Results

Patient characteristics

The median patient age was 59 years (range 35–85 years). There were 40 men and 4 women. More than 50% of patients had advanced-stage disease (stage III or IV). The disease stage (I–IV), histological diagnosis (epithelioid, biphasic, or sarcomatoid), and treatment (surgery, chemotherapy, or supportive care) are listed in Table 1.

HLA class I expression in MPMs

Representative images of immunohistochemical staining of HLA class I are shown in Fig. 1a, b. In addition, histogram of percentage of HLA class I expression is illustrated in Fig. 2. All patients had high expression of HLA class I in tumor cells; HLA class I expression was 100% in 33 patients (75%), and the lowest percentage of HLA class I expression was 70%.

Intratumoral lymphocytes in MPMs

Representative images of immunohistochemical staining of TILs are shown in Fig. 1c–e. The TIL counts are shown in Table 2. The densities of $CD4^+$ and $CD8^+$ TILs were strongly correlated ($R = 0.74$, and $p < 0.001$; data not shown). There was no correlation between the presence of intratumoral lymphocytes and major clinical features (data not shown).

Table 1 Patient characteristics ($n = 44$)

Characteristics	
Median age (range)	59 (35–85)
Men	40 (90.9%)
Women	4 (9.1%)
IMIG stage	
I	3 (6.8%)
II	17 (38.6%)
III	21 (47.7%)
IV	3 (6.8%)
Histology	
Epithelioid	26 (59.1%)
Biphasic	14 (31.8%)
Sarcomatoid	4 (9.1%)
Treatment	
Surgery	28 (63.6%)
Chemotherapy	9 (20.5%)
Best supportive care	7 (15.9%)

Association of lymphocyte infiltrates with clinical outcome

We analyzed the survival of 35 patients who underwent either surgical resection or chemotherapy. One patient who underwent surgical resection was excluded from the analysis because immunohistochemical staining of lymphocytes was not evaluable. Among the patients who received surgical resection or chemotherapy, 21 patients had epithelioid type, 10 patients had biphasic type, and 4 patients had sarcomatoid type, while disease stage was stage I in 1 patient, stage II in 12 patients, stage III in 20 patients, and stage IV in 2 patients. We found no significant differences in survival according to the density of $CD8^+$ cells (Fig. 3a). Next, we analyzed the survival of only the patients who underwent surgical resection. Among 27 patients who received surgical resection, 16 patients had epithelioid type, 7 patients had biphasic type, and 4 patients had sarcomatoid type; disease stage was stage II in 10 patients and stage III in 17 patients. Patients with a high density of $CD8^+$ cells (13 patients) had a significantly longer overall survival than those with a low density of $CD8^+$ cells (14 patients) ($p < 0.05$) (Fig. 3b). The prognosis of surgically treated patients with a high density of $CD4^+$ cells tended to be better than that of patients with a low density of $CD4^+$ cells ($p = 0.104$), although this tendency was not statistically significant (data not shown). There were no significant differences in survival according to the density of $CD56^+$ NK cells (data not shown).

In the univariate analysis for the patients who underwent extrapleural pneumonectomy, histology (i.e., epithelioid) and $CD8^+$ TILs (i.e., high density) were identified as significant prognostic factors. Furthermore, multivariate analysis revealed that a high density of $CD8^+$ TILs was an independent prognostic factor in the population (hazard ratio 0.27, 95% CI 0.09–0.83; Table 3).

Discussion

This study assessed both the HLA class I expression and intratumoral T lymphocytes in MPM. We found that the expression of HLA class I antigen was maintained in all of the examined MPMs. Notably, the presence of $CD8^+$ tumor-infiltrating lymphocytes was correlated with the survival of patients who underwent extrapleural pneumonectomy. Taken together, these results demonstrate that $CD8^+$ T cells may adequately recognize the tumor-specific antigens presented by HLA class I antigens in MPM and effectively kill early-stage mesothelioma cells.

Tumor-infiltrating lymphocytes (TILs) are found in cancer tissues. The abundance of tumor-infiltrating $CD8^+$ cells correlates with a good prognosis in colon cancer [8],

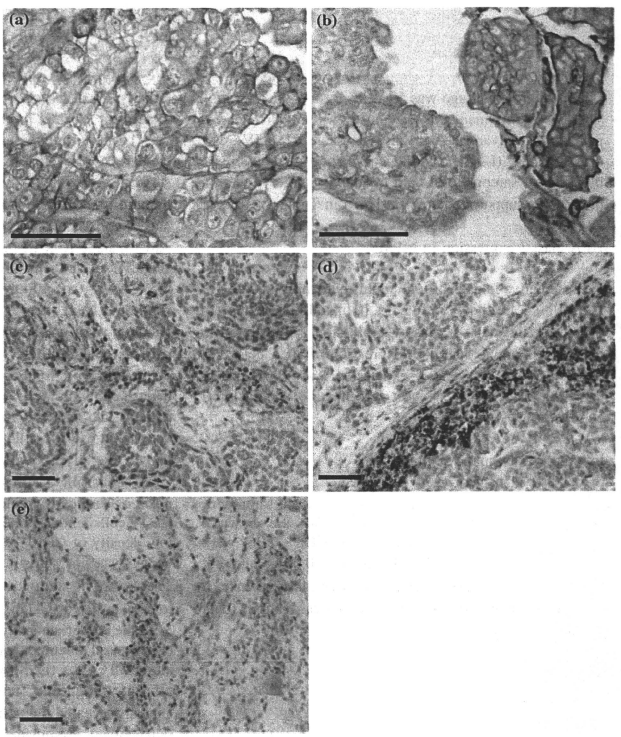

Fig. 1 Representative images of immunohistochemical staining of **a** 100% positive expression of HLA class I, cell membranes of tumor cells are completely stained; **b** 70% positive expression of HLA class I; **c** anti-CD4 antibody; **d** anti-CD8 antibody; and **e** anti-CD56 antibody (*scale bar* 50 μm)

esophageal cancer [15, 16], ovarian cancer [17], and hepatocellular carcinoma [18]. In renal cell carcinoma [19] and lung cancer [13, 20], however, tumor-infiltrating $CD8^+$ cells were not associated with prognosis. Harlin et al. [21] have recently reported that high expression of CXCR3 and CCR5 ligand chemokines generated from tumor are important to promote migration of $CD8^+$ effector cells. Differential expression of these chemokines could lead to differential frequency of lymphocytes infiltrate, which might affect prognosis of the patients. In addition, the origin and stage (early or advanced) of the tumor or subsequent therapy against the disease might account for the discrepancy of prognosis.

Therefore, we analyzed survival in a homogenous population of patients who had resectable MPMs and underwent extrapleural pneumonectomy. Gao et al. [18] reported that the intratumoral balance of regulatory and cytotoxic T cells is an independent predictor of recurrence and survival after resection of hepatocellular carcinoma. The immune defense elucidated by cytotoxic T cells might be more effective in the operable tumors which correspond to the earlier stages of the disease. Cytotoxic T cells (or reactivated T cells from memory phase) are expected to suppress the initial recurrence or metastasis after surgical treatment.

Some studies have assessed TILs in MPM [22–24]. Leigh et al. [22] reported that the presence of significant lymphoid infiltration indicates a better prognosis for longer survival. However, the TILs and their subsets were analyzed by using hematoxylin–eosin staining, but not by immunohistochemical staining. Mudhar et al. [23] analyzed the TILs in MPM by immunohistochemical staining and reported no association between survival and the prominence of the infiltrate of pan leukocytes, T cells, or NK cells in 15 MPM cases. Recently, Anraku et al. [24]

reported that the presence of high levels of $CD8^+$ tumor-infiltrating lymphocytes was associated with a better prognosis in patients undergoing extrapleural pneumonectomy. Although the results from these previous reports vary, they have shed light on the importance of T lymphocytes for antitumor immunity in MPM, which is consistent with our results.

The expression of HLA class I antigen is totally lost or downregulated in many types of tumors. Marincola et al. [25] reported that the frequency of the total loss or downregulation of HLA class I ranged from 31 to 70% among various types of tumors. In lung cancer, the frequency of total loss ranged from 27 to 80.5%, and the frequency of the downregulation of HLA class I ranged from 13.2 to 35.4% [13, 26–28]. In the present study, the expression of HLA class I was positive in all MPM patients, whereas there was no case that completely lacked HLA class I expression. This finding indicates that MPM might be a type of tumor in which HLA class I expression is relatively maintained. The high HLA class I expression in the present study may be attributed to the novel antibody EMR8-5, which can react with the heavy chains of all alleles of HLA-A, B and C in formalin-fixed, paraffin-embedded tissue sections [29]. Another antibody, HC10, has been used in many previous studies; this antibody preferentially reacts with HLA-B and C but weakly reacts with HLA-A.

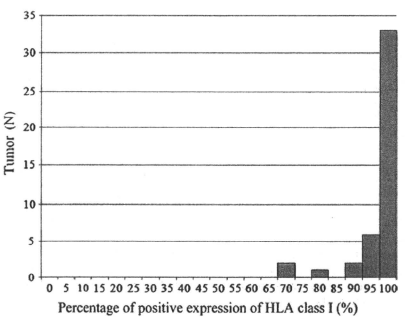

Fig. 2 Histogram of percentage of HLA class I expression; 100% of HLA class I expression in 33 patients (75%), 95% in 6 patients (14%), 90% in 2 patients (4%), 80% in 1 patient (2%), and 70% in 2 patients (4%)

Table 2 The numbers of TILs per slide

	Mean ± SD	Range	Median
$CD4^+$ TILs	51.1 ± 41.8	0.2–159.7	37.3
$CD8^+$ TILs	103.3 ± 106.9	8.8–547.5	64.5
$CD56^+$ TILs	5.4 ± 8.3	0.0–41.8	1.8

Past studies assessed Ki-67 [20] and granzyme B [30]; activation markers of $CD8^+$ TILs and reported the association between these activation markers and prognosis. Helper $CD4^+$ cells play a pivotal role in the activation and expansion of $CD8^+$ T cells [31]. In contrast, regulatory T cells which express the $CD4^+$, $CD25^+$ and Foxp3 phenotype are found in the tumor microenvironment and are thought to dampen T cell immunity [32]. The activation markers of $CD8^+$ T cells and phenotype of $CD4^+$ T cells were not evaluated in the present study. However, infiltration of $CD8^+$ T cells predicted favorable prognosis and there was the strong correlation between frequency of $CD8^+$ and $CD4^+$ T cells, suggesting that both type of cells would interact each other and subsequently orchestrate antitumor immune response.

In conclusion, we found that all of the MPM patients in our study were positive for the expression of HLA class I antigen and that a high density of $CD8^+$ TILs was a significant prognostic factor for longer survival in surgically resected MPMs. These results suggest that $CD8^+$ TILs have an important role in antitumor immunity of patients with MPM and that the stimulation of $CD8^+$ lymphocytes can be a potential therapeutic strategy for the disease. Although several immunotherapies for MPM, intralesional granulocyte–macrophage colony-stimulating factor infusion [33], intrapleural interleukin-2 [34], interferon alpha

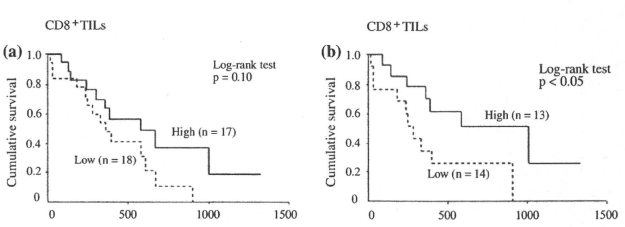

Fig. 3 Kaplan–Meier curves show overall survival after treatment (extrapleural pneumonectomy or chemotherapy) according to the density of $CD8^+$ TILs (**a**), and overall survival after extrapleural pneumonectomy according to the density of $CD8^+$ TILs (**b**)

Table 3 Univariate and multivariate analysis with the Cox proportional hazards model for patients who underwent extrapleural pneumonectomy

Variable	Univariate		Multivariate	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Histology				
Epithelioid versus non-epithelioid	0.24 (0.08–0.7)	<0.01	0.19 (0.06–0.6)	<0.01
Age (years)				
≥65 versus <65	1.18 (0.4–3.49)	0.76		
Sex				
Women versus men	1.23 (0.27–5.58)	0.79		
Stage				
III + VI versus I + II	1.48 (0.52–4.2)	0.47		
$CD4^+$ TILs				
High versus low	0.42 (0.14–1.24)	0.12		
$CD8^+$ TILs				
High versus low	0.34 (0.12–0.99)	<0.05	0.27 (0.09–0.83)	<0.05
$CD56^+$ TILs				
High versus low	0.66 (0.25–1.78)	0.41		

HR hazards ratio, *CI* confidence interval

[35], and recombinant anti-mesothelin immunotoxin SS1P [36, 37] have been tested, none of them are available for clinical practice. Further investigations on immunological function or specific antigens are warranted to develop robust immunotherapies against MPM.

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Phase II Study of Sequential Triplet Chemotherapy, Irinotecan and Cisplatin Followed by Amrubicin, in Patients with Extensive-Stage Small Cell Lung Cancer: West Japan Thoracic Oncology Group Study 0301

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Introduction: Combination chemotherapy of irinotecan, a topoisomerase I inhibitor, and cisplatin is a standard treatment in patients with extensive-stage small cell lung cancer (SCLC). Amrubicin, a novel 9-aminoanthracycline, inhibits topoisomerase II. We investigated a sequential triplet chemotherapy consisting of irinotecan and cisplatin followed by amrubicin in patients with extensive-stage SCLC.

Methods: Eligible patients were aged 20 to 70 years and had Eastern Cooperative Oncology Group performance status of 0 or 1, measurable lesions, and adequate organ functions. Chemotherapy consisted of irinotecan 60 mg/m^2 on days 1 and 8 plus cisplatin 60 mg/m^2 on day 1 every 3 weeks for three cycles and then amrubicin 40 mg/m^2 alone on days 1 to 3 every 3 weeks for three cycles.

Results: From September 2004 to September 2006, 45 patients were enrolled, 43 were evaluable for response and survival, and 44 were evaluable for toxicity. Twenty-eight patients (64%) completed the full planned chemotherapy. One patient achieved complete response and 33 had partial response for an overall response rate of 79%. Median progression-free survival was 6.5 months. Median overall survival was 15.4 months. Major toxicity was myelosuppression. Grade 3 or 4 neutropenia, anemia, thrombocytopenia, and febrile neutropenia occurred in 57%, 7%, 0%, and 7% of patients during irinotecan/cisplatin cycles and in 91%, 27%, 9%, and 15% of patients during amrubicin cycles, respectively.

Conclusions: The sequential triplet chemotherapy, irinotecan and cisplatin followed by amrubicin, is an effective and well-tolerated treatment in patients with extensive-stage SCLC. Further investigation of this treatment is warranted.

Key Words: Amrubicin, Small cell lung cancer, Sequential chemotherapy, Triplet chemotherapy.

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Small cell lung cancer (SCLC) accounts for approximately 15% of all lung cancers. Disease extension of SCLC is classified as limited stage or extensive stage. Limited-stage SCLC is defined as tumor confined to the hemithorax of origin, the mediastinum, and the supraclavicular lymph nodes, whereas extensive-stage SCLC as tumor spread outside these limits. For extensive-stage SCLC, chemotherapy is the mainstay of treatment. SCLC is highly sensitive to chemotherapy, with a response rate of 70% to 90% in first-line treatment. However, for most patients with extensive-stage SCLC, the disease recurs within several months, and the 5-year survival rate is less than 1%.[1] It is necessary to develop a new treatment for this serious disease.

Irinotecan, a derivative of camptothecin, inhibits topoisomerase I and shows strong antitumor effect for SCLC. The Japan Clinical Oncology Group conducted a randomized phase III trial (JCOG 9511) comparing irinotecan plus cis-

platin with etoposide plus cisplatin in patients with extensive-stage SCLC.[2] This trial was terminated early, because of a highly statistically significant difference in survival between the two arms. The median overall survival was 12.8 months in the irinotecan/cisplatin arm and 9.4 months in the etoposide/cisplatin arm ($p = 0.002$). In Japan, the combination of irinotecan and cisplatin is recognized as a standard treatment for extensive-stage SCLC.

Amrubicin, a novel 9-aminoanthracycline, inhibits topoisomerase II[3] and also shows strong antitumor effect for SCLC. The West Japan Oncology Group, formerly named the West Japan Thoracic Oncology Group (WJTOG), conducted a phase II study of amrubicin in previously untreated patients with extensive-stage SCLC.[4] In 35 patients treated, a response rate of 76% and a median overall survival of 11.7 months were shown. These figures compare favorably with standard doublet chemotherapy.

Some preclinical studies reported that a combination of topoisomerase I and II inhibitors shows a synergistic cytotoxicity.[5] For SCLC, a combination of this type, irinotecan and etoposide (a topoisomerase II inhibitor), was investigated clinically and showed promising results.[6,7] The similar combination of irinotecan and amrubicin is worthwhile to investigate.

Concurrent administration of a triplet combination requires dose reduction of each drug because of toxicities, especially myelosuppression. A sequential chemotherapy, i.e., a doublet followed by the other drug, can be used to avoid the need for dose reduction. In addition, Norton and Simon[8] presented a theoretical model describing the possibility of a sequential chemotherapy.

Therefore, we investigated a sequential triplet chemotherapy consisting of irinotecan and cisplatin followed by amrubicin in patients with extensive-stage SCLC (WJTOG 0301). The purpose of this study was to evaluate the efficacy and safety of this treatment.

PATIENTS AND METHODS

Patient Selection

Eligible patients were aged 20 to 70 years, had histologically or cytologically proven SCLC, extensive-stage disease, Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1, no prior chemotherapy, neither palliative radiation nor surgery of 14 days, measurable lesions, life expectancy of at least 2 months, and adequate organ functions (white blood cell [WBC] $\geq$4000/μL, neutrophil $\geq$2000/μL, platelet $\geq$100,000/μL, hemoglobin $\geq$10 g/dL, aspartate aminotransferase [AST] and alanine aminotransferase [ALT] $\leq$2 $\times$ upper limit of normal [ULN], total bilirubin $\leq$1.5 $\times$ ULN, creatinine $\leq$ULN, arterial partial pressure of oxygen $\geq$60 mm Hg, no abnormality requiring treatment on electrocardiogram, and left ventricular ejection fraction on echocardiogram $\geq$60%). Patients with any of the following conditions were excluded: symptomatic brain metastases, pleural or pericardial effusion requiring drainage, interstitial pneumonitis, active infection, watery diarrhea or ileus, active gastroduodenal ulcer, continuous administration of steroid or nonsteroidal anti-inflammatory drug, uncontrolled diabetes mellitus or angina pectoris, other active malignancy, and pregnancy or lactation.

All patients gave written informed consent. This study was approved by the institutional review boards at each participating institution.

Treatment Schedule

Chemotherapy consisted of irinotecan 60 mg/m^2 on days 1 and 8 plus cisplatin 60 mg/m^2 on day 1 every 3 weeks for 3 cycles and then amrubicin 40 mg/m^2 alone on days 1 to 3 every 3 weeks for three cycles. Irinotecan was administered as a 90-minute intravenous infusion, cisplatin as a 90-minute intravenous infusion with adequate hydration, and amrubicin as a 5-minute intravenous injection. Prophylactic administration of granulocyte colony-stimulating factor (G-CSF) was allowed at the discretion of the treating physician.

The minimum requirements for the administration of irinotecan and cisplatin were as follows: WBC $\geq$3000/μL, neutrophil $\geq$1500/μL, platelet $\geq$100,000/μL, AST and ALT $\leq$2.5 $\times$ ULN, total bilirubin $\leq$1.5 $\times$ ULN, creatinine $\leq$ULN, PS of 0 to 2, body temperature $\leq$37.5°C, no diarrhea, no interstitial pneumonitis, and other nonhematological toxicity $\leq$grade 2. The minimum requirements for administration of day-8 irinotecan were as follows: WBC $\geq$3000/μL, platelet $\geq$100,000/μL, body temperature $\leq$37.5°C, no diarrhea, no interstitial pneumonitis, and other nonhematological toxicity $\leq$grade 2. The minimum requirements for administration of amrubicin were as follows: WBC $\geq$3000/μL, neutrophil $\geq$1500/μL, platelet $\geq$100,000/μL, AST and ALT $\leq$2.5 $\times$ ULN, total bilirubin $\leq$1.5 $\times$ ULN, creatinine $\leq$1.5 $\times$ ULN, PS of 0 to 2, body temperature $\leq$37.5°C, no interstitial pneumonitis, and other nonhematological toxicity $\leq$grade 2.

If any of the following toxicities was observed, the doses of irinotecan, cisplatin, and amrubicin were reduced to 50, 50, and 35 mg/m^2, respectively: WBC $<$1000/μL, febrile neutropenia (neutrophil $<$1000 /μL), platelet $<$25,000 /μL, or grade 3 nonhematologic toxicity. If creatinine $>$ULN, the dose of cisplatin was reduced to 50 mg/m^2. If creatinine $>$2.0 mg/dL, the administration of cisplatin was discontinued. If grade 4 nonhematological toxicity or pneumonitis $\geq$grade 2 was observed, the study treatment was stopped.

Response and Toxicity Evaluation

Before treatment, a complete medical history was obtained, and physical examination was performed. The following examinations were carried out: complete blood count (CBC) with differential WBC count, blood chemistry, arterial blood gas analysis, urinalysis, electrocardiography, and echocardiography. Staging procedures consisted of chest radiograph, computed tomography (CT) of chest and upper abdomen, magnetic resonance imaging (MRI) or CT of brain, bone scintigraphy, and bone marrow aspiration. During treatment, CBC with differential WBC count, blood chemistry, and chest radiograph were examined at least once a week, and electrocardiography and CT and/or MRI for response evaluation were examined once a month. After treatment, chest radiograph was performed once a month, and CT and/or MRI were performed every 3 months.

Response was evaluated according to the Response Evaluation Criteria in Solid Tumors.[9] Extramural review of eligibility and response of all patients were performed. Toxicity was evaluated in accordance with the Common Terminology Criteria for Adverse Events, Version 3.0.[10]

Statistical Analysis

The primary end point of this study was response rate. Secondary end points were progression-free survival (PFS), overall survival, and toxicity. Survival curves were drawn using the Kaplan-Meier method.[11]

Assuming that a response rate of 90% would indicate potential usefulness, whereas a rate of 75% would be the lower limit of interest, with $\alpha = 0.05$ (one side) and $\beta = 0.20$, 38 patients were required. Allowing for a 15% loss to follow-up, enrollment of a total of 45 patients was planned.

RESULTS

Patient Characteristics

From September 2004 to September 2006, 45 patients were enrolled in this study. Two patients had limited-stage disease. One patient, who was able to receive thoracic radiation, was excluded from all analyses. The other patient, who was not able to receive thoracic radiation due to pleural dissemination, was included in analysis of toxicity and excluded from analysis of response and survival. Therefore, 43 patients were evaluable for response and survival, and 44 were evaluable for toxicity.

Patient characteristics are shown in Table 1. The median age was 63 years, 37 patients (84%) were men, and 31 patients (70%) had PS of 1. Thirty-nine patients (89%) had distant metastases. Frequent sites of distant metastases were brain, liver, bone, and adrenal gland. Of five patients without distant metastases, four had contralateral hilar lymph node involvement and one had pleural dissemination. No patient received prior treatment, including surgery and radiation.

TABLE 1. Patient Characteristics ($n = 44$)

Characteristic	n (%)
Sex	
Male	37 (84)
Female	7 (16)
Age (yr)	
Median (range)	63 (47–70)
ECOG performance status	
0	13 (30)
1	31 (70)
Distant metastases	
Present	39 (89)
Absent	5 (11)
Sites of distant metastasis	
Brain	10 (23)
Liver	10 (23)
Bone	10 (23)
Adrenal gland	10 (23)
Lymph node	7 (16)
Lung	6 (14)
Bone marrow	3 (7)
Other	3 (7)
Prior therapy	
None	44 (100)

ECOG, Eastern Cooperative Oncology Group.

TABLE 2. Treatment Delivery ($n = 44$)

Treatment Cycle	n (%)
Irinotecan/cisplatin	
Cycle 1	44 (100)
Cycle 2	40 (91)
Cycle 3	37 (84)
Amrubicin	
Cycle 1	33 (75)
Cycle 2	30 (68)
Cycle 3	28 (64)

TABLE 3. Tumor Response ($n = 43$)

	n (%)
Complete response	1 (2)
Partial response	33 (77)
Stable disease	1 (2)
Progressive disease	3 (7)
Not evaluable	5 (12)
Overall response	34 (79) (95% CI, 64–90)

CI, confidence interval.

Treatment Delivery

Of 44 patients, 37 patients (84%) received three cycles irinotecan/cisplatin and 28 patients (64%) completed the full planned chemotherapy, i.e., three cycles irinotecan/cisplatin followed by three cycles amrubicin (Table 2). Dose reduction of irinotecan/cisplatin and amrubicin was necessary in six and seven patients, respectively.

Response and Survival

Of 43 patients, 1 achieved complete response and 33 had partial response, for an overall response rate of 79% (95% confidence interval, 64–90%) (Table 3). Of the 33 partial responders, tumor shrinkage met partial response criteria during an irinotecan/cisplatin cycle in 30 patients and during an amrubicin cycle in 3. In the complete responder, tumor disappearance was achieved during an irinotecan/cisplatin cycle.

The survival curves are shown in Figure 1. The median PFS was 6.5 months (95% confidence interval, 4.9–7.4 months), with a 1-year survival rate of 8%. The median overall survival was 15.4 months (95% confidence interval, 11.7–18.0 months), with a 1-year survival rate of 61%.

Chemotherapy After Progression (Second-Line Treatment)

Thirty-five patients received chemotherapy after progression as follows: etoposide plus carboplatin in 10 patients;

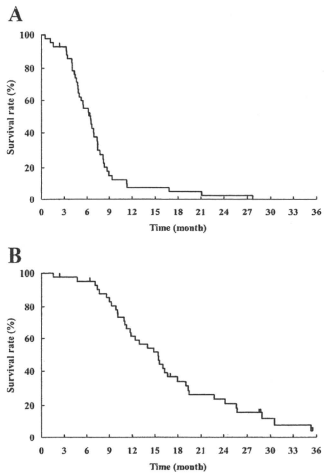

FIGURE 1. Survival curves (n = 43). *A*, Progression-free survival, median 6.5 months (95% confidence interval, 4.9–7.4 months), with a 1-year survival rate of 8%. *B*, Overall survival, median 15.4 months (95% confidence interval, 11.7–18.0 months), with a 1-year survival rate of 61%.

irinotecan plus cisplatin in 6; amrubicin in 5; topotecan plus carboplatin in 4; irinotecan plus amrubicin in 2; irinotecan in 2; and irinotecan plus etoposide, irinotecan plus carboplatin, etoposide plus cisplatin, etoposide, topotecan, and cyclophosphamide plus doxorubicin plus vincristine in 1 patient each.

Toxicity

Toxicities during irinotecan/cisplatin cycles are listed in Table 4. Of 44 patients, grade 3 or 4 leukopenia, neutropenia, anemia, thrombocytopenia, and febrile neutropenia occurred in 6 (14%), 25 (57%), 3 (7%), 0 (0%), and 3 patients (7%), respectively. G-CSF was administered in 12 patients (27%). One patient received transfusion of red blood cell concentrates. One patient (2%) developed grade 3 diarrhea. Grade 3 anorexia was observed in seven patients (16%).

Toxicities during amrubicin cycles are listed in Table 5. Of 33 patients, grade 3 or 4 leukopenia, neutropenia, anemia, thrombocytopenia, and febrile neutropenia occurred in 15 (45%), 30 (91%), 9 (27%), 3 (9%), and 5 patients (15%), respectively. G-CSF was administered in 20 patients (61%). One patient received transfusion of red blood cell concentrates and platelet concentrates, and two other patients received transfusion of red blood cell concentrates. Nonhematological toxicity was not common. One patient (3%) developed grade 3 pneumonitis. This patient was treated with steroid pulse therapy and recovered soon thereafter. No treatment-related death was observed.

TABLE 4. Toxicities During the Irinotecan/Cisplatin Cycle (n = 44)

	Grade					
	0	1	2	3	4	≥3
WBC	11	15	12	4	2	6 (14%)
Neutrophil	9	1	9	20	5	25 (57%)
Hemoglobin	3	23	15	3	0	3 (7%)
Platelet	24	19	1	0	0	0 (0%)
Febrile neutropenia	41	0	0	3	0	3 (7%)
AST/ALT	24	15	3	2	0	2 (5%)
Creatinine	35	7	2	0	0	0 (0%)
Nausea	14	14	12	4	0	4 (9%)
Vomiting	24	11	7	2	0	2 (5%)
Anorexia	11	19	7	7	0	7 (16%)
Fatigue	13	21	8	2	0	2 (5%)
Diarrhea	28	10	5	1	0	1 (2%)
Pneumonitis	44	0	0	0	0	0 (0%)
Infection	39	0	3	2	0	2 (5%)
Rash	37	6	0	1	0	1 (2%)

WBC, white blood cell; AST, aspartate aminotransferase; ALT, alanine aminotransferase.

TABLE 5. Toxicities During the Amrubicin Cycle (n = 33)

	Grade					
	0	1	2	3	4	≥3
WBC	0	3	15	12	3	15 (45%)
Neutrophil	1	0	2	18	12	30 (91%)
Hemoglobin	0	5	19	5	4	9 (27%)
Platelet	13	13	4	0	3	3 (9%)
Febrile neutropenia	28	0	0	5	0	5 (15%)
AST/ALT	25	8	0	0	0	0 (0%)
Creatinine	30	3	0	0	0	0 (0%)
Nausea	18	12	3	0	0	0 (0%)
Vomiting	31	2	0	0	0	0 (0%)
Anorexia	17	12	3	1	0	1 (3%)
Fatigue	10	18	4	1	0	1 (3%)
Diarrhea	31	1	1	0	0	0 (0%)
Pneumonitis	31	1	0	1	0	1 (3%)
Infection	29	0	2	2	0	2 (6%)
Rash	30	2	1	0	0	0 (0%)

WBC, white blood cell; AST, aspartate aminotransferase; ALT, alanine aminotransferase.

DISCUSSION

We performed a phase II study of sequential triplet chemotherapy consisting of irinotecan and cisplatin followed by amrubicin in patients with extensive-stage SCLC and demonstrated a response rate, median PFS, and median overall survival of 79%, 6.5 months, and 15.4 months, respectively. The primary end point of this study was response rate, and the expected and the threshold rates were set 90% and 75%, respectively. The actual response rate in this study (79%) was lower than the expected rate but higher than the threshold. JCOG 9511 reported a response rate, median PFS, and median overall survival of

irinotecan/cisplatin arm of 84%, 6.9 months, and 12.8 months, respectively.[2] Comparing this study with JCOG 9511, the response rate and PFS were similar, whereas overall survival was longer in this study. Taking the longer overall survival into consideration, the results of this study were regarded as promising. There is a possibility that the exclusion of PS 2 patients in this study, which were included in JCOG 9511, could have resulted in the longer overall survival. In addition, we could not find any specific trend that would show prolonged overall survival among second-line treatments.

Two randomized trials that compared irinotecan/cisplatin with etoposide/cisplatin were conducted mainly in North America as confirmation studies of JCOG 9511. One was reported by Hanna et al.[12] and the other was conducted by the Southwest Oncology Group (S0124).[13] Although JCOG 9511 showed survival advantage in the irinotecan/cisplatin arm over the etoposide/cisplatin arm, these North American trials did not show significant difference between the two arms. Irinotecan/cisplatin is a standard chemotherapy for SCLC in Japan, whereas etoposide/cisplatin remains standard in North America. It was reported that the response rate, median PFS, and median overall survival of irinotecan/cisplatin arm were 48%, 4.1 months, and 9.3 months in the trial by Hanna et al. and 60%, 5.7 months, and 9.9 months in S0124, respectively. This study showed better survival than the North American trials. However, great caution is needed when comparing this study with the North American trials. S0124 reported the possibility that inherent genetic differences might exist between the study populations, resulting in divergent outcomes with the same cytotoxic agents.[13] A similar suggestion was made for non-small cell lung cancer.[14] Population-related pharmacogenomics is important because the varied results for the same treatment could be attributed to ethnic differences.

Clinical studies of amrubicin for SCLC had been performed, in both first-line and second-line treatment, entirely in Japan.[15] The WJTOG study in first-line treatment reported a response rate of 76% and median overall survival of 11.7 months.[4] These figures compare favorably with standard doublet chemotherapy. Onoda et al.[16] conducted a phase II study of amrubicin in second-line treatment. They treated 16 patients with refractory disease and 44 patients with sensitive relapsed disease and demonstrated a response rate and median overall survival of 50% and 10.3 months in the refractory group and 52% and 11.6 months in the sensitive group, respectively. Furthermore, the North Japan Lung Cancer Study Group conducted a randomized phase II trial of amrubicin in comparison with topotecan in second-line treatment.[17] That trial showed a response rate and median PFS of 38% and 3.5 months for the amrubicin arm and 13% and 2.2 months for the topotecan arm, respectively. Multivariate analysis revealed that amrubicin has more influence than topotecan on overall survival. Amrubicin is one of the most promising new drugs for the treatment of SCLC.

The ECOG reported a phase III trial of topotecan versus observations after cisplatin and etoposide in extensive-stage SCLC.[18] They showed that four cycles of cisplatin/etoposide induction therapy followed by four cycles of topotecan improved PFS but failed to improve overall survival or quality of life in extensive-stage SCLC. Results of the North Japan Lung Cancer Study Group trial suggested that amrubicin is more effective than topotecan for SCLC. The ECOG trial failed to show survival benefit; however, it did show that amrubicin, instead of topotecan, has potential to lead to better survival in extensive-stage SCLC.

Bozcuk et al.[19] reported a meta-analysis of maintenance/consolidation chemotherapy in the management of SCLC. They analyzed 14 randomized trials, encompassing 2550 patients, and concluded that maintenance/consolidation chemotherapy improves survival in SCLC. Sequential amrubicin was stopped for three cycles in this study. If further cycles of amrubicin as maintenance treatment are given, PFS might be further prolonged.

The major toxicity of sequential amrubicin was myelosuppression, whereas nonhematological toxicity was not common. In the above-mentioned WJTOG study, amrubicin was administered at 45 mg/m^2 on days 1 to 3 as monotherapy.[4] To avoid severe myelosuppression in this study, amrubicin was decreased to 40 mg/m^2 on days 1 to 3 as sequential chemotherapy. This study confirmed that this dose of sequential amrubicin was feasible.

Kaneda et al.[20] reported a phase I study of irinotecan and amrubicin. They administered irinotecan on days 1 and 8 and amrubicin on days 1 to 3. They concluded that this combination was not tolerated because of severe myelosuppression. Although concurrent combination of irinotecan and amrubicin is not tolerable, this study showed that sequential combination of these drugs is tolerable. Irinotecan and amrubicin were administered without G-CSF support in both this study and the study by Kaneda et al.

In conclusion, the sequential triplet chemotherapy of irinotecan and cisplatin followed by amrubicin is an effective and well-tolerated treatment in patients with extensive-stage SCLC. Further investigation of this treatment is warranted.

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医薬品相互作用研究
総　説
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ゲフィチニブによる非小細胞肺癌に対する個別化医療

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Key Words: Non-small-cell lung cancer, EGFR, EGFR-TKI

はじめに

肺癌は、本邦における癌死亡原因の第一位であり、年間約85,000人が罹患し約70,000人が死亡している。この高い死亡率は、早期発見が困難であり、手術不能例の予後が極めて不良であることを示している。肺癌は病理組織診断により、小細胞肺癌と、それ以外の全ての組織型を包括する非小細胞肺癌(NSCLC)に大別される。発生頻度でみると、非小細胞肺癌が圧倒的に多く、その中でも腺癌の頻度が最も高い。手術不能非小細胞肺癌の全身療法では化学療法が中心的役割を果たしてきたが、多くの臨床試験で示されている生存期間やQOL(Quality of Life)の改善は統計学的に有意な結果であれ、わずかな改善にとどまっていた。近年の分子生物学的手法の進歩は、癌細胞の増殖や転移のメカニズムを分子レベルで解明し、それに基づく創薬、つまり分子標的治療薬の出現につながった。非小細胞肺癌では上皮成長因子受容体チロシンキナーゼ阻害薬が、効果予測因子としての遺伝子変異が発見されたことから、個別化医療への応用の点で特に注目されている。本稿では主にゲフィチニブについて、がん個別化医療の観点を中心に概説する。

上皮成長因子受容体チロシンキナーゼ阻害薬

上皮成長因子受容体(EGFR)はerbB受容体ファミリーに属する膜貫通型受容体蛋白で、細胞外リガンド結合ドメイン、膜貫通ドメイン、細胞内チロシンキナーゼドメインより構成される。リガンドであるEGFなどの増殖因子が結合すると二量体を形成し、細胞内チロシンキナーゼのATP結合部位にATPが結合することで活性が亢進し、さらにその下流のシグナル伝達系が活性化される。これら一連のシグナル伝達系の活性化は細胞の増殖、血管新生、浸潤、転移、アポトーシスの抑制などを起こす（図１）。低分子チロシンキナーゼ阻害薬は、標的とするチロシンキナーゼのATP結合部位にATPと競合的に結合することでチロシンキナーゼ活性を阻害する。生体内に100種類以上存在するチロシンキナーゼのATP結合部の構造は類似しているが、上皮成長因子受容体チロシンキナーゼ阻害薬(EGFR-TKI)であるゲフィチニブやエルロチニブはEGFR(ERB B1/HER1)を選択的に阻害する。

臨床的背景因子のよる個別化医療の試み

ゲフィチニブは世界に先駆けて、2002年に我が国において承認されている。日本、ヨーロッパ、オーストラリアの共同で行われた第Ⅱ相試験（IDEAL 1）では全体での奏功率が18.4％、日本人27.5％、日本人以外10.4％と人種差があり、日本人（アジア人）で有効性が高いことが示された[1]。その後に実施された臨床試験や日本での大規模な後ろ向き解析では腺癌、女性、非喫煙者、アジア人に有効性が高く、これら臨床因子が効果予測因子であることが示された[2,3]。これらの結果をもとに、アジア人、非～軽喫煙者、腺癌を対象とした、初回治療でのゲフィチニブと標準化学療法（カルボプラチン＋パクリタキセル）の無作為化第Ⅲ相試験（IPASS:IRESSA Pan-Asia Study）が日本を含む東アジア9カ国で実施された。約1200例が参加したこの試験では、主要評価項目である無増悪生存期間（PFS）はゲフィ

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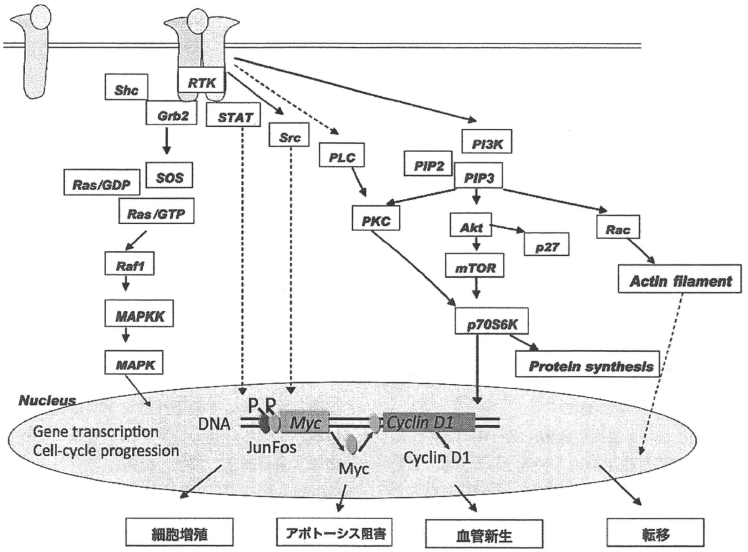
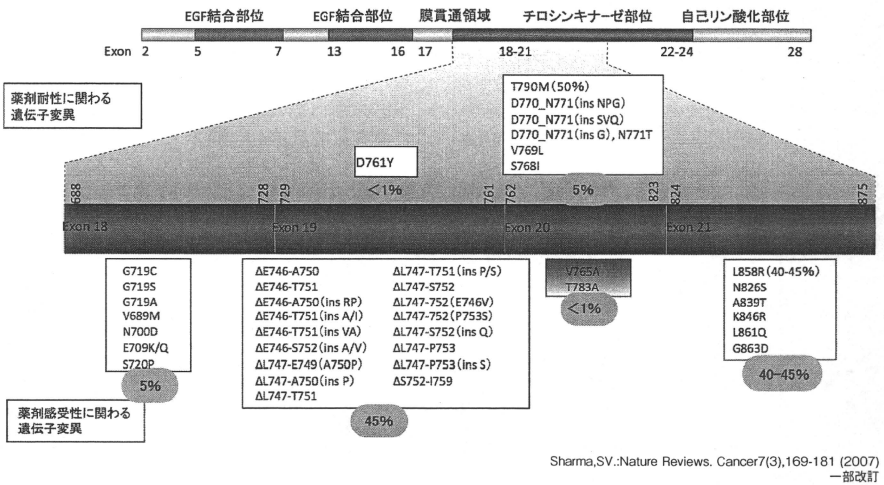


図1　EGFR系によるシグナルの流れと関与する蛋白



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一部改訂

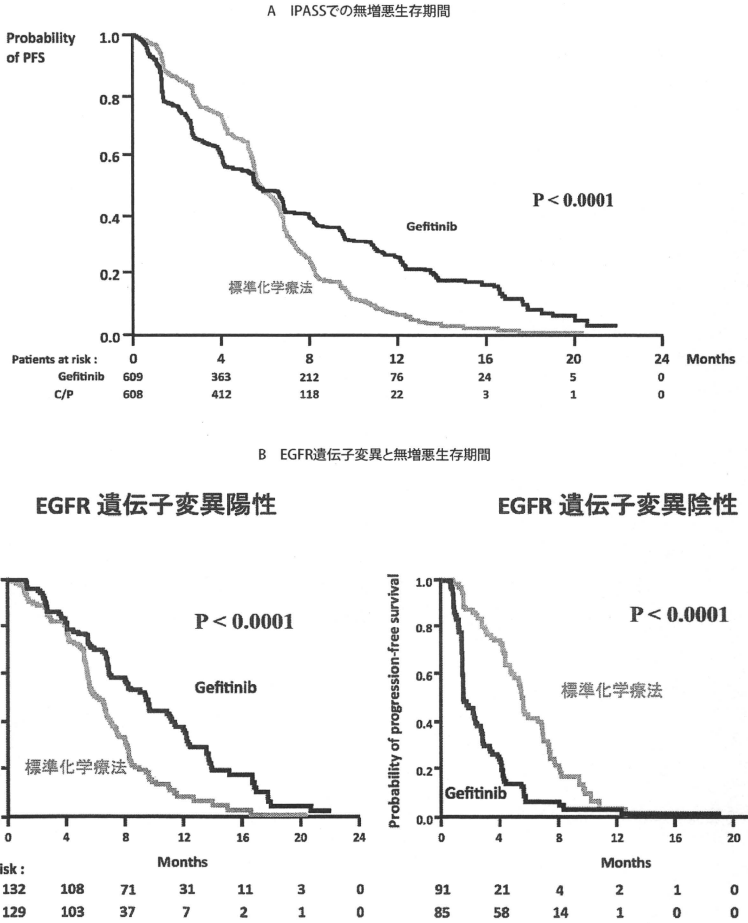
図2　EGFR遺伝子変異の種類とその頻度　（エクソン18-21）

チニブの標準化学療法に対するハザード比0.74 (p<0.001)、中央値はゲフィチニブ群5.7ヶ月、標準化学療法群5.8ヶ月で、ゲフィチニブ群の非劣性、優越性が示された（図3A）[4]。副次評価項目の奏功率はゲフィチニブ群43%、標準化学療法群32% (p<0.001)で、QOLについてもゲフィチニブ群の優越性が示されている。この試験では、臨床的効果予測因子で選別した患者群におけるゲフィチニブによる初回治療の有用性が示された。

バイオマーカーに基づいた個別化治療

臨床的背景因子によりゲフィチニブに対する効果予測がある程度可能であるとするこれらの成績は、真の効果予測因子であるバイオマーカー発見への研究を加速させた。2004年、ついにEGFRの特定部位における遺伝子変異が、ゲフィチニブの効果予測因子である可能性が2つの論文によって示された[5][6]。EGFR遺伝子変異はチロシンキナーゼ領域に限局し、とくにexon21の5アミノ酸欠失変異とexon21のL858R点突然変異が約90%を占める(図2)。これらの変異はリン酸化が持続す

図3　IPASSでの無増悪生存期間（文献4より引用）



る活性型変異であり、EGFR-TKIに対する親和性が増強している。その後、EGFR遺伝子変異陽性のNSCLCを対象としたゲフィチニブの初回治療における前向き第Ⅱ相試験が複数実施され、その統合解析の結果が報告された(ICAMP)[7]。後ろ向き試験も含めたこれらの成績ではEGFR遺伝子変異陽性例での奏功率は70～80%、変異陰性例では10%未満であった。さらに、前述のIPASS試験では、副次評価項目として行われた、EGFR遺伝子変異などのバイオマーカー別の治療成績が示された。EGFR遺伝子変異陽性例ではゲフィチニブ群が標準化学療法より明らかに優れており、奏功率ではゲフィチニブ71%、標準化学療法43%であった(図3B)。一方、EGFR遺伝子変異陰性例では逆に標準化学療法群で有意にPFSが良好であることが示された。

EGFR遺伝子変異陽性例における初回ゲフィチニブ療法

IPASSで示されたEGFR遺伝子変異陽性例での有用性は、あくまでも後解析として示されたものである。そこで、EGFR遺伝子変異陽性例でのゲフィチニブの初回治療としての有用性を検討する2つの前向き試験が本邦で実施された(NEJ002, WJTOG 3405)。2つの第Ⅲ相臨床試験ではシスプラチン+ドセタキセル(WJTOG 3405)、カルボプラチン+パクリタキセル(NEJ002)を標準化学療法として、ゲフィチニブと比較している。WJTOG3405では、PFSでのゲフィチニブの優越性が示された(ゲフィチニブ群9.2ヶ月、標準化学療法群6.3ヶ月、ハザード比0.489、p<0.001)[8]。NEJ002では初回治療としてのゲフィチニブがPFSで標準化学療法に勝ることを検証するために320例の集積を目標として開始された。しかし、200例での中間解析においてPFS中央値でゲフィチニブ群の明らか優越性が示されたため、試験は中止された。総計230例が登録され、PFS(中央値)がゲフィチニブ群10.8ヶ月、標準化学療法群5.4ヶ月(ハザード比0.3、p<0.001)であった[9](図4A)。両グループの全生存期間に有意差は無かったが(図4B)、ゲフィチニブ群30.5ヶ月、標準化学療法群23.6ヶ月と良好な傾向にあり、毒性面を考慮すると概ねイレッサ群で軽い傾向にあった。ゲフィチニブ群では間質性肺炎での死亡例を1例認めている。これらの前向き試験により、初回治療におけるゲフィチニブの意義が確認された。

おわりに

ゲフィチニブによる非小細胞肺癌に対する個別化医療について概説した。EGFR-TKI に続き、EML4-ALKの発見とALK阻害薬の開発の様に、効果予測バイオマーカーが確認されている新たな分子標的治療薬の開発が期待されていることから、がん治療における患者ごとのオーダーメイド化、個別化は今後さらに進むと考えられる。一方で、多様な分子標的治療薬の毒性発現を患者ごとに予期するバイオマーカーの発見も今後の重要な課題である。

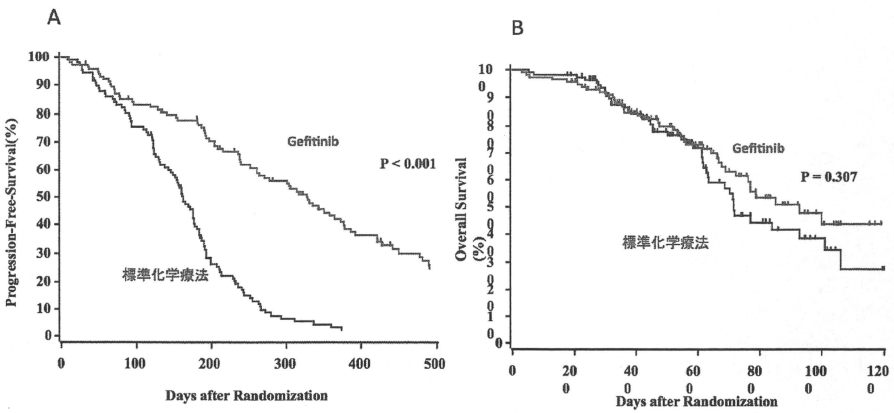


図4　NEJ002の無増悪生存期間(A)と全生存期間(B)(文献9より引用)

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新薬展望 2011

第Ⅲ部 治療における最近の新薬の位置付け〈薬効別〉～新薬の広場～

肺癌治療薬

吉澤 弘久*

肺癌に対し，多くの新薬の開発治験が進行中である。2011年に上市される新薬は現時点では確定していないが，現在治験が進行中で今後上市が期待されている分子標的治療薬であるALK (anaplastic lymphoma kinase) 阻害薬について紹介する。

■キーワード：Crizotinib，anaplastic lymphoma kinase (ALK)，ALK阻害薬

1 はじめに

上皮成長因子受容体チロシンキナーゼ阻害薬 (EGFR-TKI) の出現と，その効果予測因子である上皮成長因子受容体 (EGFR) 遺伝子変異の発見は，肺癌領域における個別化治療を大きく進めた。以後，多くの分子標的治療薬の開発が進められてはいるが[5]，現状で上市への可能性が期待されている薬剤は限られている。ここでは，現在開発治験が進行中の分子標的治療薬である，ALK (anaplastic lymphoma kinase) 阻害薬について述べる。

2 EML4-ALK遺伝子とALK阻害薬

慢性骨髄性白血病 (CML) では染色体の構造異常，つまり転座が発症メカニズムに重要であることが，古くから知られている。CMLでは転座によって形成されたABLキナーゼとBCRの融合蛋白が[5]，高いチロシンキナーゼ活性を発揮するため，過剰な細胞増殖を誘導している。このチロシンキナーゼ阻害薬 (TKI) であるイマチニブは，BCR-ABL陽性CMLに対して極めて高い治療効果を示す。固形癌では，このような染色体転座が癌化や細胞増殖に強く関与することは極めて稀であるとされてきた。自治医科大学の曽田，間野らは，微小管会合蛋白の一種である EML4 (echinoderm microtuble-associated protein-like 4) と受容体型チロシンキナーゼALKをコードする融合型遺伝子EML4-ALK遺伝子[1]が[5]，ALK領域の高い酵素活性に依存して強く癌化に関わること[2]，非小細胞肺癌 (NSCLC) でのスクリーニングで6.7%が同遺伝子陽性であることを報告した。その後の報告でも，この遺伝子はNSCLCの4～5%に認められることが確認されている[3][4]。BCR-ABL陽性CMLに対してイマチニブが高い治療効果を示すと同様に，ALK阻害薬がEML4-ALK遺伝子陽性NSCLCに有効であることが期待されることから，現在複数のALK阻害薬が開発されている。その中で，Crizotinib (PF-02341066) は元来METチロシンキナーゼ阻害薬として開発されていたが，同様にALK阻害作用を持つdual-inhibitorである。Crizotinibは臨床適用可能な用量ではALK，c-METを抑制するが[5]，他のキナーゼに対する抑制は少ないとされている。(図1)。

3 Crizotinibの臨床試験

2010年の米国臨床腫瘍学会で，経口ALK阻害薬であるCrizotinib (PF-02341066) の臨床試験の成績が報告された[5]。この試験は，2つのStage

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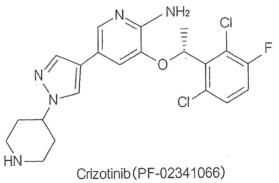

Crizotinib(PF-02341066)

Kinase	IC_{50} (nM) mean	Selectivity ratio
c-MET	8	−
ALK	20	2×
RON	298	34×
	189	22×
Axl	294	34×
	322	37×
Tie-2	448	52×
TrkA	580	67×
TrkB	399	46×
Abl	1,159	166×
IRK	2,887	334×
Lck	2,741	283×
Sky	> 10,000	> 1,000×
VEGFR2	> 10,000	> 1,000×
PDGFR β	> 10,000	> 1,000×

(Pfizer Inc. Data on File より)

図1 Crizotinib (PF-02341066)

Crizotinib の各種キナーゼに対する影響を ELISA Capture 法で測定した。Crizotinib は臨床適用可能な用量においては ALK，c-MET を抑制する。他のキナーゼに対する抑制は低い。

ELISA：enzyme-linked immunosorbent assay，IC_{50}：50%抑制濃度，ALK：anaplastic lymphoma kinase

(筆者作成)

表1 患者背景

Stage Ⅱに登録された 82 例の患者背景。平均年齢 51 歳（25 ～ 78 歳）と通常の肺癌患者より若い傾向にあり，Performance status 0/1 (24 例 /44 例，29/54%)，非喫煙者 (62 例，76%)，腺癌 (79 例，96%) が多くを占めている。

平均年齢（範囲）：歳	51（25 ～ 78）	
性別：男性 / 女性	43/39	
Performance status*：n (%)	0	24 (29)
	1	44 (54)
	2	13 (16)
	3	1 (1)
人種：n (%)	白人	46 (56)
	アジア人	29 (35)
喫煙歴：n (%)	喫煙歴なし	62 (76)
	禁煙者	19 (23)
	喫煙者	1 (1)
既往歴：n (%)	腺癌	79 (96)
	扁平上皮癌	1 (1)
	その他	2 (2)
前治療レジメン数：n (%)	0	5 (6)
	1	27 (33)
	2	15 (18)
	≧ 3	34 (41)
	報告なし	1 (1)

* Performance status：Eastern Cooperative Oncology Group による分類

(文献 6 より一部改変)

で構成されており，用量設定のための Stage Ⅰには前治療無効の固形腫瘍患者 37 例が登録された。Stage Ⅰでは用量規制毒性に加えて，250mg 1 日 2 回投与時の半減期が約 53 時間であること，PK (pharmacokinetics) では非線形性を認めないこと，食事の影響を受けないこと，CYP（チトクロム P450）3A4 を中等度に抑制することなどが明らかとなった。c-MET を発現した NSCLC 患者を対象に有効性を検討する Stage Ⅱには 82 例が登録されている[6]。Stage Ⅱに登録された患者背景では，平均年齢 51 歳（25 ～ 78 歳）と通常の肺癌患者より若い傾向にあった。さらに非喫煙者 (62 例，76%)，腺癌 (79 例，96%) が多くを占めている。(表 1)。腫瘍縮小効果をウォーターフォールプロットで見ると，腫瘍サイ

EGFR-TKI：上皮成長因子受容体チロシンキナーゼ阻害薬，EGFR：上皮成長因子受容体
ALK：anaplastic lymphoma kinase，CML：慢性骨髄性白血病，TKI：チロシンキナーゼ阻害薬
EML4：echinoderm microtuble-associated protein-like 4，NSCLC：非小細胞肺癌

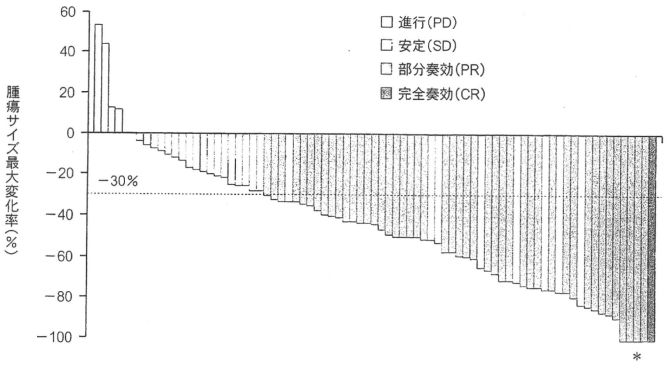

図2 ウォーターフォールプロットで見る腫瘍縮小効果

腫瘍縮小効果をウォーターフォールプロットで見ると，腫瘍サイズ最大変化率は縮小側に大きく偏っていることが分かる。

*100%の変化を認めた患者では，非標的病変を有していた

(Pfizer Inc. Data on File より)

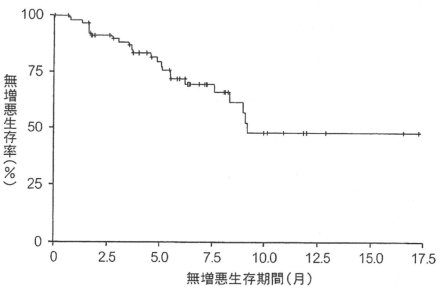

図3 無増悪生存期間 (PFS)

報告時点での治療期間中央値は 5.7 カ月で，奏効期間は 1 ～ 15 カ月であった。追跡期間中央値が 6.4 カ月の時点で，6 カ月の予測 PFS 率は 72% (95% 信頼区間：61 ～ 83%) であった。

(文献 6 より一部改変)

ズ最大変化率は縮小側に大きく偏っていることが分かる。(**図2**)。奏効率は 57% (95%信頼区間：46 ～ 68%) で CR (完全寛解) が 1 例，病勢コントロール率は 87% (95%信頼区間：77 ～ 93%) と高い奏効率，病勢コントロール率が示された。また登録時 Performance Status (PS) 2 ～ 3 の 14 例中 8 例 (57%) で奏効が認められており，PS 不良例においても高い治療効果が示されている。

報告時点での治療期間中央値は 5.7 カ月で，奏効期間 1 ～ 15 カ月であった。無増悪生存期間 (PFS) の追跡期間中央値が 6.4 カ月の時点で，6 カ月の予測 PFS 率は 72% (95%信頼区間：61 ～ 83%) であった。(**図3**)。前治療が Crizotinib での治療効果に与える影響は小さく，3 レジメン以上の高度前治療例においても奏効率は 56% (19/34) であった。(**表2**)[7]。これまでに EML4-

表2 前治療の影響

前治療が[5] Crizotinib での治療効果に与える影響は小さく，3レジメン以上の高度前治療例においても奏効率は56% (19/34) であった。

前治療レジメン数*	奏効率 % (n/N)
0	80 (4/5)
1	52 (14/27)
2	67 (10/15)
≧3	56 (19/34)

*1例で不明

(文献7より)

ALK 陽性症例では EGFR-TKI の効果予測因子である EGFR 遺伝子変異，KRAS 遺伝子変異が認められないこと，EGFR-TKI での治療効果は極めて低いが[5]，プラチナベースの化学療法にはワイルドタイプと同等の効果を示すことが示されている。(**表3**)[8]。有害事象では，消化管 (Grade 1/2 の嘔気52% /1%，下痢46% /1%)，視覚障害 (Grade 1 の明 / 暗順応の変化) が主で，この薬剤の忍容性の高さが示されている。(**表4**)。

この試験では Crizotinib 250mg 1日2回投与で実施されているが[5]，至適投与法のさらなる検討や，ALK 融合型蛋白の検出法として高感度の免疫染色法 PCR (polymerase chain reaction) 法[4)9)]，

表3 Genotype による治療効果

EML4-ALK 陽性症例では EGFR-TKI の効果予測因子である EGFR 遺伝子変異が認められないことが示されている。よって EGFR-TKI での治療効果は極めて低い。一方プラチナベースの化学療法にはワイルドタイプと同等の効果を示す。

〈プラチナベース化学療法〉

	ALK (N = 12)	EGFR (N = 8)	WT/WT* (N = 34)
奏効率 (%)	25	50	35
無増悪期間 (月)	9	10	8

〈EGFR-TKI〉

	ALK (N = 10)	EGFR (N = 23)	WT/WT* (N = 23)
奏効率 (%)	0	70	13
無増悪期間 (月)	5	16	6

*両者とも変異無し
ALK：anaplastic lymphoma kinase，EGFR：上皮成長因子受容体，WT：wild type
EML4：echinoderm microtuble-associated protein-like 4，TKI：チロシンキナーゼ阻害薬

(文献8より)

表4 有害事象 (10%以上の発現頻度)

有害事象では消化管 (Grade 1/2 の嘔気52%/1%，下痢46%/1%)，視覚障害 (Grade 1 の明 / 暗順応の変化) が主である。

有害事象	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Total n (%)
嘔気	43 (52)	1 (1)	0	0	44 (54)
下痢	38 (46)	1 (1)	0	0	39 (48)
嘔吐	35 (43)	1 (1)	0	0	36 (44)
視覚障害*	34 (42)	0	0	0	34 (42)
便秘	18 (22)	2 (2)	0	0	20 (24)
末梢浮腫	13 (16)	0	0	0	13 (16)
めまい	12 (15)	0	0	0	12 (15)
食欲不振	11 (13)	0	0	0	11 (13)
倦怠感	8 (10)	0	0	0	8 (10)

*明 / 暗順応の変化 (眼科検査で異常なし)

(文献6より一部改変)