Therefore, a total of 1296 patients were eligible for this analysis. In total, 499 patients were treated with the brand-name cisplatin formulation (Group 1) and 797 patients were treated with the generic formulation (Group 2) (Fig. 1). The patient characteristics are shown in Table 1. The median age was 63 years (range 27–81 years), and the female patients accounted for 23% of all the patients. No statistical differences in sex, age, PS or CRN_{pre} were observed between the two groups. The most common chemotherapy regimen was cisplatin plus vinorelbine; however, this regimen was less frequently used in Group 2, whereas cisplatin plus gemcitabine was more frequently used. The median number of chemotherapy cycles was three in both groups, but more patients received four cycles of chemotherapy in Group 2 (Fig. 2).

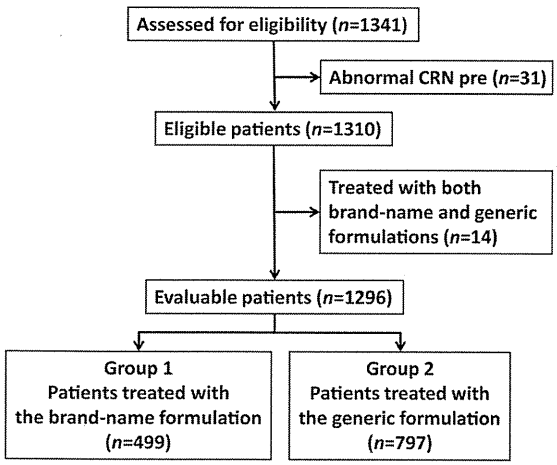

Figure 1. Diagram of the study. CRN_{pre}, pretreatment serum creatinine level.

Table 1. Patient characteristics

	Group 1[a] ($n = 499$), N (%)	Group 2[b] ($n = 797$), N (%)	P value
Sex			
Male	392 (79)	611 (77)	0.4532
Female	107 (21)	186 (23)	
Age (years)			
Median (range)	62 (28–78)	63 (27–81)	0.7368
Performance status			
0–1	486 (97)	788 (99)	0.0744
2–3	13 (3)	9 (1)	
Pretreatment serum creatinine level			
Median (range)	0.7 (0.4–1.1)	0.7 (0.4–1.1)	0.1742
Regimen of chemotherapy			
CDDP + VNR	356 (71)	447 (56)	<0.0001
CDDP + ETP	57 (12)	121 (15)	
CDDP + GEM	36 (7)	149 (19)	
CDDP + others	50 (10)	80 (10)	
Number of cycles			
1	53 (11)	72 (9)	<0.0001
2	187 (37)	184 (23)	
3	136 (27)	241 (30)	
4	114 (23)	294 (37)	
5	3 (1)	1 (0)	
6	6 (1)	5 (1)	
Median (range)	3 (1–6)	3 (1–6)	<0.0001

CDDP, cisplatin; VNR, vinorelbine; GEM, gemcitabine; others included irinotecan, docetaxel, vinorelbine + mitomycin C, paclitaxel and S-1.
[a]Patients treated with the brand-name cisplatin formulation.
[b]Patients treated with a generic cisplatin formulation

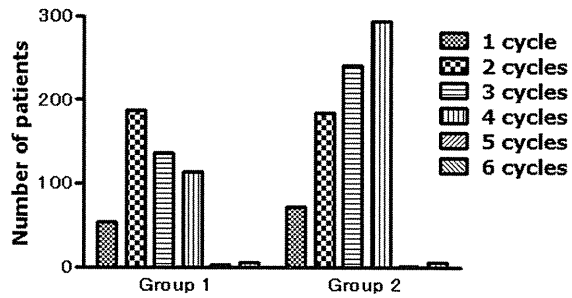

Figure 2. Number of chemotherapy cycles in 499 patients treated with the brand-name cisplatin formulation (Group 1) and 797 patients treated with the generic formulation (Group 2).

The median (range) CRN_{max} levels during the first cycle of chemotherapy were 1.0 (0.5–4.1) mg/dl and 1.0 (0.6–4.2) mg/dl in the male patients in Groups 1 and 2, respectively ($P = 0.0378$), whereas they were 0.7 (0.5–1.8) mg/dl and 0.7 (0.4–1.9) mg/dl in the female patients in Groups 1 and 2, respectively ($P = 0.3949$). The CTC-AE grade for CRN_{max} during the first cycle was not statistically different between Groups 1 and 2 in both male ($P = 0.6732$) and female patients ($P = 0.9518$) (Table 2).

The median (range) CRN_{max} levels during all the chemotherapy cycles were 1.1 (0.5–4.1) mg/dl and 1.1 (0.5–4.4) mg/dl in all the patients in Groups 1 and 2, respectively ($P = 0.0237$). The median (range) CRN_{max} levels during all the cycles of chemotherapy were 1.2 (0.5–4.1) mg/dl and 1.2 (0.6–4.4) mg/dl in the male patients in Groups 1 and 2, respectively ($P = 0.0029$), whereas they were 0.8 (0.5–2.6) mg/dl and 0.9 (0.5–2.2) mg/dl in the female patients in Groups 1 and 2, respectively ($P = 0.3745$). The CTC-AE grade for CRN_{max} during all the cycles was statistically different between Groups 1 and 2 in the male patients ($P = 0.0431$). Grade 0 CRN_{max} decreased from 49% to 42%, whereas grade 1 CRN_{max} increased from 32% to 41% between the male patients in Groups 1 and 2. An identical tendency was observed in the female patients. Grade 0 CRN_{max} decreased from 39% to 31%, whereas grade 1 CRN_{max} increased from 31% to 41% between the female patients in Groups 1 and 2 ($P = 0.1455$). In all the patients, grade 0 CRN_{max} decreased from 47% to 39% and grade 1 CRN_{max} increased from 32% to 41% between Groups 1 and 2 ($P = 0.0094$). Grade 2 or 3 CRN_{max} was not different between Groups 1 and 2 in both the male and female patients (Table 3). The time to serum CRN elevation was not statistically different between Groups 1 and 2 ($P = 0.161$) (Fig. 3). A male sex or an age of 71 years or older was significantly associated with a shorter time to a serum CRN elevation grade 1 or worse in a univariate analysis (Table 4).

A multivariate analysis showed that a female sex [hazard ratio (HR): 1.528, 95% confidence interval (CI): 1.296–1.803] and an age of 71 years or older (HR: 1.362, 95% CI: 1.127–1.645) were significant risk factors for the time to serum CRN elevation. Group 2 was not a significant risk

Table 2. Serum creatinine levels and toxicity grades during the first cycle of chemotherapy

	Group 1[a] ($n = 499$), N (%)	Group 2[b] ($n = 797$), N (%)	P value
Median (range)			
Total	0.9 (0.5–4.1)	0.9 (0.4–4.2)	0.1269
Male	1.0 (0.5–4.1)	1.0 (0.6–4.2)	0.0378
Female	0.7 (0.5–1.8)	0.7 (0.4–1.9)	0.3949
CTC-AE grade			
Total			
0	339 (68)	514 (64)	0.6244
1	123 (24)	218 (27)	
2	34 (7)	61 (8)	
3	3 (1)	4 (1)	
Male			
0	282 (72)	418 (68)	0.6732
1	83 (21)	147 (24)	
2	24 (6)	42 (7)	
3	3 (1)	4 (1)	
Female			
0	57 (53)	96 (52)	0.9518
1	40 (38)	71 (38)	
2	10 (9)	19 (10)	

CTC-AE, Common Toxicity Criteria-Adverse Event Ver. 3.0.
[a]Patients treated with the brand-name formulation.
[b]Patients treated with a generic formulation.

Table 3. Serum creatinine levels and toxicity grades during all cycles of chemotherapy

	Group 1[a] ($n = 499$), N (%)	Group 2[b] ($n = 797$), N (%)	P value
Median (range)			
Total	1.1 (0.5–4.1)	1.1 (0.5–4.4)	0.0237
Male	1.2 (0.5–4.1)	1.2 (0.6–4.4)	0.0029
Female	0.8 (0.5–2.6)	0.9 (0.5–2.2)	0.3745
CTC-AE grade			
Total			
0	236 (47)	314 (39)	0.0094
1	159 (32)	326 (41)	
2	100 (20)	150 (19)	
3	4 (1)	7 (1)	
Male			
0	194 (49)	256 (42)	0.0431
1	126 (32)	249 (41)	
2	69 (18)	100 (16)	
3	3 (1)	6 (1)	
Female			
0	42 (39)	58 (31)	0.1455
1	33 (31)	77 (41)	
2	31 (29)	50 (27)	
3	1 (1)	7 (1)	

[a]Patients treated with the brand-name cisplatin formulation.
[b]Patients treated with a generic cisplatin formulation.

factor for the time to serum CRN elevation (HR: 1.096, 95% CI: 0.943–1.276) (Table 5).

DISCUSSION

A previous retrospective analysis from the NCCH in Tokyo, Japan, demonstrated that a grade 2 or 3 CRN_{max} was observed in 9.4% of the male patients treated with the brand-name cisplatin formulation and 20.9% of the male patients treated with a generic formulation identical to that used in our study during all the chemotherapy cycles ($P < 0.001$) (8). In our study, grade 2 or 3 CRN_{max} was observed in 19 and 17% of the male patients of the two groups, respectively. Three thousand milliliters on day 1 and 2000 ml of intravenous infusion fluids on days 2–5 were administered at the NCCH, with identical antiemetic prophylaxis of a 5HT3 antagonist and dexamethasone and 40 g of mannitol on day 1. However, 2,500 ml of intravenous infusion fluids on day 1, 1000 ml on days 2 and 3, and 500 ml on days 4 and 5 were administered in our hospital. The median age of patients was 60 years in the NCCH study and 63 years in this study. The reason why our study could not confirm a

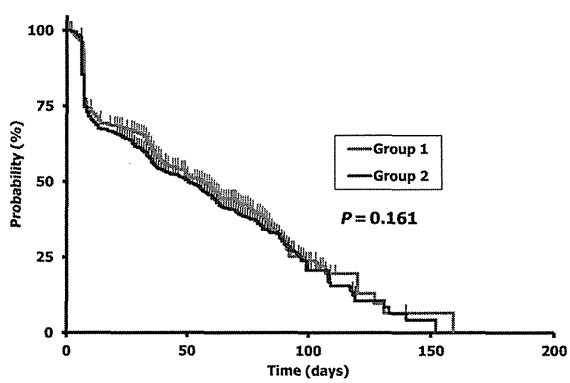

Figure 3. Kaplan–Meier curves for time to serum creatinine elevation. The patients in Group 1 were treated with the brand-name cisplatin formulation, while the patients in Group 2 were treated with the generic formulation. The probability means the percentage of patients who did not develop elevation of the serum creatinine level. Patients who did not develop serum creatinine elevation grade 1 or worse were censored at the end of the cisplatin-based chemotherapy. Therefore, these Kaplan–Meier curves reveal when serum creatinine elevated after the initiation of cisplatin-based chemotherapy.

Table 4. Time to serum creatinine elevation grade 1 or worse (univariate analysis)

	Median time to serum creatinine elevation (days)	95% confidence interval	*P* value
Gender			
Male	60	53.7–66.3	<0.001
Female	29	21.5–36.5	
Age			
≤70 years old	56	49.9–62.1	0.003
≥71 years old	34	19.4–48.6	
Cisplatin group			
Group 1	56	46.1–65.9	0.161
Group 2	50	42.0–58.0	

Patients in Group 1 were treated with the brand-name cisplatin formulation, whereas patients in Group 2 were treated with a generic cisplatin formulation.

Table 5. Multivariate analysis of risk factors associated with time to serum creatinine elevation.

Variable	Hazard ratio	95% confidence interval	*P*-value
Female sex	1.528	1.296–1.803	<0.001
Age ≥71 years old	1.362	1.127–1.645	0.001
Group 2	1.096	0.943–1.276	0.229

Patients in Group 2 were treated with a generic cisplatin formulation.

high frequency of grade 2–3 CRN_{max} in the generic cisplatin formulation group is unknown. Although grade 1 CRN_{max} was more common in the generic cisplatin formulation group, this was attributed to the larger number of patients receiving four cycles of chemotherapy in this group. A multivariate analysis also demonstrated that the generic cisplatin formulation group was not a statistically significant risk factor associated with the time to serum CRN elevation. We concluded that the generic cisplatin formulation did not increase renal toxicity compared with the brand-name cisplatin formulation.

The main objective of using generic drugs, rather than the brand-name drugs, is cost savings (10). Generic drugs are usually approved without clinical trials, although the same high quality, strength, purity and stability as brand-name drugs are required. Our study suggested that the generic cisplatin formulation did not increase renal toxicity, compared with the brand-name formulation. This kind of survey is needed for other generic drugs, especially anticancer drugs that can cause severe or life-threatening toxicities. We believe it is important to confirm the safety of generic drugs. If possible, it is desirable to conduct clinical trials to evaluate the safety and efficacy of generic drugs before approval. However, a large-scale clinical trial needs great cost and is impracticable to conduct.

Magnesium was not included in the hydration fluid. Several randomized trials have demonstrated that the addition of magnesium is effective for reducing cisplatin-induced renal toxicity (11,12). Grade 2–3 CRN_{max} was observed in ~20% of patients, which sounds still high. A four-arm cooperative study in Japan demonstrated that the incidence of grade 2–3 serum CRN elevation was 7–9% in the cisplatin-based chemotherapy group (13). We analyzed consecutive patients who were treated with cisplatin-based chemotherapy; therefore, more patients who had co-morbidity and were ineligible for clinical trials might have been included in this study, resulting in a higher incidence of grade 2–3 serum CRN elevation than those in clinical trials. To reduce cisplatin-induced renal toxicity, we have added magnesium to the hydration fluid administered prior to cisplatin since 2010. We plan to analyze whether preloading with magnesium before chemotherapy can further reduce cisplatin-induced renal toxicity.

Our retrospective analysis has several limitations. First, other risk factors for cisplatin nephrotoxicity, such as smoking status, pretreatment serum albumin level or the co-administration of non-steroidal anti-inflammatory agents, were not investigated. Secondly, aprepitant, which is a standard antiemetic agent nowadays (14), was approved in late 2009 in Japan. None of the patients in our study received aprepitant. The introduction of aprepitant might reduce anorexia induced by cisplatin and might prevent dehydration and renal dysfunction. Thirdly, the frequency of chemotherapy delay, dose reduction or termination of chemotherapy due to renal toxicity was not investigated. This information will be helpful to understand the clinical impact of the renal toxicity.

In conclusion, the incidence of grade 2–3 CRN_{max} was not higher in the generic cisplatin group, although the incidence of grade 1 CRN_{max} was higher. However, more patients in the generic cisplatin formulation group received four cycles of chemotherapy than in the brand-name cisplatin group. The time to serum CRN elevation was not statistically different between the two groups.

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Conflict of interest statement

None declared.

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Clinical Study

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Efficacy and Safety of Platinum Combination Chemotherapy Re-Challenge for Relapsed Patients with Non-Small-Cell Lung Cancer after Postoperative Adjuvant Chemotherapy of Cisplatin plus Vinorelbine

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Key Words

Non-small-cell lung cancer · Adjuvant chemotherapy · Re-challenge · Platinum combination chemotherapy · Recurrence

Abstract

Background: There is no standard therapy for relapsed patients who have received postoperative platinum-based adjuvant chemotherapy for resected non-small-cell lung cancer (NSCLC). We investigated the efficacy and safety of platinum combination chemotherapy re-challenge for such patients. ***Methods:*** Medical records from 3 institutes from April 2005 to July 2012 were retrospectively reviewed. Patients who underwent complete surgical resection were eligible if they received postoperative adjuvant chemotherapy consisting of cisplatin plus vinorelbine once and then re-challenge with platinum combination chemotherapy. ***Results:*** Sixteen patients were enrolled in this study. After re-challenge with platinum combination chemotherapy, we observed an overall response rate of 31.2% (5/16) and a disease control rate of 81.2% (13/16). Median progression-free survival and overall survival from the start of the re-administration of platinum combination chemotherapy were 6.5 and 28.0 months, respectively. Frequently observed severe adverse events (≥grade 3) included neutropenia (31.2%), thrombocytopenia (31.2%), leukopenia (12.5%) and hyponatremia (12.5%). Frequently observed non-hematological toxicities (≥grade 2) were anorexia (37.5%) and nausea (37.5%). ***Conclusion:*** Re-challenge with platinum combination chemotherapy was effective and safe; therefore, this therapy should be considered as a treatment option for relapsed patients after postoperative cisplatin-based adjuvant chemotherapy for resected NSCLC. © 2014 S. Karger AG, Basel

Introduction

Non-small-cell lung cancer (NSCLC) accounts for approximately 80–85% of lung cancer cases, and the 5-year survival rate of lung cancer resection patients

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is reported to be approximately 60%. The postoperative 5-year survival rate of stage II–IIIA NSCLC patients, in particular, is unsatisfactory at 30–60% [1]. The most effective treatment for early-stage (I–IIIA) NSCLC is surgical resection. The efficacy of postoperative adjuvant chemotherapy has been documented since 2004 [2, 3]. A meta-analysis conducted by the Lung Adjuvant Cisplatin Evaluation (LACE) group, combining individual patient data from 4,584 patients from 5 large adjuvant cisplatin (CDDP) chemotherapy trials (ALPI, BLT, IALT, ANITA and JBR.10), was published in 2008 [4]. The LACE analysis confirmed that there was a statistically significant benefit in overall survival (OS) for patients treated with chemotherapy compared with those receiving observation alone (HR, 0.89; 95% CI, 0.82–0.96; p = 0.005), corresponding to an absolute gain of 5.4% at 5 years. The benefits of chemotherapy were confined to patients with resected stage II or III NSCLC. Subgroup analysis of the LACE study indicated that among the various drugs co-administered with CDDP, only vinorelbine (VNR) significantly prolonged survival (p = 0.04). Although the OS advantage at 5 years was 15 percentage points, recurrence was documented in 36.0% of patients treated with CDDP plus VNR [3].

The efficacy of re-administration of cytotoxic anticancer drugs has been reported in patients with small-cell lung cancer who respond to the initial treatment with the same drugs [5]. Recently, it was reported that in NSCLC patients who responded to an initial treatment of gefitinib, the disease could be successfully controlled by re-challenge with gefitinib [6, 7]. However, the efficacy and safety of re-challenge with platinum for relapsed patients receiving postoperative adjuvant chemotherapy of CDDP plus VNR is unknown.

In the present study, we investigated the efficacy and safety of re-challenge with platinum combination chemotherapy for relapsed patients who had received postoperative adjuvant chemotherapy of CDDP plus VNR for resected NSCLC. Re-challenge with platinum-based chemotherapy should be considered a treatment option for relapsed NSCLC patients after postoperative CDDP-based adjuvant chemotherapy.

Methods

Patients

The medical records of surgically resected NSCLC patients treated with adjuvant chemotherapy of CDDP plus VNR at 3 institutes (Shizuoka Cancer Center, Juntendo University Hospital, and National Hospital Organization Nishigunma Hospital) between April 2005 and July 2012 were retrospectively reviewed. Eligible patients were as follows: (1) patients with surgically resected NSCLC who were treated with adjuvant chemotherapy of CDDP plus VNR and (2) patients who relapsed after administration of adjuvant chemotherapy and received re-treatment with platinum combination chemotherapy. In accordance with the fundamental policy at our institutes, the inclusion of patients undergoing adjuvant chemotherapy was based on the following criteria: (1) age less than 75 years, (2) pathological stage II–IIIA and (3) performance status of 0 or 1. Each institute's institutional review board independently approved this study.

Treatment Methods

Postoperative adjuvant chemotherapy was administered as follows: 80 mg/m^2 CDDP on day 1 and 25 mg/m^2 VNR on days 1 and 8. This combination was repeated every 3 weeks, and each 3-week treatment schedule was counted as 1 cycle. Treatment changes such as dose reduction, dose skipping or dose delay were decided by the physician. Treatment choice for re-challenge with platinum-based chemotherapy after recurrence was also decided by the physician.

Response and Toxicity Evaluation

Radiographic tumor response was evaluated according to response evaluation criteria in solid tumors, RECIST, version 1.1. Tumor response was evaluated and classified as follows: complete response (CR), disappearance of all target lesions; partial response (PR), at least a 30% decrease in the sum of diameters of target lesions, with the baseline sum of diameters as the reference; progressive disease (PD), at least a 20% increase in the sum of diameters of target lesions, with the smallest sum during the study as reference (this included the baseline sum if that was the smallest during the study), and stable disease (SD), neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, with the smallest sum of diameters during the study as the reference. Chemotherapy-related toxicities were graded according to the National Cancer Institute Common Terminology Criteria version 4.0 (NCI-CTC v.4.0).

Statistical Analyses

Relapse-free survival (RFS) after surgical resection was clinically evaluated using the Kaplan-Meier method to assess the time to relapse or death. Progression-free survival (PFS) and OS were also evaluated using the Kaplan-Meier method. All p values were reported as two sided, and values less than 0.05 were considered statistically significant. Statistical analyses were performed using GraphPad Prism version 5.0 software for Windows (GraphPad Software, San Diego, Calif., USA).

Results

Patient Characteristics

Postoperative adjuvant chemotherapy of CDDP plus VNR was received by 134 NSCLC patients, of which 47 (35.1%) had relapsed. Of the 47 patients, 16

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Table 1. Patient characteristics at the time of recurrence (n = 16)

Gender	
Male	11 (68.7)
Female	5 (31.3)
Age, years	
Median	63
Range	53–71
Postoperative stage	
IIA	4 (25)
IIB	1 (6.3)
IIIA	11 (68.7)
Clinical stage at the time of recurrence	
IV	16 (100)
Histology	
Adenocarcinoma	15 (93.7)
Squamous cell carcinoma	1 (6.3)
Operation	
Lobectomy	15 (93.7)
Pneumonectomy	1 (6.3)
Performance status	
0	10 (62.5)
1	6 (37.5)
EGFR mutation status	
Mutant	2 (12.5)
Wild type	12 (75.0)
Unknown	2 (12.5)
RFS, days	
Median	635.5
Range	98–2,338
Interval from the last dose of adjuvant chemotherapy to the first dose of chemotherapy at the time of recurrence, days	
Median	583
Range	48–2,282

Values are presented as number with percentage in parentheses, unless otherwise indicated.

Table 2. Compliance with adjuvant chemotherapy of CDDP plus VNR

	Patients, n
Discontinued after cyle 1	1[a]
Completed cycle 3	2
Completed cycle 4	13
Patients who completed more than 3 cycles	15/16 (93.7%)

[a] The reason for discontinuation was prolonged myelosuppression.

Table 3. First-line chemotherapy at the time of recurrence

Chemotherapy regimens	Patients, n
CBDCA + PEM + Bev	5
CBDCA + PEM	3
CDDP + PEM	3
CBDCA + PTX + Bev	2
CDDP + DTX	1
CDDP + GEM	1
CDDP + PEM + VEGFR-TKI	1

CBDCA = Carboplatin; PEM = pemetrexed; PTX = paclitaxel; DTX = docetaxel; GEM = gemcitabine; Bev = bevacizumab; VEGFR-TKI = vascular endothelial growth factor receptor-tyrosine kinase inhibitor.

received platinum combination chemotherapy, 5 received single-agent chemotherapy, 14 received epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs), and 12 received other treatments including best supportive care and radiotherapy alone. EGFR-TKIs were administered to the patients harboring sensitive *EGFR* mutations. In this study, we focused on 16 NSCLC patients using platinum combination chemotherapy.

The characteristics of the patients are shown in table 1. Of the patients, 68.7% were male and the median age was 63 years (range 53–71) at the time of recurrence. At surgery, pathological stages IIA, IIB and IIIA were observed in 25, 6.3 and 68.7% of patients, respectively. From the histological perspective, adenocarcinoma and squamous cell carcinoma were observed in 93.7 and 6.3% of patients, respectively. Lobectomy was performed in 93.7% of patients, and 6.3% underwent a pneumonectomy. The median RFS time was 635.5 days (range 98–2,338). The interval from the last dose of adjuvant chemotherapy to the first dose of chemotherapy at the time of recurrence was 583 days (range 48–2,282).

Compliance with Adjuvant Chemotherapy

Of the 16 patients treated with adjuvant chemotherapy, 15 (93.7%) patients completed more than 3 cycles of CDDP plus VNR (table 2). The reason for discontinuation of chemotherapy was toxicity (prolonged myelosuppression) in 1 patient.

First-Line Chemotherapy at the Time of Recurrence

The first-line chemotherapy regimens after progression to postoperative adjuvant chemotherapy are shown in table 3. The most common first-line chemotherapy administered was carboplatin and pemetrexed plus bevaci-

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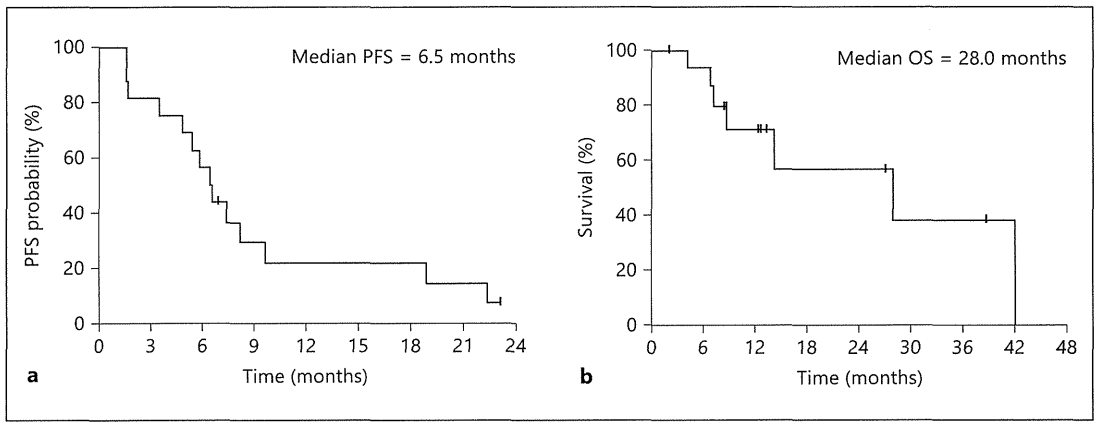

Fig. 1. Kaplan-Meier curve of PFS (**a**) and OS (**b**) from the start of re-administration of platinum combination chemotherapy.

Table 4. Compliance with re-administration of platinum-based chemotherapy

Patients who completed more than 3 cycles	12/16 (75.0)
The reasons for incomplete treatment	
Progression	2/16 (12.5)
Toxicity	2/16 (12.5)
Number of treatment cycles[a]	
Median	4
Range	2–6
Treatment-related death	0 (0)

Values in parentheses are percentages.
[a] Except for maintenance therapy.

Table 5. Patient response to re-administration of platinum-based chemotherapy

CR, n	0
PR, n	5
SD, n	8
PD, n	3
Response rate, %	31.2
Disease control rate[a], %	81.2

[a] CR + PR + SD.

zumab. CDDP- and carboplatin-based combination chemotherapies were administered to 6 and 10 patients, respectively. More than 3 cycles of platinum combination chemotherapy were completed by 12 of 16 patients (75%; table 4). The reasons for discontinuation of chemotherapy were progression in 2 patients (12.5%) and toxicity in 2 patients (12.5%). The two toxicities observed were thromboembolic event and prolonged myelosuppression, respectively. The median number of treatment cycles was 4 cycles (range 2–6). No treatment-related deaths were noted in this study.

Treatment Efficacy and Toxicity

Among the 16 patients, 5, 8 and 3 patients showed PR, SD and PD, respectively (table 5). The response rate was 31.2%, and the disease control rate was 81.2%. Median PFS and OS from the beginning of the next platinum-based combination chemotherapy were 6.5 and 28.0 months, respectively (fig. 1a, b). Patients were divided into 2 groups on the basis of RFS: 5 patients experienced RFS for <12 months, and 11 patients experienced RFS for ≥12 months. Among patients with RFS <12 months, 3 patients had PR and 2 had SD. Among patients with RFS ≥12 months, 2 patients had PR, 6 had SD and 3 had PD. Median PFS was 5.8 months for patients with RFS <12 months, and 8.2 months for those with RFS ≥12 months (log-rank p = 0.19; fig. 2a). Furthermore, the median OS was 14.3 months for patients with RFS <12 months, and 42.0 months for those with RFS ≥12 months (log-rank p = 0.12; fig. 2b).

The incidence of toxicity upon re-challenge with platinum combination chemotherapy after recurrence is shown in table 6a and b. We observed neutropenia in 31.2% of patients (grade 3/4 toxicity), leukopenia in 12.5%, anemia in 6.2% and thrombocytopenia in 31.2%. Febrile neutropenia was not observed. Frequently observed non-hematological toxicities were grade 2 or

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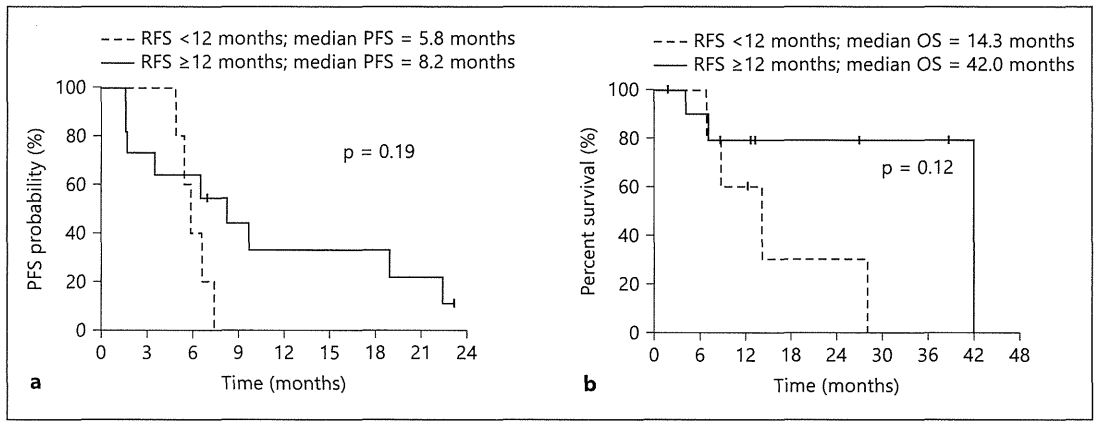

Fig. 2. Kaplan-Meier curve of PFS (**a**) and OS (**b**) from the start of re-administration of platinum combination chemotherapy depending on RFS duration.

greater severe anorexia (37.5%) and nausea (37.5%). Non-hematological toxicities were grade 3 or greater severe hyponatremia (12.5%) and arthralgia (6.2%). No grade 5 hematological or non-hematological toxicities were observed.

Discussion

To our knowledge, this is the first study to evaluate the efficacy and safety of re-challenging NSCLC patients with platinum combination chemotherapy after surgery and postoperative platinum-based adjuvant chemotherapy. We found that platinum combination chemotherapy retreatment was effective and safe; therefore, this therapy should be considered as a treatment option for NSCLC patients who have relapsed after postoperative CDDP-based adjuvant chemotherapy.

Although non-platinum-containing chemotherapy regimens are used as alternatives, combinations of platinum and other anticancer agents, such as carboplatin plus paclitaxel, CDDP plus gemcitabine, CDDP plus pemetrexed, and carboplatin and paclitaxel plus bevacizumab, are considered standard first-line chemotherapy regimens for advanced NSCLC worldwide [8–10]. Since no standard chemotherapy is provided after postoperative adjuvant chemotherapy, we consider that platinum combination chemotherapy is a treatment option for patients who have relapsed after postoperative first-line platinum-based adjuvant chemotherapy. Indeed, various platinum-based chemotherapy regimens are used in practice (table 3).

Table 6. Incidence of toxicity upon re-challenge with platinum combination chemotherapy after recurrence

a Hematologic adverse events

	Gr1	Gr2	Gr3	Gr4	≥Gr3, %
Leukopenia	5	3	2	0	12.5
Neutropenia	1	4	4	1	31.2
Anemia	1	2	1	0	6.2
Thrombocytopenia	2	3	4	1	31.2

b Non-hematologic adverse events

	Gr1	Gr2	Gr3	Gr4	≥Gr3, %
Fatigue	7	1	0	–	
Anorexia	4	6	0	0	
Nausea	5	6	0	–	
AST increased	1	0	0	0	
ALT increased	3	0	0	0	
Creatinine increased	2	1	0	0	
Hyponatremia	0	–	2	0	12.5
Febrile neutropenia	–	–	0	0	
Sensory neuropathy	2	1	0	0	
Epistaxis	3	0	0	0	
Thromboembolic event	0	2	0	0	
Arthralgia	0	0	1	–	6.2
Hypertension	0	1	0	0	

CTCAE version 4.0. ALT = Alanine aminotransferase; AST = aspartate aminotransferase.

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The response rate and disease control rate in the present study were identical to those for first-line chemotherapy for NSCLC. Ohe et al. [11] reported that the response rates in a Japanese large phase III trial for advanced NSCLC were 31.0% for CDDP plus irinotecan, 32.4% for carboplatin plus paclitaxel, 30.1% for CDDP plus gemcitabine, and 33.1% for CDDP plus VNR. Although the number of patients in our study was small, this study was comparable to the first-line setting for metastatic NSCLC. In addition, the present study analyzed PFS and OS for patients re-treated with platinum combination chemotherapy. We found that the median PFS and OS from the start of the second platinum-based combination chemotherapy were 6.5 months and 28.0 months, respectively. The PFS in the present study was identical to that in a previous study. For example, median time to progression and OS were, respectively, 4.7 and 13.9 months for CDDP plus irinotecan, 4.5 and 12.3 months for carboplatin plus paclitaxel, 4.0 and 14.0 months for CDDP plus gemcitabine, and 4.1 and 11.4 months for CDDP plus VNR [11]. The OS is relatively greater in the present study than in that reported by Ohe et al. [11], and the difference in patient type may explain the improved OS observed in our study. OS for postoperative relapsed patients is better than OS for relapsed patients with non-operated advanced NSCLC [12].

To substantiate possible differences in the efficacy of re-challenge in patients who relapsed within a short duration (RFS <12 months) and long duration (RFS ≥12 months) after postoperative adjuvant chemotherapy, we also evaluated these subgroups separately. There was no significant difference between these 2 groups for PFS and OS (fig. 2a, b). Median OS was 14.3 months for patients with RFS <12 months, and 42.0 months for those with RFS ≥12 months. Although there was no significant difference between these 2 groups in OS, patients who relapsed after a longer duration following postoperative adjuvant chemotherapy tended to have a good prognosis. We also analyzed patients by separating them into groups by RFS <6 months and RFS ≥6 months; however, only 2 patients had RFS <6 months. Therefore, these groups were excluded from further statistical analysis.

The toxicity induced by platinum combination chemotherapy re-challenge was in the range of the published platinum combination chemotherapy data in a first-line setting [9–11]. In a subset of approximately 12.5% of patients, treatment was terminated because of toxicity. The discontinuation rates were comparable to those in the first-line setting, and cumulative toxicity of platinum might have been absent. In particular, toxicities such as hearing impairment, neurotoxicity, renal dysfunction and allergic reactions caused by repeated use of platinum combination chemotherapy re-challenge were not notable.

This study has several limitations. First, it was a retrospective analysis and the toxicities may have been underestimated. Reducing, skipping or delaying the planned chemotherapy was based on the attending physician's bias. Therefore, to minimize biases, all consecutive patients treated within our institutes were included in the analyses and the patients' original charts were thoroughly reviewed. Second, the sample size was small. Although we should have been able to compare the platinum combination chemotherapy group with a single-agent chemotherapy group as a control, we were unable to do this because of lack of a single-agent group (only 5 patients received single-agent chemotherapy). Although erlotinib and docetaxel show similar efficacy for second-line treatment, *EGFR* mutation might help to predict outcome of erlotinib treatment [13]. Because OS is significantly longer among the *EGFR*-mutant patients treated with EGFR-TKIs [14], we cannot compare the platinum combination chemotherapy group with the EGFR-TKIs group as a control. Nonetheless, we consider that the results of the present investigation are worthwhile because cases of platinum combination chemotherapy re-challenge after recurrence for patients who received postoperative platinum-based adjuvant chemotherapy are not frequent. Thus, the results of our investigation might contribute to a better understanding of the clinical benefit of platinum combination chemotherapy re-challenge after recurrence.

Re-challenge with platinum-based chemotherapy should be considered a treatment option for relapsed NSCLC patients after postoperative CDDP-based adjuvant chemotherapy. Considering that the present study was retrospective and consisted of a relatively small number of patients, prospective studies in a large number of patients are warranted to assess the effect of platinum combination chemotherapy re-challenge.

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特集　呼吸器悪性腫瘍の集学的治療

非小細胞肺癌に対する術後補助化学療法*

鈗持広知**

Key Words : adjuvant chemotherapy, non-small cell lung cancer, surgery, cisplatin

はじめに

切除可能な肺癌における，周術期の治療については多くの検討が行われてきた．術後の放射線療法に関してのメタアナリシスでは，生存期間を有意に短縮することが報告されており，現時点で推奨されるエビデンスはない[1]．また，2004年以降，非小細胞肺癌に対する術後補助化学療法の有用性が報告されるようになった．本稿では，日本肺癌学会から出されている2012年版肺癌診療ガイドラインの記載とともに，術後補助療法における現在のエビデンスを述べる．

術後シスプラチン併用療法

肺癌診療ガイドラインには，「病理病期II期，IIIA期完全切除例に対して，シスプラチンの投与が可能であれば術後にシスプラチン併用化学療法を行うよう勧められる．(グレードB)」と記載されている．

完全切除されたI～III期の非小細胞肺癌患者1,867人を対象に，シスプラチンを含む併用化学療法を行う群と手術単独群を比較した試験(International Adjuvant Lung Cancer Trial；IALT)では，生存期間中央値，5年生存割合はそれぞれ，化学療法群50.8か月，44.5%，手術単独群44.4か月，40.4%であり，術後化学療法群の生存期間がわずかではあったが有意に延長していた〔ハザード比(HR) 0.86(95%CI 0.76～0.98)，$P<0.03$〕[2]．また，完全切除されたIB～II期の非小細胞肺癌患者482人を対象に，シスプラチン＋ビノレルビン併用化学療法を4コース行う群と手術単独群を比較する第III相試験(JBR. 10)では，生存期間中央値，5年生存割合は術後化学療法群で94か月，69%，手術単独群で73か月，54%で，シスプラチン＋ビノレルビンの術後化学療法により生存期間の有意な延長が認められた〔HR 0.69(95%CI 0.52～0.91)，$P=0.04$〕(図1)．しかし，サブグループ解析ではII期では有意な生存期間の延長効果が認められたものの，IB期では認められなかった[3]．さらに，完全切除されたIB～IIIA期の非小細胞肺癌患者840人を対象に，シスプラチン＋ビノレルビン併用化学療法を4コース行う群と手術単独群を比較した試験(Adjuvant Navelbine® International Trialist Association；ANITA)でも，生存期間中央値，5年生存率はシスプラチン＋ビノレルビン群65.8か月，51.2%，手術単独群43.7か月，42.6%で有意な改善が認められた〔HR 0.80(95%CI 0.66～0.96)，$P=0.017$〕．しかし，サブグループ解析ではJBR. 10と同様，IB期における生存期間の延長効果は認められなかった[4]．

シスプラチンベースの術後化学療法の比較試験に登録された4,584例のメタアナリシス(Lung

* Adjuvant chemotherapy for non-small cell lung cancer.

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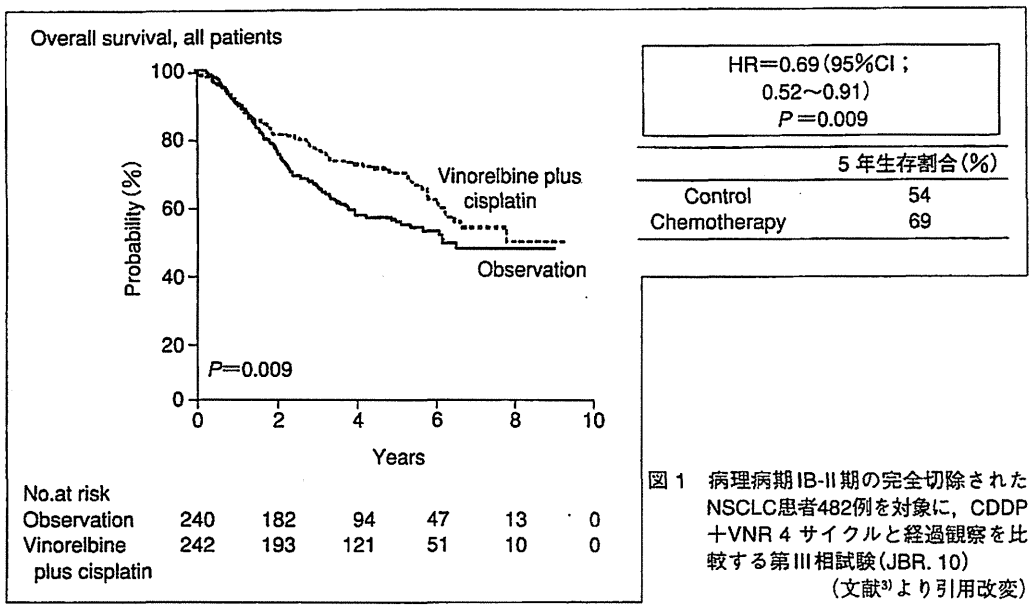

図1　病理病期IB-II期の完全切除されたNSCLC患者482例を対象に，CDDP＋VNR 4サイクルと経過観察を比較する第III相試験(JBR. 10)
(文献[3]より引用改変)

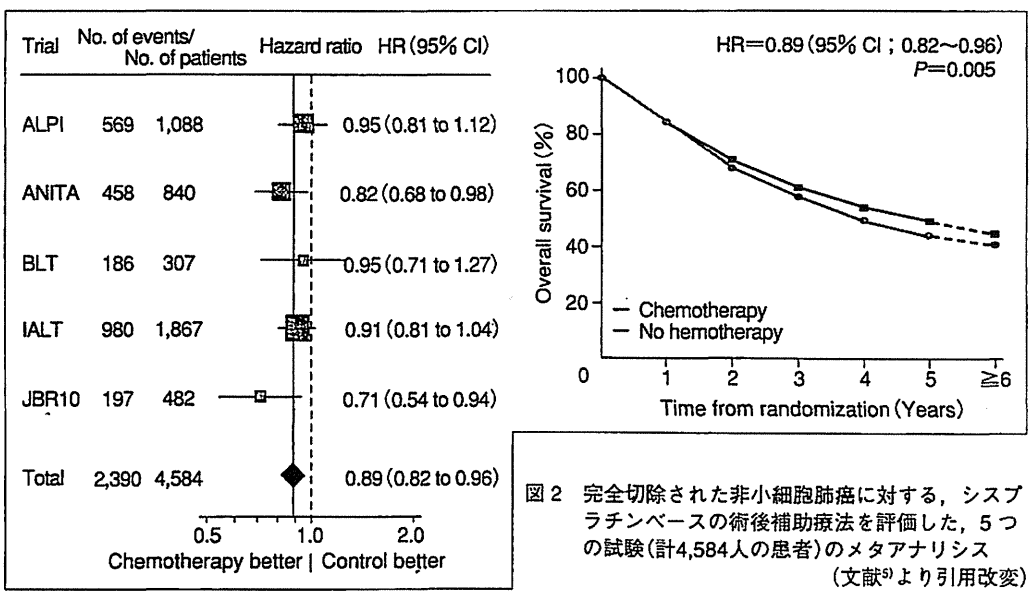

図2　完全切除された非小細胞肺癌に対する，シスプラチンベースの術後補助療法を評価した，5つの試験(計4,584人の患者)のメタアナリシス
(文献[5]より引用改変)

Adjuvant Cisplatin Evaluation；LACE)では，全体での死亡に対するHRは0.89 (95%CI 0.82～0.96)であり，シスプラチン併用化学療法により生存期間が有意に延長することが示された(P=0.005)(図2)．シスプラチンに併用する薬剤としては，ビノレルビンのみが有意な延命効果を示した．病期別にみると，II期およびIII期では術後化学療法により生存期間は有意に改善したが，IB期では改善する傾向のみ，IA期では逆に悪化する傾向が認められた[5]．

これまでの比較試験，メタアナリシスの結果から，病理病期II～IIIAに対してはシスプラチンを含む術後補助化学療法の有効性が示されており，シスプラチンベースの化学療法が標準治療である．使用するレジメンに関しては，LACEの結果も合わせて考えると，現在のところビノレ

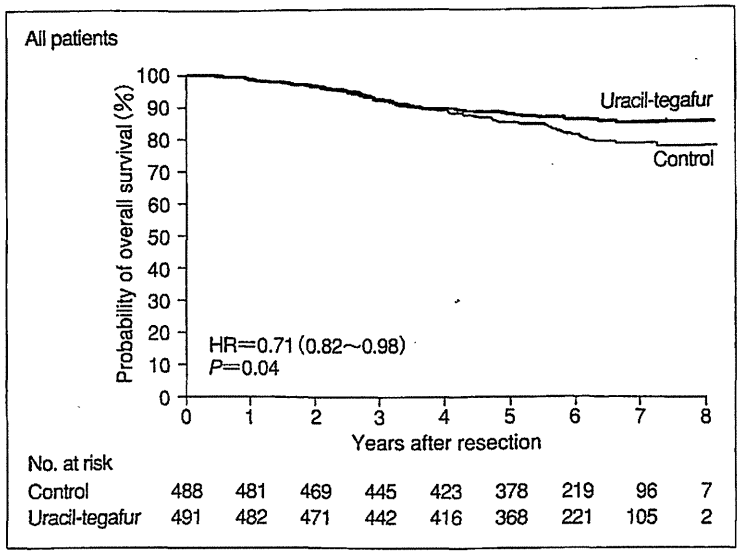

図3　病理病期Ⅰ期の完全切除された肺腺癌に対するウラシル・テガフール配合剤と経過観察を比較するランダム化試験　（文献[9]より引用改変）

ルビン＋シスプラチンのエビデンスレベルが最も高いと考えられる．

ACCP(American College of Chest Physician)やESMO(European Society of Medical Oncology)のガイドラインでも，完全切除された病理病期Ⅱ～Ⅲ期の非小細胞肺癌で，PSの良好な患者に対してはプラチナ製剤を含む術後補助化学療法が推奨されている(IA)[6)～8)]．上記のデータがすべて国外のデータであることなどから，肺癌診療ガイドライン2012年版では，推奨グレードBとなっている．日本人のデータを発信することで，本邦でのプラチナ製剤を含む術後補助化学療法の位置づけが確立することが望まれる．

術後テガフール・ウラシル配合剤(UFT®)療法

肺癌診療ガイドラインには，「腫瘍径2 cmを超える術後病期IA期および術後病期IB期非小細胞肺癌に対して，テガフール・ウラシル配合剤療法を行うよう勧められる．(グレードB)」と記載されている．

病理病期Ⅰ期の完全切除された肺腺癌患者999人を対象に，ウラシル・テガフール配合剤(UFT®)250 mg/日を2年間内服する群と，経過観察群を比較する試験が行われた．UFT®を内服した群で，生存期間の有意な改善を認めた〔HR 0.71(95% CI 0.52～0.98)，P=0.04〕(図3)．また，サブグループ解析において，T2(TNM分類)の患者でHR 0.48〔(95% CI 0.29～0.81)，P=0.005〕と良好な結果であったのに対し，T1の患者ではHR 0.97〔(95% CI 0.64～1.46)，P=0.87〕であり，有用性は認められなかった[9)]．さらには，術後化学療法としてUFT®と無治療を比較した6つの試験のメタアナリシスでも，UFT®の有用性が示された〔HR 0.74(95% CI 0.61～0.88)〕[10)]．これらの結果から，UFT®は病理病期IB期の完全切除された肺腺癌の，術後補助化学療法の標準治療と考えられる．

さらには，病理病期Ⅰ期(腫瘍径＞2 cm)の非小細胞肺癌(NSCLC)を対象に，UFT®とテガフール・ギメラシル・オテラシルカリウム配合剤(S-1)の有効性を比較する第Ⅲ相試験が現在進行中である．

術後プラチナ併用療法

肺癌診療ガイドラインには，「非小細胞肺癌の術後病期IB期で腫瘍径4 cm以上(T2aN0M0の一部)やⅡA(T2bN0M0)，ⅡB〔T3(＞7c)N0M0〕期のものは，プラチナ併用療法を行うことを考慮しても良い．(グレードC1)」と記載されている．

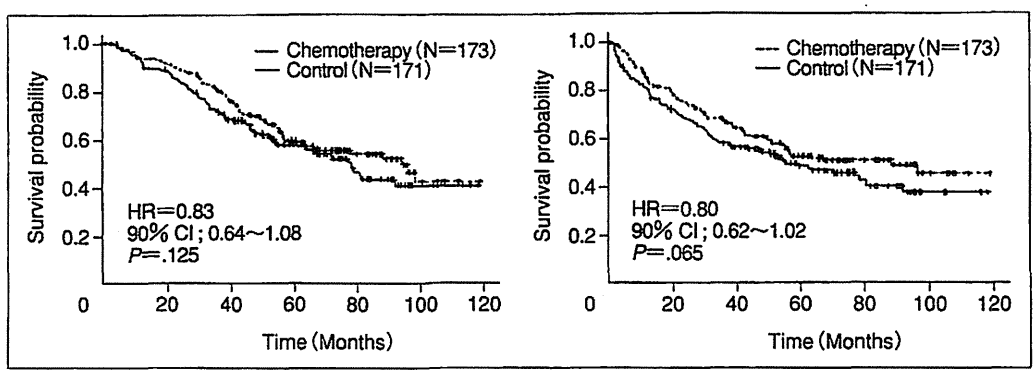

図4　病理病期IB期の完全切除された非小細胞肺癌に対するCBDCA＋PTX併用療法と経過観察を比較するランダム化試験(CALGGB9633)　(文献[11]より引用改変)

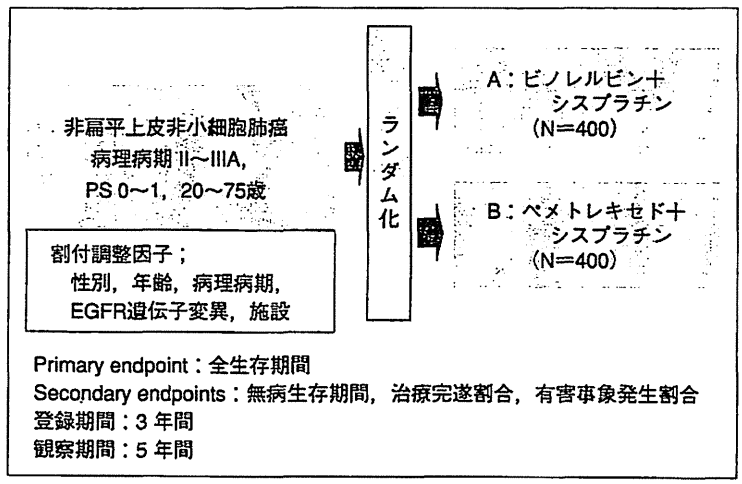

図5　完全切除非扁平上皮非小細胞肺癌に対するペメトレキセド＋シスプラチン併用療法とビノレルビン＋シスプラチン併用療法のランダム化比較第III相試験

1．カルボプラチン＋パクリタキセル併用療法

病理病期IB期の完全切除された非小細胞肺癌患者344人を対象に，カルボプラチン＋パクリタキセル併用療法と経過観察のランダム化比較試験(CALGB9633)が行われたが，生存期間の延長効果は認められなかった〔HR 0.83(95%CI 0.64～1.08)，P=0.12〕(図4)[11]．このため，現時点ではカルボプラチンを含む併用療法で有効性は示されていない．

2．ペメトレキセド＋シスプラチン併用療法

進行非扁平上皮非小細胞肺癌では，ペメトレキセドの有用性が報告されている．また，完全切除された非小細胞肺癌患者132人を対象とした，ペメトレキセド＋シスプラチンとビノレルビン＋シスプラチンのランダム化第II相試験が行われ，グレード3/4の血液毒性の頻度はペメトレキセド＋シスプラチン群で低く，忍容性が高い結果であった[12]．しかし，本邦におけるペメトレキセドの適応症は「切除不能な進行・再発の非小細胞肺癌」であり，術後補助化学療法としての適応はなく，日常臨床で術後補助化学療法としてペメトレキセドを使用することは難しい．

このため，日本の7つの臨床試験グループによる，高度医療評価制度を利用した，「完全切除非扁平上皮非小細胞肺癌に対するペメトレキセド＋シスプラチン併用療法とビノレルビン＋シ

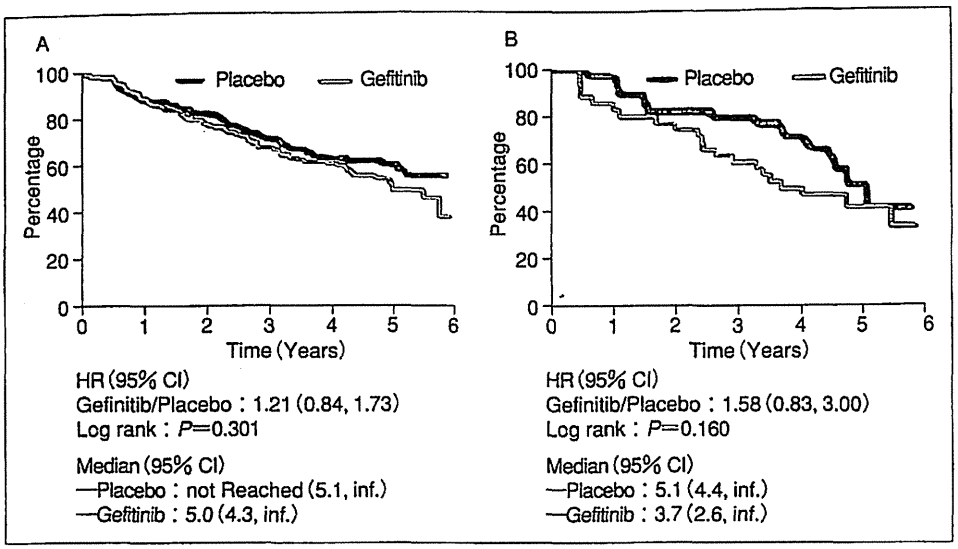

図 6 Overall survival by *EGFR* mutation status and treatment
A：Wild tipe, B：Sensitizing mutation（文献[15]より引用改変）

スプラチン併用療法のランダム化比較第III相試験（JIPANG）」が現在行われている（図 5）．本試験はペメトレキセドの適応拡大につなげることを目的とするとともに，進行癌で有効な薬剤が術後補助化学療法でも有効かを検証することが目的である．術後補助化学療法においては，研究者主導で適応外の薬剤を利用した臨床試験が今後増えることが予想される．

術後に対する分子標的薬

肺癌診療ガイドラインには，「術後に対するEGFR-TKIによる治療は行うように勧めるだけの根拠が明確でない．（グレードC2）」と記載されている．

1．EGFRチロシンキナーゼ阻害剤

EGFR遺伝子変異陽性の非小細胞肺癌に対する，EGFRチロシンキナーゼ阻害剤（EGFR-TKI）の有用性はすでに報告されている．EGFR遺伝子変異陽性非小細胞肺癌の術後補助化学療法におけるEGFR-TKIの有用性については，現在検討されており，日常臨床で使用することは推奨されない．

今までには，病理病期 IB～IIIA期の非小細胞肺癌（EGFR遺伝子変異は問わない）を対象に，ゲフィチニブ 250 mg/日を 2 年間内服する群と，プラセボ群を比較する第III相試験が行われた（BR.19試験）．しかし，503人が登録された時点で試験は中止となり，両群で全生存期間に有意差はなく，HR 1.23（95％CI 0.94～1.64, P=0.136）と生存曲線はプラセボ群がわずかに上に行く結果となった．EGFR遺伝子変異によるサブグループ解析では，EGFR遺伝子変異陽性（n=76）であっても，HR 1.58（95％CI 0.83～3.00, P=0.160）とプラセボ群で良好な傾向にあった（図 6）．一方で，EGFR遺伝子変異陽性の病理病期IA期～IIIA期非小細胞肺癌に対して，エルロチニブ 150 mg/日を 2 年間内服する，単アームの第II相試験の結果が報告された．2 年の無病生存期間割合が94％（95％CI 79.5～98.5）と良好な成績が報告された[13]．しかし，観察期間が短い第II相試験であり，慎重な解釈が必要である．

EGFR遺伝子変異陽性非小細胞肺癌に対する，EGFR-TKIの効果に関しては，現時点では進行癌と同様の効果は得られていない．現在，西日本がん研究機構（WJOG）では，多施設共同医師主導治験で，「非小細胞肺癌完全切除後 II～III期のEGFR変異陽性例に対するシスプラチン＋ビノレルビン併用療法を対照としたゲフィチニブの術後補助化学療法のランダム化比較第III相試験（IMPACT）」が現在進行中であり，この結果で術後補助化学療法におけるEGFR-TKIの有用性が明

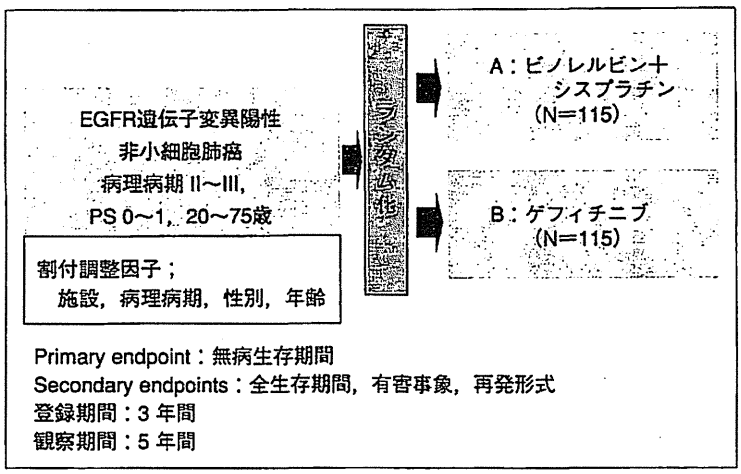

図7　非小細胞肺癌完全切除後 II～III 期のEGFR変異陽性例に対するシスプラチン＋ビノレルビン併用療法を対照としたゲフィチニブの術後補助化学療法のランダム化比較第III相試験

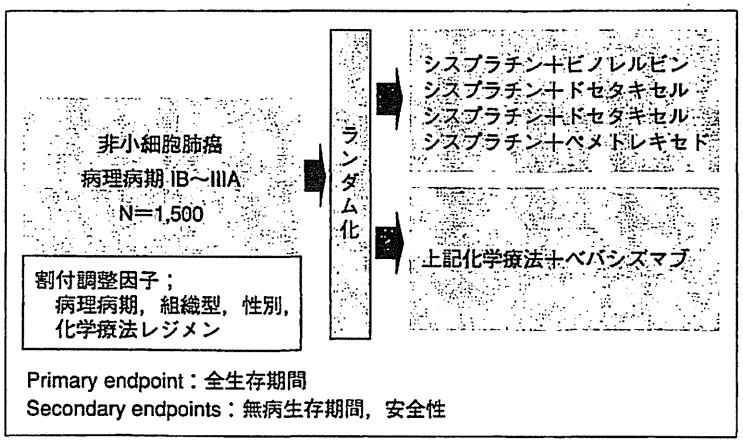

図8　完全切除非小細胞肺癌に対する術後補助化学療法＋ベバシズマブのランダム化比較第III相試験

らかになることが期待される(図7)．さらには，分子標的薬が今後肺癌の術後補助化学療法で積極的に評価されるかを見極める上で，重要な試験と考える．

2．ベバシズマブ

ベバシズマスブは，血管内皮成長因子(VEGF)に対するモノクローナル抗体であり，進行非扁平上皮非小細胞肺癌に対する有効性がすでに報告されている．病理病期IB～IIIA期のNSCLCを対象に，シスプラチンベースの化学療法(4サイクル)と，シスプラチンベースの化学療法(4サイクル)＋ベバシズマブ(1年)の大規模な比較試験(予定登録数1,500人)が現在進行中であり，結果が期待される(図8)[14]．

おわりに

非小細胞肺癌の術後補助化学療法は，2012年版の肺癌診療ガイドラインにおいて推奨グレードAとして推奨される治療法はなく，本邦からのデータが必要とされている．近年の分子標的治療薬の開発により，進行または再発非小細胞肺癌の治療は進歩を認めている．しかし，多くの薬剤が進行または再発非小細胞肺癌で適応となっているため，術後補助化学療法の開発には，

医師主導治験や高度医療評価制度を利用した研究者主導での臨床試験が必要になる．今後も術後補助化学療法の発展には，研究者の尽力が不可欠である．

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