Table V. Previous phase II-III studies of platinum doublet and COX-2 inhibitor in NSCLC.

Design	Author (year)	No. of patients	COX-2 inhibitor	Chemotherapy	Response rate (%)	Median PFS (months)	Median OS (months)	(Refs.)
Phase II	Edelman *et al* (2008)	45	Celecoxib	CBDCA+GEM	NA	4.3[a]	11.8	(23)
	Wang *et al* (2008)	44	Celecoxib	CDDP+GEM CDDP+VNR CDDP+DOC	45.0	6.0	18.0	(24)
	Suzuki *et al* (2009)	44	Meloxicam	CBDCA+PTX	43.0	5.4[b]	15.9	(35)
	This study	50	Meloxicam	CBDCA+DOC	36.0	5.7[b]	13.7	
Phase III	Groen *et al* (2011)	281	Celecoxib	CBDCA+DOC	38.0	4.5	8.2	(21)
		280	Placebo		30.0	4.0	8.2	
	HR					0.8	0.9	
	95% CI					0.6-1.1	0.6-1.2	
	P-value					0.25	0.32	
	Koch *et al* (2011)	158	Celecoxib	3rd generation	36.0	6.1	8.9	(22)
		158	Placebo	Drug + platinum	31.0	6.5	7.9	
	HR					1.01	1.0	
	95% CI					0.77-1.33	0.79-1.26	
	P-value					0.94	0.97	

[a]Failure-free survival. [b]Time-to-progression. COX-2, cyclooxygenase-2; NSCLC, non-small-cell lung cancer; PFS, progression-free survival; OS, overall survival; CBDCA, carboplatin; GEM, gemcitabine; NA, not available; CDDP, cisplatin; VNR, vinorelbine; DOC, docetaxel; PTX, paclitaxel; HR, hazard ratio to placebo; CI, confidence interval.

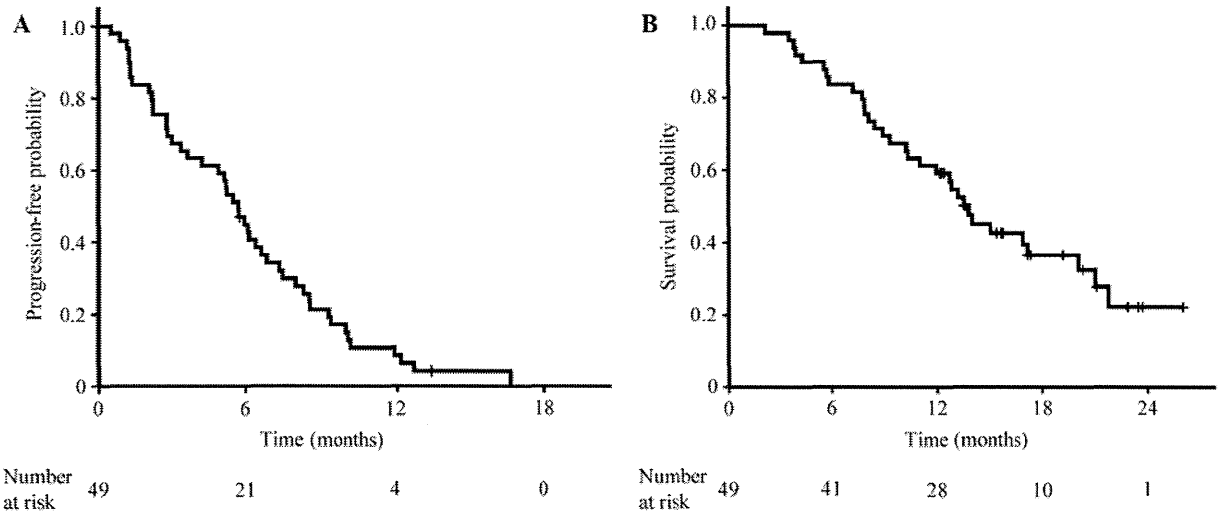

Figure 3. Survival outcomes after treatment. Kaplan-Meier estimates of (A) time-to-progression and (B) overall survival. Vertical bars, censored cases at the data cut-off point.

overall treatment efficacy was favorable, but was not enhanced by COX-2 inhibitors in terms of tumor response (36.0%), OS (13.7 months) and 1-year survival ratio (56.0%). Previous phase II-III trials of docetaxel and carboplatin without COX-2 inhibitors for advanced NSCLC demonstrated that the ORR, OS and 1-year survival rate were 16.0-55.0%, 9.0-13.9 months and 44.0-58.0%, respectively (15,18-20). The incidence of adverse events, such as grade 3/4 neutropenia (80.0%) and febrile neutropenia (8.0%), was similar to those previously reported (51.1-79.0 and 3.3-26.0%, respectively). The frequencies of grade 3/4 myopathy (2.0%) and arthralgia (0.0%) were comparable to or lower compared to those reported by several phase II trials using carboplatin plus docetaxel without a COX-2 inhibitor (3.0-4.0 and 3.0%, respectively) (15,18).

Two recent phase III trials (Table V) (21,22) that used a design identical or similar to that of our study, failed to demonstrate any survival benefit with the addition of a COX-2 inhibitor to chemotherapy in patients with advanced NSCLC. Groen *et al* (21) demonstrated no statistical difference regarding survival between NSCLC patients with tumors

positive and those with tumors negative for COX-2 expression, as determined by IHC.

To elucidate whether COX-2 inhibitors are beneficial for NSCLC patients, we must consider several aspects of COX-2-based strategy based on previous studies (Table V) and reports.

First, there have been no prospective phase III trials with the design of a COX-2 inhibitor or placebo used only in COX-2-positive patients with NSCLC. Groen *et al* (21) investigated the association between COX-2 positivity and progression-free survival (PFS) and OS as a subgroup analysis. A phase II trial (23) demonstrated that prospectively defined subset analysis indicated a survival advantage with a COX-2 inhibitor and chemotherapy in patients with moderate-to-high COX-2 expression. Another group conducted a phase II trial using COX-2 inhibitors combined with platinum-based chemotherapy in 44 previously untreated patients with COX-2-positive advanced NSCLC confirmed by IHC; that study reported promising results, with a median PFS and OS of 6 and 18 months, respectively (24).

Another reason supporting that we should focus on only COX-2-positive patients is the possibility of negative pharmacological effects of COX-2 inhibitors on patients with COX-2-negative tumors. Our results and those of a previous phase II trial (23) suggested that patients who do not express COX-2 may exhibit worse outcomes when treated with COX-2 inhibitors. The inhibition of COX-2 reportedly results in an imbalance between anti- and prothrombotic factors, with a predominance of thromboxane (TX)A_2 at the expense of prostacyclin, which may trigger a series of cardiovascular complications (25). TXA_2-TXA_2 receptor signaling facilitates tumor colonization through interaction of tumor cells with platelets and endothelial cells in the tumor microenvironment (26). TXA_2 is also known to promote tumor metastasis (27). Therefore, it is hypothesized that, by inhibiting COX-2, the COX-1 pathway may become dominant in normal cells, thereby assisting tumor growth in COX-2-negative cells. Other investigators reported that celecoxib treatment induced epithelial-to-mesenchymal transition, which promoted cell invasion and rendered cells resistant to chemotherapy (28). These negative effects may obscure the positive effects in COX-2-expressing patients.

Second, we have not fully pursued the subpopulation benefits for a COX-2 inhibitor on both the clinical and molecular basis. Kozak *et al* (29) found that markedly elevated urinary levels of the major PGE_2 metabolite, which is a downstream signaling molecule of COX-2, were observed in patients with digital clubbing. Patients with high urinary levels of PGE_2 may benefit from COX-2 inhibitors. Another group demonstrated that low pretreatment plasma levels of vascular endothelial growth factor are predictive of a positive effect of celecoxib on survival (30).

The molecular analysis-based selection of therapeutic agents for patients with advanced lung cancer is associated with significant benefits. The identification of epidermal growth factor receptor gene mutations (31) and the anaplastic lymphoma kinase fusion gene (32) contributed to predicting susceptibility to drugs such as gefitinib/erlotinib or crizotinib. The examination of the genetic background of a tumor may be crucial for identifying patients who may benefit from COX-2 inhibitors. Although the genes of the COX pathway are rarely mutated in cancer cells (33), epigenetic alterations, such as DNA methylation, are recurrent events associated with longer recurrence times and improved OS in gastric cancer patients (34). Further investigation is required to determine the association of the genetic and epigenetic deregulation of the COX pathway with clinical outcome in lung cancer.

As shown in Table V, the OS in Asian patients with NSCLC appears to be longer compared to that in non-Asian patients (21-24,35). Pharmacoethnic differences in the response of cancer patients to certain drugs was recently reported (36). However, the diversity of the metabolic action of COX-2 inhibitors among different ethnicities has yet to be elucidated. Thus, identifying such differences may help achieve a better understanding of the molecular mechanism(s) underlying the response to COX-2 inhibitors.

In conclusion, although administered to only 'unselected' patients in a randomized phase III trial that yielded negative results, COX-2 inhibitors may be worth further consideration for the treatment of NSCLC patients.

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Original article

Phase II study of amrubicin combined with carboplatin for refractory relapsed small-cell lung cancer: North Japan Lung Cancer Group Trial 0802

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ABSTRACT

Background: Amrubicin (AMR), a new anthracycline agent, has shown promising results for advanced small-cell lung cancer (SCLC), although the efficacy of AMR alone against refractory relapsed SCLC is insufficient. This study was conducted to evaluate the safety and efficacy of the combination of AMR and carboplatin (CBDCA) in patients with refractory relapsed SCLC.

Methods: Patients with advanced SCLC who relapsed within 90 days after the completion of first-line chemotherapy received AMR (30 mg/m^2, days 1–3) and CBDCA (area under the curve 4.0 mg mL^{-1} min^{-1}, day 1) every 3 weeks. The primary endpoint of this study was the overall response rate (ORR), and the secondary endpoints were progression-free survival (PFS), overall survival, and the toxicity profile. Assuming that an ORR of 45% in eligible patients would indicate potential usefulness and an ORR of 20% would be the lower limit of interest, with α=0.10 and β=0.10, at least 24 patients were required.

Results: Among 29 eligible patients, the ORR was 34% (90% confidence interval, 20–48). The median PFS was 3.5 months, whereas the median survival time was 7.3 months. The most common grade 3–4 toxicity was neutropenia (79%), although only one patient (3%) suffered from febrile neutropenia. Non-hematological toxicities were of moderate severity and no treatment-related death was observed.

Conclusions: This is the first prospective study of AMR combined with CBDCA for refractory relapsed SCLC, which was effective and well tolerated. However, further investigation of this regimen is warranted.

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1. Introduction

Lung cancer is currently the leading cause of cancer death in many countries, and small-cell lung cancer (SCLC) accounts for 12–15% of all lung cancer cases [1]. SCLC is chemosensitive, and the standard first-line chemotherapy for advanced SCLC is platinum-doublet regimens such as cisplatin (CDDP) plus etoposide (ETP) or CDDP plus irinotecan (CPT) [2,3]. Despite high response rates to first-line chemotherapy, most patients experience SCLC relapse. The efficacy of second-line chemotherapy differ according to the relapse type (sensitive relapse, defined as relapse after >90 days from the completion of first-line chemotherapy or refractory relapse, defined as relapse during first-line chemotherapy or within 90 days after completion of first-line chemotherapy). There has been no standard treatment for patients with refractory relapsed SCLC, and few single agents have shown a response rate of >10% [4].

Amrubicin (AMR), a new anthracycline agent, has shown some promising results for advanced SCLC. A Japanese phase II study of the intravenous administration of single-agent first-line AMR therapy (45 mg/m^2) for 3 consecutive days demonstrated a high overall response rate (ORR) (75.8%) and long median survival time (MST) (11.7 months) [5]. AMR was also more effective than topotecan (TOP) for chemosensitive relapsed SCLC in our previous phase II trial (response rates, 38% and 13%, respectively), although the response rate of AMR for refractory relapsed SCLC was only 17% (that of TOP was 0%) [6], a finding compatible with the result of AMR in a similar population in a subsequent large phase II study by Ettinger [7].

Since some of the patients with refractory relapsed SCLC did not receive a sufficient dose of platinum agent during first-line chemotherapy, we thought that second-line chemotherapy consisting of AMR combined with platinum might be worth investigating. Thus, we conducted this phase II study to evaluate the safety and efficacy of the combination of AMR and CBDCA in patients with refractory relapsed SCLC.

2. Patients and methods

2.1. Patient selection

This multicenter phase II trial was conducted in accordance with the principles outlined in the Helsinki Declaration of the World Medical Association, and the protocol was approved by the institutional review board of each participating institution (Approval date: December 15, 2008; Approved No: 2008-365). Patients >20 years of age with histologically or cytologically confirmed SCLC who had progressed during first-line chemotherapy or had relapsed within 90 days after the completion of first-line chemotherapy were enrolled in this study. Other eligibility criteria included an Eastern Cooperative Oncology Group performance status (PS) of 0–2, measurable lesions according to Response Evaluation Criteria in Solid Tumors (RECIST), an estimated life expectancy ≥ 3 months, and adequate organ function (white blood cell count ≥ 4000/mm^3, absolute neutrophil count ≥ 2000/mm^3, platelet count ≥ 100,000/mm^3, hemoglobin ≥ 9.0 g/dL, serum bilirubin ≤ 1.5 mg/dL, aspartate aminotransferase and alanine aminotransferase ≤ 100 IU/L, creatinine level ≤ 1.5 mg/dL, and arterial oxygen pressure ≥ 60 mmHg). Written informed consent was obtained from all enrolled patients. Patients with symptomatic brain metastasis, interstitial lung disease, massive effusion requiring drainage, or severe comorbidities such as uncontrolled diabetes or cardiac disease were excluded. This trial was registered at UMIN (ID: R000001597).

2.2. Treatment schedule

The AMR was diluted in 50 mL of normal saline and administered by 10-min intravenous infusion at a dose of 30 mg/m^2 on days 1–3 of each treatment cycle. CBDCA was diluted in 250 mL of 5% glucose solution or normal saline and administered at infusion intervals of ≥ 30 min at a dose of area under the curve (AUC) 4.0 mg mL^{-1} min^{-1} after AMR on day 1. The doses of both agents were determined according to our previous phase I study of this combination for patients with untreated SCLC [8]. The treatment was repeated every 21 days. Premedication with corticosteroids and an antiemetic 5-HT$_3$ antagonist was recommended. The dose of AMR was reduced by 5 mg/m^2 each in the subsequent cycle in cases of severe toxic effects such as grade 3 or more non-hematological toxicities, thrombocytopenia ≤ 20,000/mm^3, grade 4 neutropenia lasting ≥ 4 days, or febrile neutropenia in the previous cycle. Use of granulocyte colony-stimulating factor (G-CSF) was permitted for neutropenia but not for prophylaxis. No prophylactic antibiotic support was planned. All patients were scheduled to receive at least three cycles of treatment unless their disease progressed, unacceptable toxicity occurred, the patient refused further treatment, or the physician

decided to discontinue the treatment. Subsequent chemotherapy after disease progression was not limited.

2.3. Patient assessment

Patient assessments, including a physical examination, a complete blood count, and biochemistry analysis, were repeated once a week after the initial evaluation. Tumor measurement was performed during the baseline assessment by computed tomography (CT) and was repeated every month until the best response to the protocol treatment was identified. Complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD) were determined based on RECIST version 1.0. CR and PR were confirmed by re-assessment performed at least 4 weeks after the first observation. SD was confirmed by re-assessment performed at least 6 weeks after registration. After confirmation, CT scans were acquired every 2 months until PD was observed. The CT scans of all patients were extramurally reviewed to confirm the response and progression-free survival (PFS). PFS was defined as the time from the date of registration to the date of the first observation of PD or death. Overall survival (OS) was defined as the time from the date of registration to the date of death or the latest follow-up (censored case). Toxicities were evaluated according to Common Terminology Criteria for Adverse Events version 3.0.

2.4. Statistical analysis

The primary endpoint of this study was the overall response rate (ORR), and secondary endpoints were PFS, OS, and the toxicity profile. Assuming that an ORR of 45% in eligible patients would indicate potential usefulness while an ORR of 20% would be the lower limit of interest, with $\alpha=0.10$ and $\beta=0.10$, at least 24 patients were required. Survival estimation was performed using the Kaplan–Meier method.

3. Results

3.1. Patient characteristics and treatment delivery

Between September 2008 and May 2011, 30 patients were enrolled from 10 institutions. One patient was excluded because of ineligible histology. Most of patients were male with a good PS (Table 1). Most patients received a CBDCA-based regimen as first-line chemotherapy, with a median of 4 cycles (range, 2–11 cycles). The median number of treatment cycles in the current study was 4 (range, 1–7), and 83% (24 of 29) of patients received three or more cycles.

3.2. Efficacy

All 29 patients were evaluable for response. The ORR was 34% (90% confidence interval, 20–48) and the disease-control rate was 83% (Table 2). The response rate of patients treated with CBDCA-based first-line chemotherapy was 40%, whereas that of patients treated with CDDP-based first-line chemotherapy was 22%, although the difference was not statistically significant. The response rates of patients treated with ETP and of those treated with CPT as first-line chemotherapy were 35% and 33%, respectively. At the data cut-off point in September 2013, the median PFS was 3.5 months and the median survival time was 7.3 months (Fig. 1).

Table 1 – Patient characteristics.

Number of patients	29
Gender	
Male	26
Female	3
Age (years)	
Median	67
Range	50–81
Performance status	
0	9
1	16
2	4
Prior chemotherapy	
Cisplatin+etoposide	2
Carboplatin+etoposide	15
Cisplatin+irinotecan	7
Carboplatin+irinotecan	5

Table 2 – Response.

Response	Number of patients	%	90% CI
Complete response	0	0	
Partial response	10	34	
Stable disease	14	48	
Progressive disease	5	17	
Overall response rate	10	34	20–48
Disease control rate	24	83	

CI, confidence interval.

3.3. Safety

The toxicities (>grade 2) are summarized in Table 3. The most common adverse event in this study was neutropenia (79%), although only one patient (3%) suffered from febrile neutropenia. Thirteen patients (45%) required G-CSF support, the median duration of which was 4 days (range, 1–11). Two patients (7%) received a blood transfusion. Eight patients (28%) required AMR dose reduction due to hematological toxicity. Non-hematological toxicities were moderate. One patient died only 5 days after the initiation of protocol treatment. The attending physician reported that the cause of death was rapid progression of SCLC, and the independent data and safety monitoring committee of this study reviewed the clinical course and accepted the physician's decision. No treatment-related death was observed.

4. Discussion

This study met its primary endpoint. Since there have been few promising monotherapy options for refractory relapsed

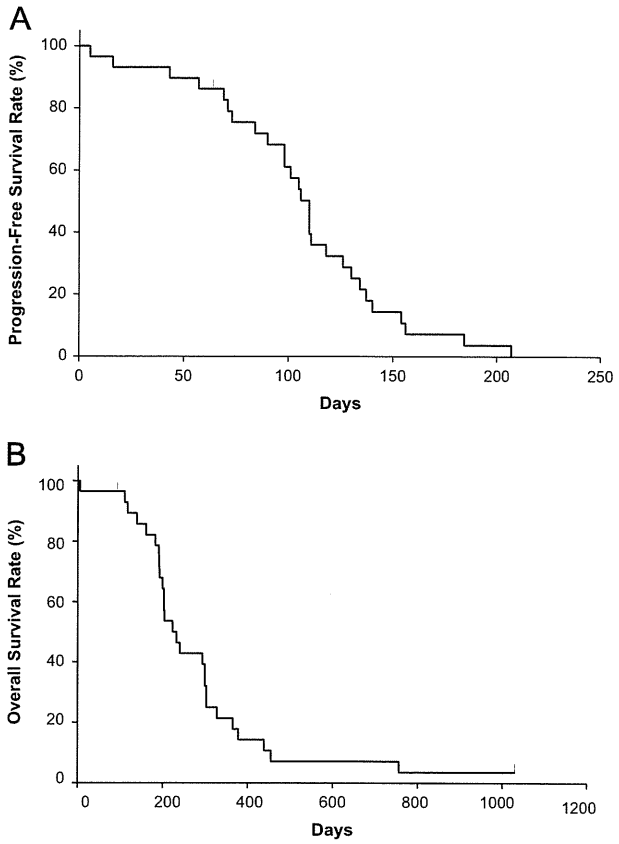

Fig. 1 – (A) Progression-free survival and (B) overall survival.

Table 3 – Toxicity profile.

Toxicity (≥ grade 2)	Grade (CTCAE)			
	Number of patients			
	2	3	4	Grade 3/4 (%)
Hematological				
Neutropenia	0	10	13	23 (79%)
Decreased hemoglobin	11	6	1	7 (24%)
Thrombocytopenia	6	4	3	7 (24%)
Febrile neutropenia	–	1	0	1 (3%)
Non-hematological				
Infection	4	2	0	2 (6%)
Nausea	2	0	0	0
Fatigue	1	0	0	0
Mucositis oral	1	0	0	1 (3%)
Stomach pain	1	0	0	0
Phlebitis	1	0	0	0
Hiccups	1	0	0	0
Pain	1	0	0	0
Interstitial lung disease	0	1	0	1 (3%)
Hyponatremia	0	2	0	2 (6%)
Hypoglycemia	0	0	1	1 (3%)

CTCAE, Common terminology criteria for adverse events.

SCLC, the combination of AMR and CBDCA is worth investigating. Contrary to our expectations, most patients in this study received sufficient cycles of platinum-doublet therapy as first-line chemotherapy. The ORR might have increased if more patients had been treated with insufficient first-line chemotherapy. According to subgroup analysis, this regimen might be suitable for patients treated with CBDCA as first-line chemotherapy. The efficacy of CBDCA plus AMR was not different in patients treated with ETP or CPT as first-line chemotherapy with platinum, which was consistent with our previous result of AMR as second-line chemotherapy [6]. Although the sample size was too small, the above-mentioned results require further validation.

In another Japanese study, even AMR alone demonstrated a quite high response rate (40%) in refractory relapsed SCLC [9], although the result might be biased due to its small sample size ($n=16$), considering the result of a subsequent larger study [7]. Other studies have used combined regimens for relapsed SCLC, some of which suggested high efficacy. However, most of those studies included both sensitive and refractory relapse patterns [4]; thus, their usefulness in refractory relapsed SCLC was unclear.

Toxicity is another important issue for such combination regimens. The above-mentioned previous regimens for relapsed SCLC were generally very toxic. For example, Kubota reported that dose-intensive CODE (CDDP, vincristine, doxorubicin, and ETP) could result in an ORR of approximately 80% in patients with refractory relapsed SCLC; however, that regimen required prophylactic G-CSF support due to severe neutropenia [10]. In contrast, AMR combined with CBDCA showed moderate toxicity in this study, which might be attributable to the dose of CBDCA being AUC 4. We reported this regimen in another study, where toxicity profiles tended to be similar and the efficacy for SCLC was sufficient (ORR was 89% as first-line treatment) [11]. Regarding the AMR dose, the current dose was one level lower than the recommended dose in our phase I and phase II studies of patients with chemotherapy-naïve SCLC because we considered that previously treated patients would be at a higher risk of myelosuppression. Although we believe this combination with the current dosage would be worth investigating in the second-line setting in terms of the risk–benefit balance, there might be scope for increasing the AMR dose to increase its efficacy.

This study has a few limitations. First, the sample size was too small to draw definite conclusions, the efficacy of this combination needs to be confirmed in a future phase III study in which the current regimen could be compared with AMR alone. Second, the drug dose might be insufficient for refractory relapsed cases. Considering that the toxicity of the current dose was moderate, there might be scope to increase the CBDCA or AMR dosage. In addition, the patients that would benefit most from the re-administration of platinum during second-line chemotherapy should be identified.

In conclusion, AMR combined with CBDCA was effective for refractory relapsed SCLC and demonstrated acceptable toxicity. Since treatment options for patients with refractory relapsed SCLC remain limited, further investigation of this regimen is warranted.

Conflict of interest

Akira Inoue received honoraria and research funding from AstraZeneca; Satoshi Oizumi received honoraria from AstraZeneca and research funding from Eli Lilly; Toshihiro Nukiwa received honoraria from Boehringer Ingelheim.

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ORIGINAL ARTICLE

Phase II trial of carboplatin and pemetrexed as first-line chemotherapy for non-squamous non-small cell lung cancer, and correlation between the efficacy/toxicity and genetic polymorphisms associated with pemetrexed metabolism: Hokkaido Lung Cancer Clinical Study Group Trial (HOT) 0902

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Abstract
Purpose This phase II study evaluated the response rate (RR) and safety of combination therapy with carboplatin (CBDCA) and pemetrexed (PEM) in Japanese patients with non-squamous non-small cell lung cancer (non-sq NSCLC). Further, the relationship between therapy efficacy/toxicity and genetic polymorphisms associated with PEM metabolism was analyzed.
Methods Forty-one patients received CBDCA at a dose targeting an area under the concentration–time curve of 5 mg/mL × min and PEM of 500 mg/m^2 on day 1 every 3 weeks. Single-nucleotide polymorphisms of the thymidylate synthase (*TYMS*) coding gene, the variable number of tandem repeat (VNTR) in the *TYMS*, and the methylenetetrahydrofolate reductase (*MTHFR*) coding gene were analyzed.
Results The overall RR was 36.6 %. Median progression-free survival and median survival time were 4.7 months [95 % confidence interval (CI) 3.9–5.6 months] and 16.2 months (95 % CI 6.1–26.2 months), respectively.

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Epidermal growth factor receptor gene mutations were detected in 6 patients (14.6 %). The VNTR in the *TYMS* significantly correlated with anemia ($p = 0.047$) and thrombocytopenia ($p = 0.038$).

Conclusions This combination therapy was effective and tolerable in patients with advanced non-sq NSCLC. The VNTR in the *TYMS* appears to be a predictive factor for anemia and thrombocytopenia in patients treated with this regimen.

Keywords Non-squamous non-small cell lung cancer · Carboplatin · Pemetrexed · Genetic polymorphisms · Methylenetetrahydrofolate reductase (MTHFR) · Thymidylate synthase (TS)

Introduction

The majority of patients with non-small cell lung cancer (NSCLC) are diagnosed at inoperable stages, and platinum-based chemotherapy remains a key strategy for the management of patients with advanced NSCLC [1–3]. Overall survival of front-line chemotherapy using pemetrexed (PEM) in combination with cisplatin (CDDP) was superior to that with other platinum doublets, particularly for patients with advanced non-squamous (non-sq) NSCLC [4–7].

PEM-based regimens have a mild toxicity profile and can improve patients' quality of life (QOL) [4, 6, 8, 9]. Further, carboplatin (CBDCA)-based regimens are also widely used and are associated with relatively mild toxicity [9–11]. However, the efficacy and safety of PEM combined with CBDCA have not been well established in Japanese patients with NSCLC.

Thymidylate synthetase (TS) is one of the main targets of PEM [12], and methylenetetrahydrofolate reductase (MTHFR) is an enzyme indispensable for folate metabolism. Both enzymes are strongly associated with cell proliferation and efficacy of pyrimidine-antagonist chemotherapies, such as the one with PEM [13, 14], and studies have demonstrated a correlation between clinical efficacy of various anticancer agents and the polymorphisms of these genes [15]. Patients with homozygous mutations for the MTHFR coding gene (*MTHFR*) C677T had a significantly increased progression-free survival (PFS) when compared to patients with wild-type or heterozygous mutations [16].

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Similarly, TS is a critical target for various chemotherapies [17, 18], including those used for the treatment of NSCLC. One study reported that TS expression correlated with PEM sensitivity in NSCLC cell lines [19]. Tanaka et al. [20] conducted a large-scale study of the Japanese population showing that TS expression was lower in adenocarcinoma than in squamous cell carcinoma of the lung.

Thus, the goal of the present phase II study was to evaluate the response rate (RR) and safety of CBDCA and PEM in Japanese patients with non-sq NSCLC. Further, the relationship between therapy efficacy/toxicity and genetic polymorphisms of folate metabolism-associated enzyme coding genes, the TS coding gene (*TYMS*) and *MTHFR*, or the variable number of tandem repeat (VNTR) in the *TYMS* in peripheral blood cells was examined.

Patients and methods

Eligibility criteria

Eligibility criteria were as follows: cytologically or histologically confirmed diagnosis of non-sq NSCLC; patients without prior systemic chemotherapy, including ones with postoperative recurrence; stage IIIB or IV disease according to the 7th edition of TNM criteria; no indications for curative chemoradiotherapy; age between 20 and 74 years; Eastern Cooperative Oncology Group (ECOG) performance status 0–1; measurable disease (Response Evaluation Criteria in Solid Tumors, ver. 1.0); and normal organ function (as defined by absolute white blood cell count $\geq 4.0 \times 10^9$/L or neutrophil count $\geq 2.0 \times 10^9$/L; hemoglobin ≥ 9.0 g/dL; platelets $\geq 100 \times 10^9$/L; alanine aminotransferase [ALT] and aspartate aminotransferase [AST] ≤ 100 IU/L [ALT and AST ≤ 150 IU/L was acceptable if liver metastasis was present]; serum creatinine ≤ 1.2 mg/dL; calculated creatinine clearance using Cockcroft-Gault formula ≥ 60 ml/min; arterial partial pressure of oxygen [PaO_2] ≥ 60 Torr or arterial hemoglobin oxygen saturation by pulse oximetry [SpO_2] ≥ 90 % at ambient air); and projected life expectancy ≥ 12 weeks. The main exclusion criteria were as follows: active infection; temperature ≥ 38 °C; severe complications, such as heart failure, renal failure, liver dysfunction, uncontrolled diabetes mellitus, and hypertension; a concomitant malignancy within the last 5 years; central nervous system metastases with symptoms; uncontrolled pleural effusion or ascites; interstitial pneumonia or pulmonary fibrosis on chest X-ray; history of severe hypersensitivity to drug components; required concurrent treatment with systemic steroid; and pregnancy. The protocol was approved by each institutional review board. The study was performed in accordance with the ethics principles of the Declaration of Helsinki. Written informed

consent was obtained from all patients. This study was registered with the University Hospital Medical Information Network (UMIN) [UMIN000002846].

Treatment

PEM at a dose of 500 mg/m^2 on day 1 and CBDCA at a dose calculated to produce an area under the concentration–time curve (AUC) of 5.0 mg/mL × min on day 1 were administered intravenously every 3 weeks. The treatment was discontinued in the case of any of the following: disease progression; unacceptable toxicity; patient refusal; death during treatment; and investigator's decision. All patients received oral folic acid (500 μg) daily and a vitamin B12 injection (1,000 μg) every 9 weeks, beginning one or more weeks before the first dose and continuing until three weeks after the last dose of study treatment. Any treatment was permitted after protocol discontinuation. Dose adjustment and cycle delay of 21 days or less were permitted to allow for resolution of toxic effects.

Assessment of toxicity and response

Toxicities or adverse events were graded according to the Common Terminology Criteria for Adverse Events (CTCAE), version 3.0. Tumor responses were assessed using chest X-ray, computed tomography, or magnetic resonance imaging (when clinically indicated), before and during treatment. Assessments were repeated at least every month unless progression was detected. Responses were recorded as complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD) in accordance with Response Evaluation Criteria in Solid Tumors (RECIST) guidelines version 1.0. Disease control rate (DCR) was defined as the sum of the objective response (CR or PR) rate and the rate of SD. Clinical response data were all confirmed by central review.

Endpoints and statistical analysis

The primary endpoint was overall RR. Secondary endpoints were safety, PFS, and overall survival (OS). Duration of tumor response was defined as the time between the date of the first objective assessment of CR or PR and the date when PD or death was recorded from any cause. PFS was defined as the time between the date of registration and the date of PD or death from any cause. OS was defined as the time between the date of registration and the date of death from any cause. The Kaplan–Meier method was used to estimate PFS and OS.

On the assumption that threshold RR and expected RR would, respectively, be 20 and 40 %, a sample size of 36 patients was required by the Simon's and Fleming's designs with a one-sided α error of 0.05 and a β error of 0.20. A total of 40 patients were planned to enroll considering later exclusion of patients. All analyses were based on the intent-to-treat population.

Genetic analyses

Analyses of genetic variants were performed with the investigator blinded to patient characteristics and clinical outcome. Five milliliters of peripheral blood was taken from each patient who had enrolled in this study and who had consented to the genetic analysis. DNA was extracted from each blood sample for analysis of the *MTHFR* single-nucleotide polymorphisms (SNPs), C677T and A1298C. Then, each extracted DNA was used to determine the TS genotypes of the VNTR in the five prime untranslated region (5′-UTR) of *TYMS*, two tandem repeat (2R)/3R/4R, and the 3R-SNP, G/C, in *TYMS* by polymerase chain reaction (PCR) and PCR-restriction fragment length polymorphism (PCR–RFLP), using the forward primer, 5′-AAAAG GCGCGCGGAAGGGGTCCT-3′, and reverse primer, 5′-TCCGAGCCGGCCACAGGCAT-3′. DNA amplification was performed three times per sample, using the GeneAmp® PCR System 9700 (Applied Biosystems, Life Technologies Japan, Inc., Tokyo, Japan). PCR with the genomic DNA template was performed in reaction mixtures containing 1 × PCR buffer II without $MgCl_2$, $MgCl_2$ solution, 200 μM of deoxyribonucleoside triphosphates, 500 nM of each primer, 0.5 units of AmpliTaq® DNA Polymerase, and 100 ng of genomic DNA (all of these reagents were obtained from Applied Biosystems). The cycling conditions were one cycle of 94 °C for 5 min, 35 cycles of 94 °C for 40 s, 62 °C for 60 s, 72 °C for 40 s, with a final extension at 72 °C for 5 min. Aliquots of amplified fragments were separated on 4 % agarose gels, and the TS VNTR genotype was determined, with 2R 116 bp, 3R 144 bp, and 4R 172 bp. Samples showing the 3R genotype were analyzed further for G/C polymorphism by RFLP. PCR products were digested with *Hae*III (TaKaRa Bio, Inc., Shiga, Japan) followed by electrophoresis in 4 % agarose gel and ethidium bromide stain. The 3R fragments of 66, 37, 28, and 10 bp were classified into the 3G allele, and the 3R fragments of 94, 37, and 10 bp were classified into the 3C allele, as previously reported [21]. Analysis was performed at least three times to confirm the genotype. *TYMS* genotype was categorized into a high-expression genotype (2R/3G, 3C/3G, 3G/3G, 3G/4R) and a low-expression genotype (2R/2R, 2R/3C, 3C/3C), depending on the 5′-UTR VNTR polymorphism and the C/G polymorphism within the third VNTR.

The association between polymorphisms and RR or chemotherapy-related toxicity was analyzed by the χ^2 test or Fisher's exact test. The correlation between

polymorphisms and PFS/OS was analyzed by the log-rank test. For each test, patients were compared among each genotype, such as wild type, heterozygous, and homozygous. Statistical significance was established at $p < 0.05$.

Results

Patients characteristics

From November 2009 to November 2010, 41 patients were enrolled (Table 1). Twenty-four patients (58.5 %) died during the follow-up, mostly as a result of disease progression (23 of 24 patients). The median age of the enrolled patients was 63 years (range of 43–73 years), and 28 patients (68.3 %) were male. Of the 41 patients, 27 (65.9 %) had an ECOG performance status of 1, 36 (87.8 %) had stage IV disease, and 39 (95.1 %) were diagnosed with adenocarcinoma.

Epidermal growth factor receptor (EGFR) gene mutations were investigated in 40 of 41 patients. The mutation was not searched for one patient because diagnostic yield from the tissue sample for detection was not enough. The positive mutations were detected in six patients, four of whom had an exon 19 deletion mutation, while the other two had an L858R mutation in exon 21.

Treatment administered

The median number of treatment cycles delivered was four (range of 1–6 cycles), with 33 patients (80.5 %) completing more than three cycles.

The dose of agents was reduced in three patients (7.3 %) because of adverse events, including grade 3 general fatigue, grade 4 hematologic toxicity, and grade 4 anaphylaxis. Protocol treatment was terminated in eight patients (19.5 %) before completion of three cycles.

At the time of final analysis, 23 patients (56.2 %) received second- or third-line treatment, following the initial therapy. Sixteen patients (39.0 %) received cytotoxic chemotherapies as a second-line treatment and 3 of them received EGFR tyrosine kinase inhibitors (EGFR-TKIs) as a third-line treatment. Seven patients (17.1 %) received EGFR-TKIs as a second-line treatment and 2 of them received cytotoxic chemotherapies as a third-line treatment. Among the 10 patients (24.4 %) who were treated with an EGFR-TKI in the second- or third-line, five had an EGFR gene mutation. One patient with EGFR gene mutation did not receive an EGFR-TKI.

Response to treatment

All 41 patients were assessable for tumor responses. Fifteen patients exhibited PR, 20 patients exhibited SD, and disease progressed in six cases, resulting in a RR of 36.6 % [95 % confidence interval (CI) 22.1–53.1 %] and a DCR of 85.4 % (95 % CI, 70.8–94.4 %) (Table 2). The lower limit of the 95 % CI of the RR exceeded the threshold RR of 20 %; thus, the primary endpoint was achieved.

Table 1 Patient demographics and baseline characteristics

Parameters	($N = 41$) n (%)
Age, median (years) (range)	
Gender	
Male	28 (68.3)
Female	13 (31.7)
ECOG performance status	
0	14 (34.1)
1	27 (65.9)
Disease stage	
IIIB	5 (12.2)
IV	36 (87.8)
Histology	
Adenocarcinoma	39 (95.1)
Large cell carcinoma	2 (4.9)
EGFR gene mutation	
Wild type	34 (82.9)
Exon 19 deletion	4 (9.8)
Exon 21 L858R	2 (4.9)
Unknown	1 (2.4)
No. of chemotherapy cycle	
1	1 (2.4)
2	7 (17.1)
3	6 (14.6)
4	11 (26.8)
5	3 (7.3)
6	13 (31.7)
≥3 cycles	33 (80.5)

Table 2 Treatment efficacy

Best response	($N = 41$) n (%)
CR	0 (0.0)
PR	15 (36.6)
SD	20 (48.8)
PD	6 (14.6)
Overall response rate (RR)	36.6 % [95 % CI 22.1–53.1 %]
Disease control rate (DCR)*	85.4 % [95 % CI; 70.8–94.4 %]

CI confidence interval

* DCR = {CR + PR + SD}/{CR + PR + SD + PD}

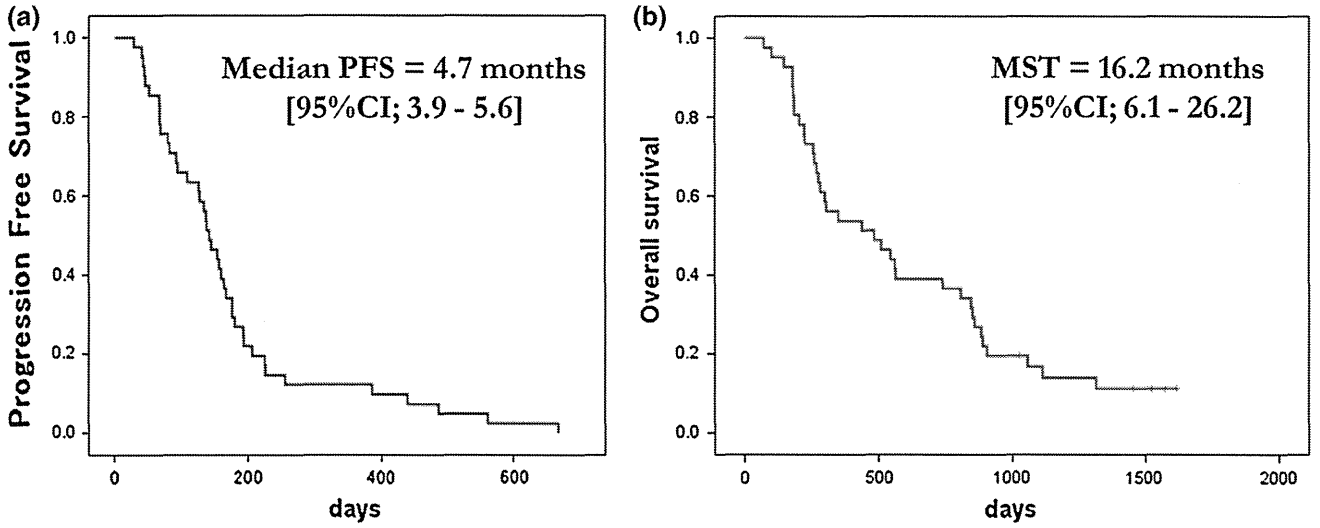

Fig. 1 Kaplan–Meier curves for (**a**) progression-free survival (PFS) and (**b**) overall survival (OS)

The final survival assessment was conducted in July 2014, 4 years and 8 months after the last patient's enrollment. With a median follow-up time of 16.2 months (range of 2.4–54.1 months), median PFS and median survival time (MST) were 4.7 months (95 % CI 3.9–5.6 months) and 16.2 months (95 % CI 6.1–26.2 months), respectively (Fig. 1). The one-year survival rate was 53.6 % (95 % CI 37.4–69.3 %).

Retrospective subanalysis of PFS and OS of patients with or without an EGFR gene mutation showed that EGFR gene mutation status did not influence the PFS (a median of 5.9 months for the mutation-positive group, as compared to 4.6 months for the mutation-negative group; $p = 0.738$), but patients with an EGFR gene mutation were associated with a trend of longer OS than those without an EGFR gene mutation (a median of 16.2 months for the mutation-positive group, as compared to 11.7 months for the mutation-negative group; $p = 0.06$).

Adverse events

All 41 eligible patients were also evaluable for toxicity analysis. The rates of grade 3 and 4 hematologic and non-hematologic adverse events during the treatment were as follows: eight patients (19.5 %) had grade ≥3 leukopenia; 12 patients (29.3 %) had grade ≥3 neutropenia; 14 patients (34.1 %) had grade ≥3 anemia; seven patients (17.1 %) had grade ≥3 thrombocytopenia. Only one patient (2.4 %) experienced grade 3 febrile neutropenia. Granulocyte colony stimulating factors (G-CSF) were given to three patients (7.3 %). The most common non-hematologic adverse event was anorexia (29/41 patients, 70.7 %); other non-hematologic adverse events were rare (Table 3). No interstitial lung disease was reported. No treatment-related death was observed.

Table 3 Toxicity profile

Toxicity	Grade, *n* (*N* = 41)				Percentage of grade 3 or 4 (%)
	1	2	3	4	
Hematologic					
Leukopenia	4	9	7	1	19.5
Neutropenia	3	8	9	3	29.3
Febrile neutropenia	–	–	1	0	2.4
Anemia	9	11	11	3	34.1
Thrombocytopenia	20	6	5	2	17.1
Non-hematologic					
Hypoalbuminemia	3	2	0	0	0.0
Liver dysfunction	16	2	1	0	2.4
High LDH	5	0	0	0	0.0
Hyponatremia	10	0	1	0	2.4
Hypopotassemia	1	2	0	0	0.0
Infection	0	2	1	0	2.4
Anorexia	23	3	3	0	7.3
Nausea	15	6	2	0	4.9
Vomiting	3	4	0	0	0.0
Allergic reaction	0	1	0	1	2.4
Stomatitis	2	0	0	0	0.0
Skin rash	1	1	1	0	2.4
Pigmentation	2	0	0	0	0.0
Alopecia	2	0	0	0	0.0
Fatigue	7	0	0	0	0.0
Constipation	2	1	0	0	0.0

Genetic polymorphisms and clinical indices

Blood samples were collected from 37 patients (90.2 %). Gene polymorphisms of C677T and A1298C in the *MTHFR* were in Hardy–Weinberg equilibrium according to Pearson's Chi-square test (C677T: $\chi^2 = 0.182 < \chi^2$ [0.05] = 3.84; A1298C: $\chi^2 = 0.946 < \chi^2$ [0.05]) (Table 4). Patients with 3R/3R and 3R/4R of the tandem repeat in 5′-UTR of *TYMS* had experienced significantly more grade 3/4 anemia ($p = 0.047$) or grade 3/4 thrombocytopenia ($p = 0.038$) than those with 2R/3R. Other variants explored in this study did not significantly correlate with hematologic toxicities (Table 5). Non-hematologic toxicities were mild, and the relationship between those events and gene variants was not evaluated. Gene variants did not significantly correlate with RR, DCR (Table 5), PFS, or OS (data not shown).

Table 4 Number of cases with *MTHFR* and *TYMS* variants

Gene	Gene variants	($N = 41$) *n* (%)
MTHFR-C677T	C/C	12 (32.4)
	C/T	17 (45.9)
	T/T	8 (21.6)
MTHFR-A1298C	A/A	26 (70.3)
	A/C	9 (24.3)
	C/C	2 (5.4)
TYMS-VNTR	2R/3R	7 (18.9)
	3R/3R	29 (78.4)
	3R/4R	1 (2.7)
SNP of the VNTR (3R)	3G (−)	2 (5.4)
	3G (+)	35 (94.6)

MTHFR methylenetetrahydrofolate reductase coding gene, *TYMS* thymidylate synthase coding gene, *VNTR* variable number of tandem repeat, *2R* 2 repeats, *3R* 3 repeats, *4R* 4 repeats, *SNP* single-nucleotide polymorphism

Table 5 χ^2 test of correlation between the treatment efficacy/toxicities and SNPs of MTHFR/TS gene

Indexes	*MTHFR*		*TYMS*	
	C677T	A1298C	VNTR	SNP of the VNTR (3R)
	p	*p*	*p*	*p*
Response rate	0.757	0.307	0.699	0.902
Hematologic toxicities				
Leukopenia	0.703	0.393	0.372	0.149*
Neutropenia	0.565	0.684	0.194	0.220*
Anemia	0.237	0.217	0.047	0.237*
Thrombocytopenia	0.598	0.393	0.038	0.598*

VNTR variable number of tandem repeat

* Fisher's exact test

Discussion

Although CDDP and CBDCA have substantially different toxicity profiles, a meta-analysis comparing CDDP- and CBDCA-based chemotherapy failed to establish which regimen is associated with superior survival [5, 22–24]. CBDCA was used in this study, as non-hematologic toxicity and strong subjective symptoms (e.g., nausea, vomiting, and general fatigue) predominate in patients treated with CDDP, whereas hematologic toxicity with relatively less symptoms is observed more commonly in patients treated with CBDCA [20, 23, 24]. In a phase III study conducted in Norway, an AUC of 5.0 mg/mL × min of CBDCA was selected for patients in the CBDCA plus PEM arm [9] and resulted in good clinical efficacy with a tolerable toxicity profile. We also adopted the same dose of CBDCA in this study, and the treatment efficacy of our CBDCA plus PEM regimen was favorable. Further, the toxicity profile was mild and tolerable. The PFS in this study seemed to be shorter than that in the other studies for Japanese patients [25, 26]. A continuation maintenance therapy with PEM was not adopted in our protocol due to the fact that the maintenance strategy [27] had not been established when our trial was launched. Compared to other Japanese phase II trials (from 5–6 cycles) [25, 26], there were fewer chemotherapy cycles in the current study, while Norwegian study reported even fewer (a median of 3.3 cycles) [9]. In our study, PD was the major cause (13 patients, 52 %) of undergoing 4 or less cycles of the chemotherapy. The dose of CBDCA may be associated with the fewer cycle of chemotherapy, providing another reason for the shorter PFS.

PEM targets folate-dependent reactions and acts on TS, a key enzyme for DNA synthesis [28, 29]. Alteration of TS activity due to polymorphisms in the cognate coding gene influences outcomes in patients with NSCLC [13, 30, 31]. MTHFR is an essential enzyme for one-carbon metabolism needed for DNA synthesis, repair, and methylation [32]. The alteration of MTHFR activity plays a role in carcinogenesis [33, 34], which supports the notion that *MTHFR* polymorphisms may affect patient outcomes [13, 15, 32]. Only an increasing repeat number of VNTR in 5′-UTR of *TYMS* correlated with anemia and thrombocytopenia, suggesting that this genetic marker might be useful for the prediction of hematologic toxicity in response to PEM. In order to avoid the severe hematologic toxicities in patients with the 3R/3R variant, we should consider switching the regimen, reducing the initial dose of PEM, or upwardly adjusting the minimum number of red blood cells or platelets required for starting the treatment.

A significant correlation between the *MTHFR*-C677T allele and improved clinical outcome has been found in another study [16]. However, we were not able to show the same result. One of the reasons appears to be race/ethnicity in those variants. In breast cancer, race/ethnicity has been reported to modify the association between the two SNPs of *MTHFR* and breast cancer survival [35]. It is known that PEM targets another enzyme associated with folate metabolism other than TS, such as dihydrofolate reductase (DHFR), which inhibits a cytotoxic effect of antifolates, thereby reducing treatment efficacy [36]. Indeed, a previous study showed the association between PFS and either of TS or of DHFR [37]. Collectively, a comprehensive analysis of polymorphisms of all enzymes associated with folate metabolism is required.

In terms of toxicity profile, the two Japanese studies of CBDCA (AUC = 6.0 mg/mL × min) plus PEM (500 mg/m^2) followed by maintenance PEM (500 mg/m^2) conducted by the Kyoto Thoracic Oncology Research Group (KTOGT0902) [25] and by Okamoto et al. [26], demonstrated that grade 3/4 neutropenia, anemia, and thrombocytopenia were seen in 33, 31, and 18 % and 56, 29.4, and 41.3 %, respectively. In the former study, red blood cell and platelet transfusions were required for 6.1 and 4.1 %, respectively. In our study, grade 3/4 neutropenia, anemia, and thrombocytopenia were seen, respectively, in 29.3, 34.1, and 17.1 %, whereas packed red blood cell transfusions were given to three patients (7.3 %) and platelet concentrate given to one patient (2.4 %). Non-hematologic toxicities were also mild, and our study achieved a good treatment completion rate over three courses. AUC of 5 or 6 mg/mL × min of CBDCA should be adjusted for individual patients in terms of the balance between efficacy and toxicity. In clinical practice, we assume that CBDCA plus PEM regimen can be selected for patients with non-squamous and EGFR wild-type NSCLC as a first-line therapy, particularly for those unfit for CDDP or with an ECOG performance status (PS) of two as demonstrated in a previous study [38] or elderly patients with good PS who have also a benefit of CBDCA-based platinum doublet [39, 40].

Recent phase III trials have shown favorable efficacies of EGFR-TKI in NSCLC patients with active EGFR gene mutation [41, 42]. There was no significant difference of either PFS or OS according to EGFR gene mutation status in our study, but OS of the patients with EGFR gene mutation tended to be longer than those without the mutation, presumably due to the post-treatment therapy using EGFR-TKIs. The smaller size of patients with EGFR mutation (6/40, 15 %) in our study was due to the fact that several institutes were also participating in another ongoing trial, which was recruiting NSCLC patients with EGFR gene mutation. However, our data implicate the importance of the use of EGFR-TKIs for treating patients with an active EGFR gene mutation. CBDCA plus PEM regimen seems also appropriate for those with EGFR mutant-positive NSCLC, who failed the initial EGFR-TKI therapy.

Although the development of effective treatment strategies against advanced NSCLC has progressed swiftly over the last decade, minimization of toxicities remains important for QOL purposes. The toxicity profile of chemotherapy can vary according to race, ethnicity, and genetic makeup. Gene analyses in this study are the first to demonstrate a possibility of correlation between genetic polymorphisms and hematologic toxicity in non-squamous NSCLC patients treated with PEM. Further studies to confirm this evidence are warranted.

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Conflict of interest Satoshi Oizumi received an honorarium from AstraZeneca and a grant from Eli Lilly. Others had no conflict of interest to declare.

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Prophylactic cranial irradiation in extensive small cell lung cancer

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Clinical Trials. gov number : NCT00016211の詳細

Slotmanらによる本試験(以下，Slotman試験)についての論文は「Prophylactic cranial irradiation in extensive small-cell lung cancer」として，2007年の『The New England Journal of Medicine』誌に発表された[1]。周知のとおり，その後各国のガイドラインに採用されるに至った重要な論文である。

対象は初回化学療法になんらかの反応をみせた進展型小細胞肺がん(extensive disease-small cell lung cancer；ED-SCLC)で，経過観察群と，試験治療として予防的全脳照射(prophylactic cranial irradiation；PCI)を行うPCI群とに1：1に無作為化した(**図1**)。主要評価項目は，症候性脳転移発症までの期間とされた。計286名の患者が参加し，予想どおりPCIは症候性脳転移発症までの期間を有意に抑え(ハザード比(HR)0.27(95％信頼区間(CI)：0.16～0.44)，p＜0.001)，それだけでなく無増悪生存期間(PFS)(12.0週 vs. 14.7週)，全生存期間(OS)(5.4ヵ月 vs. 6.7ヵ月)ともにPCI群で有意な延長が示された。

Slotman試験の問題点

以上が本論文の抄録から得られる情報である。しかしながら本論文を読み込むと(読み込まなくても？)不十分なデザインに基づいた試験であることが明らかであり，論文発表当初からいくつかの疑義が寄せられていた[2][3]。なかでも最大の弱点は，登録時に頭部画像検査が必須でなかったことである。つまり，試験治療が本当に「予防的」全脳照射であったのか誰も確認できていないという，今から考えると少しいいかげんな試験であった。そのほかにも主要評価項目がOSでないこと，化学療法が現在の標準治療であるプラチナ併用療法でないこと，全脳照射の方法が一律でないこと，無作為化後の頭部画像検査が定期的に行われず，転移を示唆する状況になってはじめて行うことが規定されていることなどの問題点が指摘された。

検証試験の結果

このような背景をもとに，考えうるかぎり十分堅固な試験デザインをもってPCIの有効性を再検証したのが，2014年の米国臨床腫瘍学会(ASCO)において日本から報告された第Ⅲ相臨床試験である(**図2**)[4]。本検証試験では無作為化前の頭部MRIを必須とし，PCIの線量もこれまでで最もエビデンスのある25Gy/10frsに統一した。もちろん，主要評価項目はOSとされた。結果，初回の中間解析においてPCI群が経過観察群に対してOSが上回る可能性がきわ

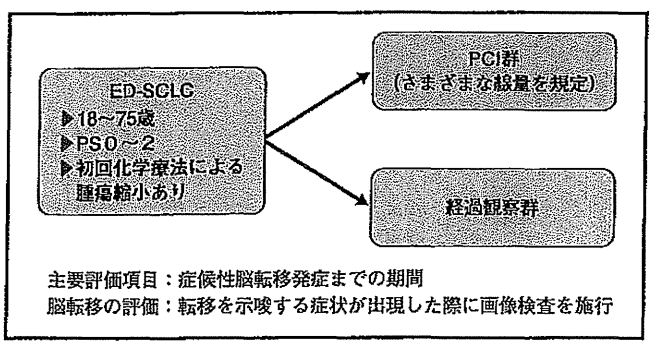

図1 Slotman試験のシェーマ

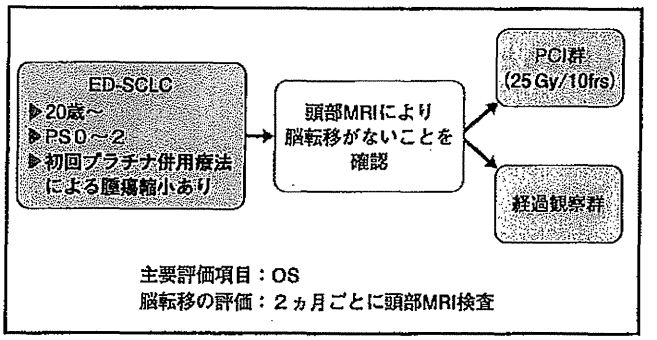

図2 日本からの検証試験のシェーマ(Slotman試験との主な違いを青字で示す)

めて乏しい(PCI群が有意に上回る確率はp＜0.001だが，OSにおけるp値は0.091であった)との結果が判明し，本検証試験は無効中止となった(**図3**)。

改めて両試験の結果を比較してみる(**表1**)。両試験間でPFSにはそれほど差はないが，OSは大きく異なっている。PFS中央値である2～3ヵ月時点において，脳転移増悪頻度がそれほど高くないため，後治療における全身化学療法の導入割合がこうした差異をもたらした可能性が高い。実際，Slotman試験において後治療(放射線治療も含む)の導入割合が45～68%であったのに対し，検証試験では両群とも80%以上の患者に対して2次化学療法が行われている。それでは，なぜ後治療にこのような差が生じたのであろうか。両試験における脳転移発症割合は検証試験においておおむね高いが，これはデザインの問題でSlotman試験では症候性脳転移が，検証試験では無症候性脳転移が多いためと思われる。つまり検証試験においては定期的なMRIによって無症候性脳転移を早期に検出したことが，高い後治療の導入割合につながり，ひいては良好な生存期間をもたらしたと考えられる。

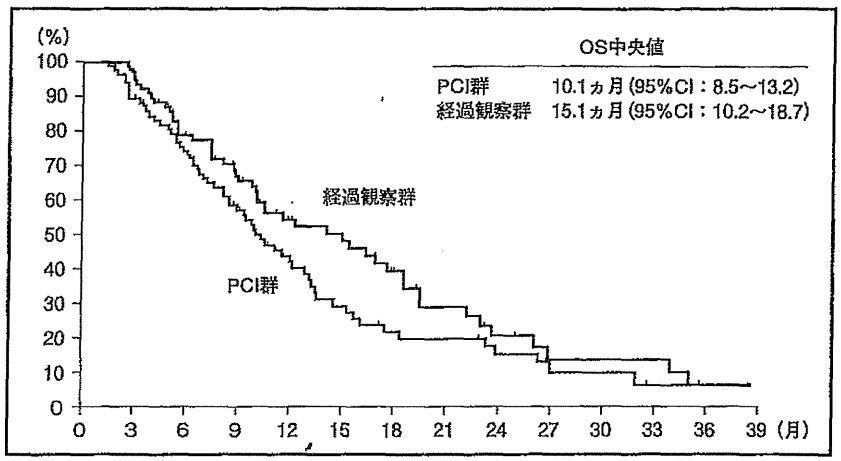

図3 日本より発表された第Ⅲ相臨床試験におけるOS

(文献4)より引用・一部改変)

表1 2つのPCI試験のまとめ

	治療	患者数	6ヵ月時点の脳転移増悪頻度(%)	12ヵ月時点の脳転移増悪頻度(%)	mPFS(月)	MST(月)
Slotmanら[1]	経過観察群	143	32	40.4	2.8	5.4
	PCI群	143	4.4	14.6	3.4	6.7
Setoら[4]	経過観察群	79	38*	58.0	2.4	15.1
	PCI群	84	12*	32.4	2.2	10.1

mPFS：PFS中央値，MST：生存期間中央値
＊：ASCO発表スライドより推定

最後に

検証試験の結果は2014年のASCOで九州がんセンターの瀬戸貴司先生より発表されたが，くしくも前の演者がBen Slotman先生であったため新旧PCI試験の発表者が壇上で相対することになった。(Ben Slotman先生には気の毒であったが)ディスカッサンタントは検証試験の結果について非常に好意的で，日本からのエビデンスがこのようなかたちで認められたことを非常に誇らしく思った。本検証試験の結果は，ED-SCLCのガイドラインを塗り替えることになると思われる。

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話　題

小細胞肺がんに対する予防的全脳照射*

赤松弘朗**　山本信之**

Key Words : prophylactic cranial irradiation, small cell lung cancer

はじめに

小細胞肺がんは肺がんの約15％を占め，転移をきたしやすく悪性度の高い疾患である[1]．診断時に切除可能であることは非常に少なく，化学療法[2]や放射線療法との同時併用[3][4]が選択される．しかし治療にいったんは奏効を示すものの再発も多く，なかでも脳転移の制御は大きな課題である．小細胞肺がんにおける脳転移は初診時約20％にみられるだけでなく，経過中にも50～65％で発症するとされている[5]．これは疾患としての性質だけでなく，血液脳関門の存在により全身治療である抗がん剤の効果が十分得られないことも一因とされており，実際脳転移に対する化学療法の効果は非常に乏しいことが示されている[6]．

予防的全脳照射(prophylactic cranial irradiation；PCI)はそのような背景からでてきた非常にユニークな治療戦略であり，多くのがん腫の中でも小細胞肺がんにおいてのみ採用される手法である．

本稿では小細胞肺がんに対するPCIの科学的根拠についてこれまでの知見を概説し，日常臨床への応用についてもふれる．

初回治療に完全奏効を示した小細胞肺がんに対するPCI

初回治療(化学療法・放射線療法)でいったん完全奏効(complete response；CR)が得らるものの，初再発として脳転移を呈することが多く経験されたことから，このような症例を対象としたPCIの有効性を検証する臨床試験が1980年代から本邦も含めて複数行われた[7]～[9]．その結果，PCIが脳転移再発を有意に減少させることが示されたものの，生存期間延長に結びつくかについてははっきりしなかった．Auperinらはこれら7つの臨床試験をもとに987名の個々のデータを用いたメタ解析を行い[10]，これによってPCIによる生存期間の延長(3年生存割合15.3％ vs. 20.7％，$P=0.01$)が初めて証明された(図1)．その後，Arriagataらがこのメタ解析で用いられた試験のうち主要な2報について長期成績を報告している(観察期間中央値11年)．結果，5年生存割合はPCI群18％に対し経過観察群15％と有意差はわず

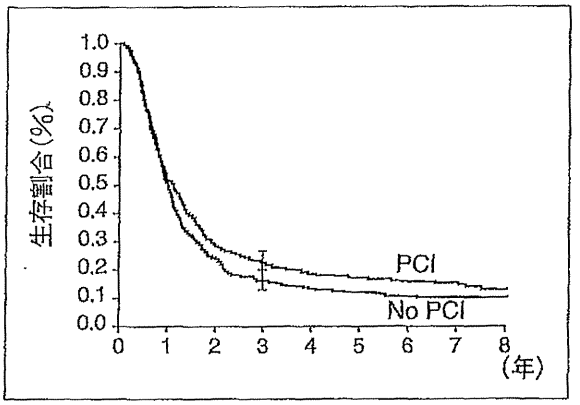

図1　初回治療に完全奏効を示した小細胞肺がんに対するPCIのメタ解析；初めてPCIによる生存期間延長が示された　(文献[10]より引用一部改変)

* Prophylactic cranial irradiation for small cell lung cancer.

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