inoculation, mice were sublethally irradiated (500 cGy) and then infused intravenously (i.v.) with T cells isolated from tumor-draining LNs. LN cells were stimulated with anti-CD3 mAb (2C11) and cultured in CM containing 40 U/ml of interleukin (IL)-2 for 3 days to obtain a sufficient number of T cells for in vivo experiments, as described previously [17]. The perpendicular diameter of subcutaneous tumors was measured with calipers.

Cytokine ELISAs

T cells were stimulated with immobilized anti-CD3 mAb or tumor antigen–pulsed BM–DCs in CM. Supernatants were harvested and assayed for IFN-γ, IL-4, and IL-17 content by a quantitative "sandwich" enzyme immunoassay using a murine IFN-γ, IL-4, and IL-17 ELISA kit (Genzyme, Cambridge, MA) according to the manufacturer's instructions.

In vitro proliferation assay

Melanoma cells were labeled with 5 μM 5-(6)-carboxyfluorescein diacetate succinimidyl diester (CFSE; Molecular Probes Inc., Eugene, OR) in HBSS at 37°C for 15 min and washed twice before CD3 stimulation. The ratio of CFSE-labeled tumor cells to unlabeled tumor cells was 1:10. Tumor cells were cultured in CM at 1×10^5/ml. Tumor cells were counted every day and were analyzed using a microfluorometer to determine the number of CFSE-labeled tumor cells. Three wells were analyzed for each condition.

Statistical analysis

Comparison between groups was made by Student's *t*-test. The dynamic tumor growth data was analyzed by multivariate general linear model. Differences were considered significant for $P < 0.05$. Statistical analysis was performed with SPSS statistical software (SPSS, Chicago, IL) or GraphPad Prism 5.0 software (GraphPad Software Inc., La Jolla, CA).

Results

$CD133^+$ melanoma cells possessed distinct characteristics

For this study, we obtained purified $CD133^+$ tumor cells from murine B16-F10 melanomas (Fig. 1a) and then tested the properties of these cells. Skin tissues were not produced by 1×10^5 subcutaneously inoculated parental B16 melanoma cells, but 5×10^3 $CD133^+$ melanoma cells were sufficient to establish tumor tissues in vivo (Fig. 1b). In vitro proliferation assays showed that $CD133^-$ tumor cells proliferated more aggressively than $CD133^+$ tumor cells before they became confluent, but their proliferation was impeded by cell–cell contact inhibition. In contrast, the proliferation of $CD133^+$ tumor cells did not stop by contact inhibition, and cells piled together, developing into floating aggregates (Fig. 1c). We also tested whether $CD133^+$ melanoma cells could grow in an anchorage-independent manner. Although $CD133^-$ cells eventually died without anchorage, all $CD133^+$ tumor cells proliferated to become tumor spheres (Fig. 1d, e). $CD133^+$, but not $CD133^-$, tumor cells exhibited colony formation on soft agar (Fig. 1f).

Vaccination with $CD133^+$ tumor cells induced protective immunity against the parental melanoma

To examine whether the immune system can recognize $CD133^+$ melanoma cells, we immunized mice by subcutaneously inoculating them with 5,000 cGy-irradiated 1×10^7 parental, $CD133^-$, or $CD133^+$ melanoma cells mixed with 1×10^7 DCs. Fourteen days after immunization, 3×10^5 parental melanoma cells were subcutaneously injected. The tumor growth curves of mice that were immunized with parental tumor cells or $CD133^-$ tumor cells were identical to those of mice that had not received immunization (Fig. 2a). In contrast, tumor growth was significantly retarded in mice immunized with $CD133^+$ tumor cells.

$CD133^+$ tumor antigen–specific T cells mediated potent therapeutic efficacy

We examined the antitumor efficacy of LN T cells draining irradiated parental, $CD133^-$, or $CD133^+$ melanoma cell vaccinations with DCs. $CD62L^{low}$ (cells with downregulated CD62L expression) T cells that were isolated as antigen-primed T cells from LNs were cultured by the anti-CD3/IL-2 method, as described previously [20]. LN T cells were intravenously infused into mice bearing a 2-day-established parental melanoma skin tumor after sublethal whole-body irradiation (500 cGy). The tumors of mice treated with LN T cells primed with parental or $CD133^-$ tumor cells grew in a pattern similar to those of the untreated mice (Fig. 2b). In contrast, the tumors of mice treated by LN T cells primed with $CD133^+$ tumor cells did not grow, even though the mice had palpable tumors. Interestingly, the antitumor reactivity mediated by the LN T cells primed with $CD133^+$ tumor cells persisted for more than 60 days and no mice died of tumor. In this system, regulatory T (Treg) cells were eliminated by whole-body irradiation before antitumor T-cell infusion; however, generally, host lymphocytes recover approximately 20 days after irradiation, and Treg cells that recover as host

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Clinical responses to EGFR-tyrosine kinase inhibitor retreatment in non-small cell lung cancer patients who benefited from prior effective gefitinib therapy: a retrospective analysis

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Abstract

Background: Gefitinib was the first epidermal growth factor receptor-tyrosine kinase inhibitor (EGFR-TKI) approved for the treatment of advanced non-small cell lung cancer (NSCLC). Few treatment options are available for NSCLC patients who have responded to gefitinib treatment and demonstrated tumor progression. The present study was conducted to evaluate the efficacy and toxicity of the 2nd EGFR-TKI administration.

Methods: We retrospectively analyzed 11 patients who had obtained a partial response (PR) or stable disease (SD) with gefitinib treatment and were re-treated with EGFR-TKI after failure of the initial gefitinib treatment.

Results: Three patients (27%) were treated with gefitinib as the 2nd EGFR-TKI, and 8 patients (73%) received erlotinib. Only one patient (9%) showed PR, 7 (64%) achieved SD, and 3 (27%) had progressive disease. The disease control rate was 73% (95% CI, 43% - 91%) and the median progression-free survival was 3.4 months (95% CI, 2 - 5.2). The median overall survival from the beginning of the 2nd EGFR-TKI and from diagnosis were 7.3 months (95% CI, 2.7 - 13) and 36.7 months (95% CI, 23.6 - 43.9), respectively. No statistical differences in PFS or OS were observed between gefitinib and erlotinib as the 2nd EGFR-TKI (PFS, P = 0.23 and OS, P = 0.052). The toxicities associated with the 2nd EGFR-TKI were generally acceptable and comparable to those observed for the initial gefitinib therapy.

Conclusions: Our results indicate that a 2nd EGFR-TKI treatment can be an effective treatment option for gefitinib responders.

Background

Gefitinib was the first epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI) to become available for the treatment of non-small cell lung cancer (NSCLC). Several studies have demonstrated that gefitinib is effective for the second-line treatment of NSCLC [1-3]. Although the phase III ISEL trial failed to prove the superiority of gefitinib treatment compared to placebo in previously treated patients, a subgroup analysis demonstrated improved survival in particular populations (Asians and non-smokers) [4]. Further analyses in other studies have also revealed that clinical factors (Asians, females, non-smokers, and adenocarcinoma histology) are associated with the response to gefitinib treatment [5]. EGFR mutations, such as the deletion of exon 19 and the single L858R mutation in exon 21, have also been reported to be correlated with a longer survival and were found more frequently in Asian patients [6-8]. Recently, a superior progression-free survival (PFS) with gefitinib compared with the combination of carboplatin and paclitaxel in untreated NSCLC patients with predictors of gefitinib sensitivity was proven in two large phase III studies [9,10]. Gefitinib is now recommended for advanced

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or metastatic NSCLC patients under such circumstances as a first or a second-line treatment.

Despite the high disease control rate (DCR), gefitinib treatment is not curative and eventually there is disease recurrence, even in patients with predictors of sensitivity. For the many NSCLC patients who previously responded to gefitinib but later showed tumor progression, very few treatment options are available.

Some investigators have conducted studies to evaluate the efficacy of EGFR-TKI re-administration [11-14]. In most of those studies, both gefitinib responders and non-responders were retreated with gefitinib or erlotinib, and gefitinib responders tended to benefit from the 2nd EGFR-TKI.

Here, we retrospectively analyzed the efficacy of the 2nd EGFR-TKI administration after failure of the initial gefitinib treatment in NSCLC patients who had previously achieved disease control with gefitinib. The risks of the 2nd administration of EGFR-TKI, especially the association with adverse events in the initial gefitinib treatment, were also evaluated.

Methods

Patients

We conducted a retrospective search of the medical records at Niigata University Medical and Dental Hospital, from June 2005 through October 2009, and we identified 11 NSCLC patients who had obtained a partial response (PR) or stable disease (SD) with gefitinib treatment and undergone EGFR-TKI retreatment sometime after the failure of the initial gefitinib treatment. All patients were treated initially with oral gefitinib at a dose of 250 mg/day, which was continued until either a radiographic tumor or overt clinical progression was observed. The same dose of gefitinib, or erlotinib at a dose of 150 mg/day, was used for EGFR-TKI retreatment and continued until tumor progression was detected.

Assessment of the response and adverse events

The tumor response was evaluated by radiologic examinations according to the Response Evaluation Criteria in Solid Tumors (RECIST) [15]. Disease control was defined as complete response (CR), PR or SD. PFS and overall survival (OS) were defined as the period from the start of the treatment to the date when disease progression and death, respectively, were observed.

Adverse events were assessed according to Common Terminology Criteria for Adverse Events of the National Cancer Institute (version 3.0) [16].

Statistical analysis

PFS and OS estimates were obtained using the Kaplan-Meier method.

Table 1 Patient Characteristics 1

Characteristics	No. of Patients	%
Total enrolled	11	
Gender		
Female	8	73
Male	3	27
Age (y)		
Median	55	
Range	46-70	
ECOG performance status		
1	6	55
2	0	0
3	3	27
4	2	18
Histology		
Adenocarcinoma	10	91
Squamous	1	9
Smoking history		
Current	3	27
Ex-smoker	1	9
Never	7	64
EGFR mutation		
Exon 19 deletion	2	18
L858R	1	9
Not available	8	73

EGFR, epidermal growth factor receptor.

Results

Patient characteristics

Of the 11 identified patients who benefited from gefitinib and were retreated with EGFR-TKI, 3 patients (27%) received gefitinib and 8 patients (73%) received erlotinib as the 2nd round of EGFR-TKI. As shown in Table 1 the ages of patients ranged from 46 to 70 years (median, 55 years), and there were 8 females (73%), 7 non-smokers (64%), and 10 adenocarcinoma patients (91%). Three patients (27%) exhibited EGFR gene mutations, but the mutation statuses of the other 8 patients (73%) were not determined. All patients had received platinum-based chemotherapy before the initial gefitinib treatment. The patient characteristics, including treatment backgrounds and responses, are summarized in Table 2.

Response to the initial gefitinib treatment

During the 1st EGFR-TKI treatment with gefitinib, 8 patients achieved PR as the best response (73%, Table 3), and 3 patients (27%) were SD. The median PFS was 9.8 months, with a 95% CI of 6.6 to 16.7 months.

Response to the 2nd EGFR-TKI

Three patients (27%) received the 2nd EGFR-TKI immediately after gefitinib failure, and 8 (73%) underwent 1 cytotoxic regimen between the initial gefitinib and the

Table 2 Patient Characteristics 2

Case	Age (y)	Gender	Smoking	Histology	EGFR mutation	PFS to 1st TKI	TKI sequence	Interval from 1st and 2nd	Chemo. after 1st	PS	Response	PFS to 2nd TKI	OS from 2nd TKI
1	50	F	Current	Ad	NA	9.8	G→E	7.9	CBDCA +GEM	1	PD	0.9	13.1
2	46	F	Never	Ad	NA	11.8	G→G	4.5	DOC	1	PR	6.4	24.6
3	58	F	Ex	Ad	19 deletion	38.4	G→G	2.8	DOC	1	SD	7.3	24.1
4	70	F	Never	Sq	NA	10.2	G→E	12.8	GEM	1	SD	1.7	4.3
5	60	F	Never	Ad	NA	13	G→G	5.4	GEM	1	PD	1.6	2.1
6	63	F	Never	Ad	NA	7.4	G→E	2.6	-	3	SD	3.6	7.8
7	52	M	Never	Ad	L858R	5.8	G→E	1	-	4	SD	6.4	6.4
8	51	M	Current	Ad	NA	4.3	G→E	1.6	AMR	3	PD	0.6	0.9
9	61	F	Never	Ad	NA	8.5	G→E	2.3	VNR	3	SD	2.9	4
10	53	F	Never	Ad	NA	12.9	G→E	0	-	4	SD	6.2	7.3
11	54	M	Current	Ad	19 deletion	3.8	G→E	7.3	VNR	1	SD	3.2	5

PFS, progression-free survival; TKI, tyrosine kinase inhibitor; PS, performance status; OS, overall survival; F, female; M, male; Ex, ex-smoker; Ad, adenocarcinoma; Sq, squamous cell carcinoma; G, gefitinib; E, erlotinib; CBDCA, carboplatin; GEM, gemcitabine; DOC, docetaxel; AMR, amrubicin; VNR, vinorelbine; PR, partial response; SD, stable disease; PD, progressive disease.

2nd EGFR-TKI treatments. The median interval from the discontinuation of gefitinib to the 2nd EGFR-TKI was 2.8 months (95% CI, 1.9 - 6.9, Table 3). Only one patient (9%) demonstrated PR, 7 (64%) remained SD, and 3 (27%) had PD. The DCR was 73% (95% CI, 43% - 91%) and the median PFS was 3.4 months (95% CI, 2 - 5.2). The median OS from the beginning of the 2nd EGFR-TKI and from diagnosis were 7.3 months (95% CI, 2.7 - 13.0) and 36.7 months (95% CI, 23.6 - 43.9), respectively. No statistical differences in PFS or OS were observed between gefitinib and erlotinib as the 2nd EGFR-TKI (PFS, P = 0.23 and OS, P = 0.052).

In contrast with previous studies, we further compared the clinical courses of the patients with those of gefitinib responders who were not treated with a 2nd EGFR-TKI following gefitinib failure. We reviewed the medical records at our institute and found 9 patients with backgrounds that were similar to those of the 2nd EGFR-TKI patients (sex, age (< 70 years old or > 70 years old), histology, and response to gefitinib treatment). No statistical differences in PFS to 1st gefitinib treatment were noted between both groups (9.8 months in the 2nd TKI group and 8.7 months (95% CI, 7.6 - 9.8) in the control group, P = 0.87). All of the identified control patients had been treated with platinum-doublet chemotherapy before gefitinib but had not received 2nd EGFR-TKI. The OS from the start of the initial gefitinib treatment tended to be longer in patients who received a 2nd EGFR-TKI (median OS, 21.5 months (95% CI, 14.6 - 28.4)) compared to those in the control group (median OS, 12.3 months (95% CI, 9.4 - 15.2), P = 0.07).

Table 3 Summary of prior therapy

Characteristics	No. of patients	%
No. of chemotherapy regimens before gefitinib		
1	2	18
2	4	36
3	4	36
4	1	9
Best response to gefitinib		
PR	8	73
SD	3	27
PFS to gefitinib		
Median	9.8	
95% CI	6.6 - 16.7	
Interval from discontinuation of gefitinib to 2nd EGFR-TKI		
Median	2.8	
95% CI	1.9 - 6.9	

In the control group, 5 out of 9 patients had been treated with cytotoxic chemotherapy after gefitinib failure. To compare the efficacy of the 2nd EGFR-TKI with chemotherapy after disease progression with gefitinib, data were collected from these 5 patients in the control group who had received chemotherapy after gefitinib failure (Table 4). The DCR for chemotherapy after gefitinib treatment was 20% and comprised one SD and four PD. The median PFS and OS from the start of chemotherapy after gefitinib treatment were only 2 months (95% CI, 1.5 - 2.4) and 2.5 months (95% CI, 2.2 - 2.8), respectively. No significant differences in the PFS or OS from the start of treatment after gefitinib were observed between the patients who received a 2nd EGFR-TKI and those who underwent cytotoxic chemotherapy (PFS, P = 0.1 and OS, P = 0.12); however, a 2nd EGFR-TKI appeared to be a better option for gefitinib responders.

Table 4 Tumor response to 2nd EGFR-TKI vs. chemotherapy

Characteristics	2nd TKI group	Control group	P
OS from 1st gefitinib			
Median	21.5	12.3	0.07
95% CI	14.6 - 28.4	9.4 - 15.2	
Response to 2nd TKI or chemotherapy			
PR	1	0	
SD	7	1	
PD	3	4	
PFS to 2nd TKI or chemotherapy			
Median	3.4	2	0.1
95% CI	2 - 5.2	1.5 - 2.4	
OS from 2nd TKI or chemotherapy			
Median	7.3	2.2	0.12
95% CI	2.7 - 13	2.2 - 2.8	

Table 5 Toxicity profiles for the initial gefitinib and 2nd EGFR-TKI treatments. Adverse events were evaluated according to Common Terminology Criteria for Adverse Events of the National Cancer Institute (version 3.0).

Case	Initial gefitinib	2nd EGFR-TKI
1	-	Rash G2
2	Rash G2	-
3	-	-
4	Rash G2, Liver G1, Diarrhea G2	Rash G1, Diarrhea G1
5	Rash G1	Rash G2
6	Diarrhea G2, Taste alteration G2	Rash G1, Diarrhea G1
7	Rash G2, Liver G3	Rash G2, Liver G3
8	Rash G2	Liver G2
9	Rash G1, Nail G1, Nausea G1	Rash G1
10	Liver G1	-
11	-	Rash G1, Diarrhea G1

G, grade; Liver, serum glutamic pyruvic transminase, serum glutamic oxaloacetic transaminase and γ-glutamyltranspeptidase.

Toxicity profiles for the initial gefitinib and 2nd EGFR-TKI treatments

To determine whether the initial gefitinib treatment and EGFR-TKI retreatment caused similar adverse events, we assessed the toxicity profiles of all 11 patients (Table 5). The most common toxicity associated with both treatments was a grade 1/2 skin rash. Although one patient presented a grade 3 elevation of γ-glutamyltranspeptidase during both treatment with gefitinib and with erlotinib (patient no. 7), the other observed toxicities were generally acceptable. In 5 patients, the toxicity profiles for the initial gefitinib and the 2nd EGFR-TKI treatments were similar. None of the patients demonstrated interstitial lung disease in response to EGFR-TKI.

Discussion

To the best of our knowledge, 18 cases of patients who received gefitinib re-administration after failure of the initial gefitinib treatment have been reported to date, including 3 cases reported by our group (Table 6) [17-21]. All 18 patients responded to the initial gefitinib treatment, and most of the cases underwent cytotoxic chemotherapy between the first and second gefitinib therapy. Fourteen patients benefited from the 2nd gefitinib treatment, and the overall DCR was 78%. In our 3 patients, the toxicity of the 2nd gefitinib was similar to that observed for the initial gefitinib treatment and was acceptable. Gefitinib retreatment is likely a good option for patients who have demonstrated a response to a previous gefitinib treatment.

Clinical studies have demonstrated that erlotinib is effective even in patients who are not considered to be good responders to gefitinib, such as those with a negative EGFR mutation, squamous cell carcinoma, or a history of smoking [22]. Because erlotinib is used at its maximum tolerated dose, whereas gefitinib is used at only about one-third of its maximum tolerated dose in daily practice, the biological activity of erlotinib at standard doses may be higher than that of gefitinib [2,4,23-25]. These reports suggest that erlotinib may be active even in patients who demonstrated tumor progression during a prior gefitinib treatment. Thus, erlotinib has been selected as a treatment option for use after gefitinib failure (Table 7) [11-14,26-33]. In most studies, including the present investigation, favorable results have been documented, and the authors have concluded that erlotinib appears to be a useful treatment after gefitinib failure.

Although it is difficult to address the precise mechanism underlying these results, several studies have suggested a possible explanation for the clinical benefit of EGFR-TKI retreatment. Some cytotoxic agents have been reported to restore the sensitivity of NSCLC cells to gefitinib in vitro by increasing EGFR phosphorylation [34,35]. It is also possible that chemotherapy during the EGFR-TKI-free interval could decrease EGFR-TKI resistant tumor cells. However, no significant differences in PFS or OS were observed between our patients who received chemotherapy before the 2nd EGFR-TKI and those who received the 2nd EGFR-TKI immediately after gefitinib failure. In addition, the duration between the initial gefitinib and the 2nd EGFR-TKI treatments was not associated with the response to 2nd EGFR-TKI. Similarly to these findings, other researchers have found no evidence that either chemotherapy among the 1st and 2nd EGFR-TKIs or the duration of the EGFR-TKI-free period affects either PFS or OS in the 2nd EGFR-TKI [31,33].

Secondary EGFR mutations might be associated with the efficacy of erlotinib after gefitinib failure. MET amplification and secondary EGFR mutations, such as

Table 6 Patient characteristics of the previous studies of gefitinib readministration

Author	No. of patients	Response to gefitinib		Response to 2nd gefitinib	
		CR/PR/SD	PD	CR/PR/SD	PD
Yokouchi H et al.	9	9	-	8	1
Yoshimoto A et al.	1	1	-	1	0
Yano S et al.	3	3	-	2	1
Hashimoto N et al.	1	1	-	0	1
Kurata T et al.	1	1	-	1	0

CR, complete response.

T790 M, L747 S, D761Y, and T854A have been identified in NSCLC patients with an acquired resistance to EGFR-TKI [36-42]. T790 M mutation was found in 50%, MET amplification in 20%, and other secondary mutations in less than 5% of the NSCLC patients carrying EGFR mutations with TKI resistance [43,44]. In vitro studies have revealed that tumor cells carrying non-T790 M mutations show a partial resistance to EGFR-TKI, but are much less resistant compared to cells with T790 M. These data suggest that an increased EGFR-TKI dose might circumvent the acquired resistance caused by non-T790 M mutations. Previous studies have indicated that the serum concentration of erlotinib is several-fold higher than that of gefitinib at standard doses [24,25]. This difference in biological activities between the TKIs may contribute to the efficacy of erlotinib after gefitinib failure in patients carrying non-T790 M mutations.

In conclusion, our findings suggest that a 2nd EGFR-TKI can be a treatment option for patients who benefited from a previous gefitinib treatment. However, as shown in Table 7 some studies failed to demonstrate the efficacy of 2nd EGFR-TKI after gefitinib failure. Cho et al. mentioned that the tumor response to 1st gefitinib treatment can be a predictive marker [14]. They described that patients who showed SD during 1st gefitinib treatment had better survival with 2nd EGFR-TKI, however those who had PD to 1st gefitinib rarely responded to 2nd EGFR-TKI. The difference in the percentage of patients with a good predictor might affect the results of these trials about 2nd EGFR-TKI. Intense research has been devoted to clarifying the mechanism responsible for acquired resistance, but it is difficult to obtain clinical samples from all patients to confirm MET amplification or secondary mutations. Jackman et al. recently published a clinical definition of acquired resistance to EGFR-TKI [45]. This consensus definition will facilitate the establishment of standard entry criteria for studies investigating acquired resistance. All of our patients except one met these criteria (no. 8 in Table 2). Despite rapid tumor progression during a previous cytotoxic chemotherapy, this patient obtained SD with an initial gefitinib therapy of 4.3 months, and therefore we considered this patient to have benefited from the gefitinib treatment. Further clinical trials are required to develop a novel treatment for patients with acquired resistance.

Table 7 Patient characteristics of the previous studies of erlotinib after gefitinib failure

Author	No. of patients	Response to gefitinib		Response to erlotinib		
		CR/PR/SD	PD	CR/PR/SD	PD	DCR (%)
Lee DH et al.	23	17	6	2	21	9
Cho BC et al.	21	10	11	6	15	29
Viswanathan A et al.	5	4	1	0	5	0
Costa DB et al.	18	16	2	4	14	22
Sim SH et al.	16	11	5	4	12	25
Chang JW et al.	1	1	0	1	0	100
Garfield DH et al.	1	1	0	1	0	100
Vasile E et al.	8	8	0	5	3	63
Gridelli C et al.	3	3	0	3	0	100
Wong AS et al.	14	9	5	5	9	36
Zhou ZT et al.	21	15	6	10	11	48
Wong MK et al.	21	18	3	12	9	57

Conclusion

In the current study, we analyzed the efficacy and toxicity of a 2nd EGFR-TKI treatment in patients who demonstrated a response to prior gefitinib therapy and tumor progression. A second EGFR-TKI treatment was generally effective in patients who had benefited from the initial gefitinib therapy. The adverse events associated with a 2nd EGFR-TKI were acceptable and comparable with those observed for the initial gefitinib therapy. In Japan, gefitinib has been approved for the treatment of inoperable and recurrent NSCLC since 2002, and many patients have already experienced a need for a new treatment option following gefitinib treatment. Based on the present data, a 2nd EGFR-TKI treatment could represent a potentially new treatment for gefitinib responders. Prospective clinical trials and translational analyses in this area of research are warranted.

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Authors' contributions
SW conducted the study and drafted the manuscript. JT conceived and designed the study and collected the clinical data. TO, RK, HT, HK and TM

participated in the patient care, and collected the data. KI, JK and JB analyzed and interpreted the data. IN and HY provided the administrative support. All the authors have read and approved the final version of the manuscript.

Competing interests
The authors declare that they have no competing interests.

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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，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，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，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，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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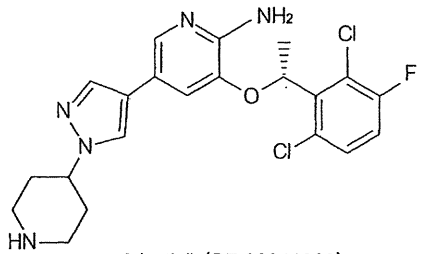

Crizotinib (PF-02341066)

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

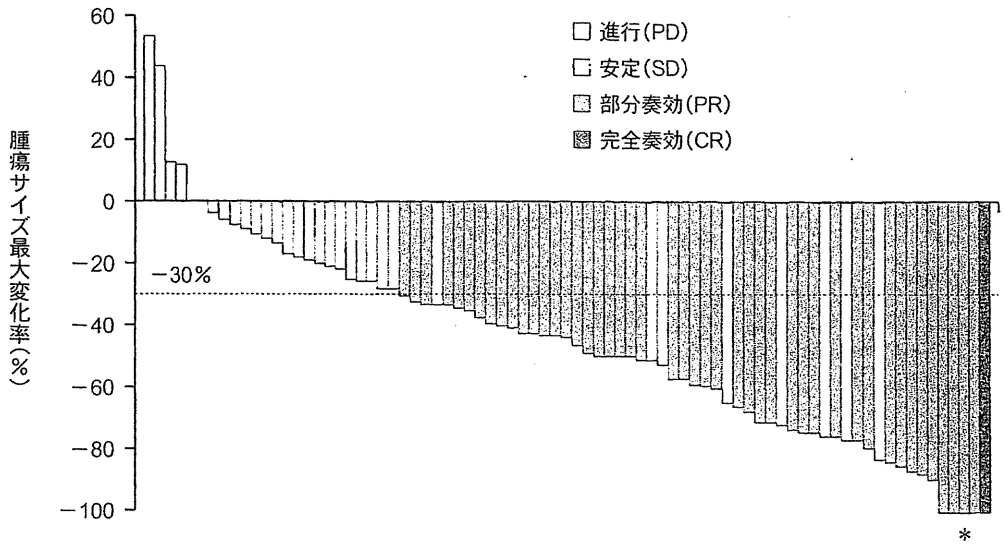

図2 ウォーターフォールプロットで見る腫瘍縮小効果

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)

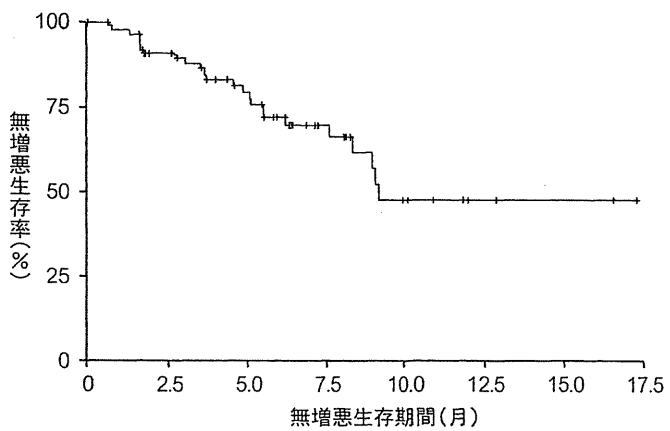

図3 無増悪生存期間 (PFS)

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，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，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)

表2 前治療の影響

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。

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，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，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)

FISH (fluorescent in situ hybridization) 法が示されているが，スクリーニングとして最適な方法の確立など，今後の検討課題も多い。

4 おわりに

現在，プラチナベース1レジメン治療後のALK陽性NSCLCを対象としてCrizotinibとペメトレキセドまたはドセタキセルの比較試験が進行中である。EGFR-TKIに続き，明確な効果予測バイオマーカーを持つ新たな分子標的治療薬であるALK阻害薬は，今後のNSCLCに対する，バイオマーカーを踏まえた個別化治療をさらに前進させるであろう。

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トピックス　アジア臨床試験の最前線〈2〉

～UHCTアライアンス3カ国視察レポート～

韓国における産学官連携による臨床試験実施体制

吉澤　弘久*・本間　真人**

本邦へのグローバル・クリニカルトライアルを積極的に誘致することを目的の一つとして設立された，大学病院臨床試験アライアンス（UHCTアライアンス）では，海外の臨床研究における代表的サイトを訪問し，交流を積極的に進めている。2011年2月には韓国，中国，シンガポールの代表的サイトを訪問した。本稿では韓国のSNUH（Soul National University Hospital），およびAMC（Asan Medical Center）の臨床試験センターとの交流より学んだ，韓国における産学官連携による臨床試験実施体制について述べる。

1．はじめに

2000年以降，韓国での臨床研究活動は急速に活発化している。**KFDA**（Korea Food & Drug Administration）が承認した臨床試験数は，1998年には国内試験が42件，国際試験は0件であったが，2010年にはそれぞれ229件，210件と急増している。（図1）。その背景には，韓国では産学官の連携により，臨床試験における国際競争力増強，専門家の育成，コアテクノロジー領域の強化を組織的に進めていることがある。臨床試験に対する支援としては，2004年より「Regional Clinical Trial Center（**RCTC**）プログラム」を開始し，さらに2007年より**KoNECT**（Korean National Enterprise for Clinical Trial）プログラムへと拡大させている。今回訪問した**SNUH**（Soul National University Hospital），**AMC**（Asan Medical Center）はこの「Regional Clinical Trial Center（RCTC）プログラム」によりRCTCとして選定されている。

2．KoNECT（Korean National Enterprise for Clinical Trial）

KoNECTは，2007年に韓国政府，アカデミア，関連企業の支援により設立された。（図2）。設立目的は臨床試験における国際競争力増強，専門家の育成，コアテクノロジー領域の強化，臨床研究の基盤整備である。RCTCプログラムは規模・質ともに優れている臨床研究サイトを厳しい競争の下に選定し，現在ではKoNECTの支援の一部として機能している。現在までに，15のRCTCが選定されているが，各RCTCは**MOHW**（Korean Ministry of Health and Welfare）から年間320万USドル相当の資金援助を5年間受け，インフラ構築やグローバル対応を行う。

このシステムは米国の**NIH-GCRC**（National Institutes of Health General Clinical Research Centers）programに類似した制度である。15のRCTCのうち8施設はソウル近郊に，3施設は釜山近郊にあり，人口密集地に集約させている。

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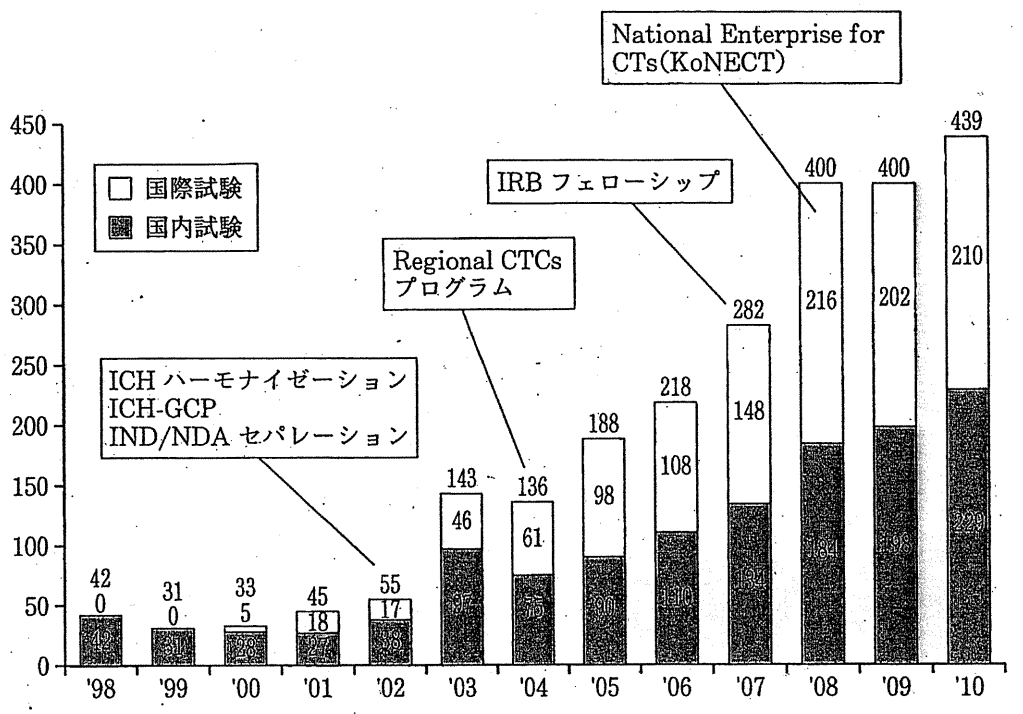

図１　KFDA によって承認された臨床試験数

ICH ハーモナイゼーション, IND/NDA セパレーション, Regional CTCs プログラム, KoNECT などの試みが臨床試験数を押し上げるきっかけとなっている.

KFDA：Korea Food & Drug Administration

ICH：International Conference on Harmonization of Technical Requirments for Registration of Pharmaceuticals for Human Use

IND/NDA：investigational new drug/new drug application

Regional CTCs：Regional Clinical Trial Centers

KoNECT：Korean National Enterprise for Clinical Trial

GCP：Good Clinical Practice，IRB：Institutional Review Board

(http://www.kfda.go.kr/index.jsp より)

RCTC プログラムに続く新たな事業についても，現在検討されている。**CTTA**(Clinical Trials Training Academy) は臨床試験の各領域専門家を育成するために設立された KoNECT の一機能である。このプログラムでは臨床試験に関わる研究者，薬理学者，臨床試験コーディネーター(**CRC**)，臨床試験モニター(**CRA**)，薬剤師，医薬専門医師，医薬疫学者，生物統計家等の育成を行っている。**CTTD** (Clinical Trials Technology Development) は，革新的な技術開発とその普及を目的としている。バイオマーカー，**PK/PD** (pharmacokinetics/pharmacodynamics) のシミュレーション技術，pharmacogenomics 等の領域の研究に対して資金援助を行い，新薬の開発力など技術開発の国際競争力の向上を目的としている。KoNECT は国内関連省庁との連携以外にも，J-Clipnet との連携や韓国国内の６大学とファイザーにより設立された，PK/PD モデリング，シミュレーションの専門

KFDA：Korea Food & Drug Administration，**RCTC**：Regional Clinical Trial Center
KoNECT：Korean National Enterprise for Clinical Trial，**SNUH**：Soul National University Hospital
AMC：Asan Medical Center，**MOHW**：Korean Ministry of Health and Welfare
NIH-GCRC：National Institutes of Health General Clinical Research Centers
CTTA：Clinical Trials Training Academy，**CTTD**：Clinical Trials Technology Development

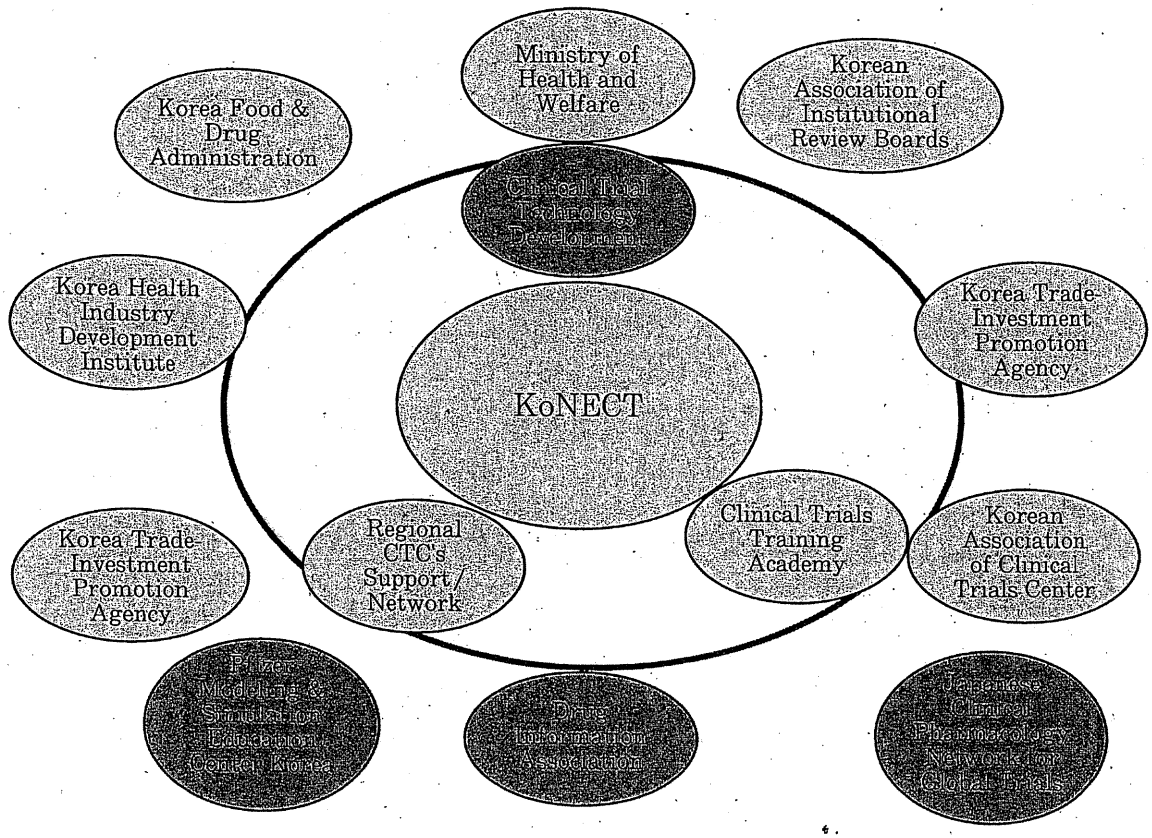

図2　KoNECTの関連組織図

Ministry of Health and Welfareを中心とする関連省庁，関連企業がサポートすることによりKoNECTは2007年に設立された．

KoNECT：Korean National Enterprise for Clinical Trial

(http://www.konect.or.kr/eng/より)

家育成を目的とするPMECK（Pfizer Modeling & Simulation Education in Korea）とも連携している。

3．SNUH（Soul National University Hospital）

韓国で最も歴史ある医学教育機関であるこの病院は1,625床，医師数1,100人，SCI（Science Citation Index）論文数1,520件（2009年）と，規模，研究活動ともにトップレベルの施設である。小児病院，Baramae病院，Bundang病院，SNUHヘルスケアシステムと，大学病院群を形成している。今回訪問したのはClinical Trial CenterのPHASE Ⅰ UNITである。ここでは第Ⅰ相試験用に46床を備え，PK/PDラボを併設している。Cancer Hospitalへは30床，小児ユニットへは2床を新たに設置する予定である。2010年の第Ⅰ相試験実施数は26件で，概ね年間20～30件を推移している。2010年のSNUH全体の試験数は，第Ⅱ相試験が45件，第Ⅲ相試験が68件となっており，第Ⅰ～Ⅱ相試験数が増加傾向にあるようだ。第Ⅰ相試験の依頼者は2010年でDomestic 11件，Global 15件である。

4．AMC（Asan Medical Center）

SNUHと同様にRCTCに選定されているAMCも韓国有数の大規模病院である。2,680床，平均1日外来受診者数10,147人（2009年），健常ボランティア候補者数2,000人で，第Ⅰ相試験病床数は29床とのことだ。AMCもGangneung病

PMECK：Pfizer Modeling & Simulation Education in Korea，IRB：治験審査委員会

院，Jeongeup病院など，7病院と病院群を形成している。

AMCで実施されている臨床試験数は，2010年において第Ⅰ相試験が14件，第Ⅱ相試験が84件，第Ⅲ相試験が88件と，SNUHと比較すると同等または若干上回っている。領域別で見ると腫瘍が最も多く，次いで消化器，循環器での試験数が多い。第Ⅰ～Ⅲ相試験のglobal trialは，2010年で102件，第Ⅰ相試験で2件，第Ⅱ相試験で40件，第Ⅲ相試験で60件であり，第Ⅰ相試験の多くはDomesticであることが分かる。治験審査委員会（IRB）は80名の委員で構成され，5パネルあり，4パネルは通常審査，1パネルは迅速審査に特化して稼働している。IRB提出から承認までの期間が2～3週間と短期間であるのは，複数のパネルが稼働している恩恵であろう。

また，AMCでは組織上，通常のsteering committee（運営委員会）とは独立してQA部門を最高責任者の諮問機関として設置し，臨床試験の質を監視している点は，グローバル・クリニカルトライアルを誘致するためのアピールポイントとして評価が高いと思われた。

5．おわりに

韓国では産学官連携の国家プロジェクトとして臨床試験，新薬開発研究を推進することにより，過去10年間においては試験数，質においても目覚ましく発展してきていることが分かる。人口の大部分がソウル近郊に集中しているため，RCTCにより強力に症例集積する方法はこれまでのところ順調に進んできたように思えるが，限られたサイトによる受託能力の限界を危惧する声もある。サイトの拡大や質の確保は可能かといった，解決すべき問題は多いようである。今回の交流では議論には上がらなかったが，中国，インドが台頭する中で，より第Ⅰ～Ⅱ相試験にシフトすることで自国のシェアを確保する動きも見えてきた。元来より自国発の高い開発能力を持つ製薬企業がほぼ皆無である韓国は，globalへのadaptionによって成長してきたという経緯も垣間見える。本邦においてもGlobal，Pan-Asiaの中での位置づけ，戦略について産学官一体となった議論を，より進めていかなければならないと感じた。

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臨床腫瘍プラクティス
The Practice of Medical Oncology

研究

肺がん化学療法時の悪心・嘔吐の実態

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太田　毅[7)※]・阿部徹哉[4)※]・宮林貴大[5)※]
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ヴァンメディカル

研　究

肺がん化学療法時の悪心・嘔吐の実態

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Summary
がん化学療法時の悪心・嘔吐は患者QOLを低下させることはもとよりコンプライアンス低下を招き，治療に悪影響を与える可能性がある。今回，肺がん化学療法を受けた患者101名を対象に悪心・嘔吐の実態調査を実施した。その結果，悪心・嘔吐の「つらさ」に対して医師と患者の間での認識に乖離が認められ，遅発期の摂食障害がシスプラチン群で66%，カルボプラチン群で44%に発現することがわかった。制吐療法を行う際，遅発期まで含めた認識と対応が必要だと考えられる。

Key words：肺がん／化学療法／急性期悪心・嘔吐／遅発期悪心・嘔吐／第一世代5-HT_3受容体拮抗薬

はじめに

がん化学療法による悪心・嘔吐は副作用の中で頻度が高く，最も辛い副作用のひとつである。肺がんの化学療法では高度から中等度催吐性薬剤であるシスプラチン（以下CDDPと略す），カルボプラチン（以下CBDCAと略す）が頻用されているため，悪心・嘔吐による治療拒否や薬剤コンプライアンス低下を招く可能性がある。

化学療法による悪心・嘔吐は制吐療法の進歩により改善しているが，海外の調査では遅発性の悪心・嘔吐において医師と患者の認識の相違が報告され[1)]，また，治療レジメンによる医師と患者の悪心・嘔吐に対する認識の相違があるとの報告もあるため[2)]，患者の実態を把握することは治療を実施する上で非常に重要である。そこで，肺がん術後補助化学療法および進行・再発肺がんに対する化学療法施行患者を対象に高度及び中等度催吐性抗悪性腫瘍薬投与に起因する消化器症状（悪心・嘔吐，食欲不振）の発現状況を実態調査した。

[1)]新潟大学医歯学総合病院生命科学医療センター ／ [2)]長岡赤十字病院呼吸器内科 ／ [3)]燕労災病院呼吸器内科 ／ [4)]新潟県立がんセンター新潟病院内科 ／ [5)]新潟県立中央病院内科 ／ [6)]済生会新潟第二病院呼吸器内科 ／ [7)]長岡中央綜合病院呼吸器内科 ／ [8)]新潟県立新発田病院内科 ／ [9)]西新潟中央病院呼吸器内科 ／ [10)]南部郷総合病院呼吸器内科 ／ [11)]新潟大学医歯学総合病院第二内科
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