Caucasians.

Anti-EGFR Antibody: Cetuximab in NSCLC

The First-Line in Lung Cancer with Erbitux (FLEX) trial was designed to demonstrate the effect of first-line cetuximab (Erbitux) combined with cisplatin plus vinorelbine in patients with NSCLC. Cetuximab significantly improved the overall survival (HR = 0.871, $P = .0441$) of patients with advanced NSCLC when added to platinum-based chemotherapy.[7] A planned subgroup analysis showed a remarkable difference in outcomes between Asian and Caucasian patients, with Asian patients living longer. The median overall survival period among 121 Asian patients was 17.6 months with cetuximab and 20.4 months with chemotherapy alone. On the other hand, the median overall survival periods of these treatment groups were 10.5 and 9.1 months, respectively, among 946 Caucasians.

Although the Asian population had better prognostic factors, such as higher percentages of adenocarcinoma, females, and never-smokers, this huge difference is difficult to explain. In addition, Asian patients were more often treated with an EGFR tyrosine kinase inhibitor after the protocol treatment. In this study, the use of cetuximab was restricted to patients whose tumors expressed EGFR; however, the criteria were not quantitative. A more definitive biomarker is essential for patient selection. How will future clinical trials of cetuximab in Asian patients be conducted? The FDA has not approved the use of cetuximab because no useful biomarker for selecting a target population for the drug exists, even though cetuximab had positive benefits on overall survival. There is, at this moment, no rationale for conducting another clinical trial of cetuximab in Asian patients because post-study subset analysis showed completely negative results in the Asian population.

Bevacizumab in Gastric Cancer

The Avastin in Gastric Cancer (AVAGAST) trial was a randomized, double-blind, placebo-controlled phase III study of first-line capecitabine (Xeloda) and cisplatin plus bevacizumab (Avastin) or placebo in patients with advanced gastric cancer. The primary endpoint of this study was not met. Heterogeneous efficacy results were obtained in both treatment arms across geographic regions.[8] In both arms, the median survival times (for chemotherapy alone and chemotherapy plus bevacizumab) were better in Asia (12.1 and 13.9 months, respectively) than in Europe (8.6 and 11.1 months, respectively) and the Americas (6.8 and 11.5 months, respectively). The hazard ratios for the chemotherapy-plus-bevacizumab group were 0.97 (0.75-1.25), 0.85 (0.63-1.14), and 0.63 (0.43-0.94) in Asian, European, and American patients, respectively.

In Asian patients, the tumor was mainly located in the gastric fundus, and tumors of the gastroesophageal junction accounted for only 6%. The frequency of liver metastasis was higher among Asian patients. The majority (66%) of Asian patients received second-line therapy. On the other hand, only 31% and 21% of European and pan-American patients, respectively, received second-line therapy. The reason for the difference in the treatment strategy was related to the tumor burden, patient status, medical practice patterns, and pharmacogenomics.

Based on the AVAGAST data, bevacizumab will not be tested in further clinical trials in Asian countries against gastric cancer, although such trials remain a possibility in Europe and the Americas.

Summary

Recent large cooperative multinational clinical trials have clarified uninvestigated factors that can influence drug effects. Some of these factors can clearly be explained by pharmacogenomic differences. However, the reasons for these pharmacogenomic differences remain unexplained. Other ethnic differences also cannot yet be clearly explained. Various factors must be kept in mind when conducting multinational trials, and stratifying patients according to region is likely to be necessary for the effective use of results pertaining to ethnic differences. ■

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Severe Interstitial Lung Disease Associated with Amrubicin Treatment

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Background: Amrubicin is a novel anthracycline agent that is well known to exert significant activity against small cell lung cancer (SCLC), but the adverse pulmonary effects of amrubicin are less well known. We investigated the incidence of acute interstitial lung disease (ILD) in SCLC patients who had been treated with amrubicin.

Methods: Medical records were used to retrospectively investigate a total of 100 cases of SCLC patients treated with single-agent amrubicin therapy at the National Cancer Center Hospital East between June 2003 and March 2008. The patients' radiographic records and clinical data were reviewed to identify patients who had developed acute ILD after being treated with amrubicin.

Results: After receiving amrubicin, seven of the 100 SCLC patients subsequently developed pulmonary infiltrates, and they were identified as cases of acute ILD associated with amrubicin. Of the seven patients who developed ILD, six were treated with corticosteroids, and the ILD improved in three of them, but the other three patients died of respiratory failure. The incidence of ILD was 33% (4/12) among the patients with pre-existing pulmonary fibrosis (PF) and 3% (3/88) among the patients without PF, and the difference between the two groups was statistically significant ($P = 0.0036$).

Conclusions: The results of this study indicated that amrubicin may cause severe ILD and that pre-existing PF was associated with a higher rate of ILD among SCLC patients treated with amrubicin. We recommend not administering amrubicin in the treatment of SCLC patients with pre-existing PF.

Key Words: Amrubicin, Interstitial lung disease, Toxicity, Small cell lung cancer, Chemotherapy.

(*J Thorac Oncol.* 2010;5: 1435–1438)

Amrubicin is a novel, totally synthetic 9-aminoanthracycline that is converted to an active metabolite, amrubicinol, as a result of reduction of its C-13 ketone group to a hydroxy group. Despite the similarity between the chemical structure of amrubicin and doxorubicin, amrubicin has a different mode of action. Amrubicin and amrubicinol are DNA topoisomerase II inhibitors, which exert their cytotoxic effects by stabilizing a topoisomerase II-mediated cleavable complex, and they are approximately 1/10 weaker than doxorubicin as a DNA intercalator. The in vitro cytotoxic activity of amrubicinol is 18 to 220 times more potent than that of its parent compound, amrubicin.[1,2] An in vivo comparison with doxorubicin showed that amrubicin has a more potent antitumor effect and lower toxic effects on the heart, which is a site of delayed toxicity with doxorubicin, and on the liver and kidneys.[3–5]

Amrubicin is a promising agent for the treatment of small cell lung cancer (SCLC).[6] Most patients with SCLC treated with standard chemotherapy, such as cisplatin plus etposide or cisplatin plus irinotecan, tend to experience a relapse within a year of the completion of treatment, and patients with relapsed SCLC historically have a poor outcome.[4,7] Some multicenter phase II trials in Japan or North America have shown that amrubicin has significant activity in patients with refractory or relapsed SCLC.[8,9] Randomized controlled trials with amrubicin for the treatment of SCLC patients are ongoing in the United States. The major toxicity of amrubicin is hematologic, and more than half of the patients treated with amrubicin develop grade 3 or 4 neutropenia. Nonhematologic toxicities, such as gastrointestinal toxicity or alopecia, are relatively mild. Surprisingly, several patients in Japanese phase II trials developed interstitial lung disease (ILD).[10,11] However, because the adverse pulmonary effects of amrubicin are less well known, in this study, we investigated the incidence of acute ILD in SCLC patients who had been treated with amrubicin.

PATIENTS AND METHODS

Medical records were used to retrospectively investigate a total of 100 consecutive cases of SCLC treated with single-agent amrubicin therapy at the National Cancer Center Hospital East between June 2003 and March 2008. The patients' radiologic reports and clinical data were reviewed to identify patients who had developed acute ILD after being treated with amrubicin. The study was approved by the institutional review board of our institution.

Three independent pulmonologists (K.Y., H.K., and Y.Y.) who had no knowledge of the patients' outcome diagnosed pre-existing lung conditions, i.e., pulmonary fibrosis (PF) and emphysematous change, based on the chest radiographic and

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computed tomographic (CT) findings before the start of amrubicin therapy. The diagnostic criteria for PF were a linear, ground-glass attenuation, or reticular shadows on chest radiographs and CT scans that were predominant in the lower zone of the lung. ILD was diagnosed on the basis of chest radiograph and CT findings (diffuse ground-glass opacity, reticular shadow, or consolidation without segmental distribution and honey-comb pattern), a serum lactate dehydrogenase (LDH) and/or KL-6, which is a mucin-like high-molecular-weight glycoprotein and shown to correlate well with the activities of several different kinds of interstitial pneumonia, elevation, and no evidence of underlying heart disease, infection, or lymphangitic carcinomatosis. Objective tumor response was assessed as complete response, partial response, stable disease ≥8 weeks, or progressive disease according to the Response Evaluation Criteria in Solid Tumors. Toxicity was graded by using the Common Terminology Criteria for Adverse Events version 3.0.

Univariate and multivariate analyses were performed to identify risk factors for ILD associated with amrubicin therapy. All comparisons between proportions were performed by the χ^2 test or Fisher's exact test, as appropriate. Multivariate analyses were performed using the logistic regression procedure to assess the relationship between several factors and the onset of ILD. *P* values less than 0.05 were considered statistically significant. Two-sided statistical tests were used in all analyses.

TABLE 1. Patient Characteristics

	Patients (n = 100)	
	N	%
Age (yr)		
Median	66	
Range	48–81	
Sex		
Female	17	17
Male	83	83
Performance status		
0/1	3/76	77
2/3	20/1	21
Smoking history		
Current/former smoker	98	98
Never smoker	2	2
No. of prior chemotherapy regimens		
1	43	43
2/3	51/6	57
Prior thoracic radiotherapy		
Yes	42	42
No	58	58
Pre-existing pulmonary fibrosis		
Yes	12	12
No	88	88
Pulmonary emphysematous change		
Yes	41	41
No	59	59
Amrubicin dose per square meter body surface area		
45 mg/m^2	37	37
40/35/30 mg/m^2	48/12/3	63

RESULTS

Patient Characteristics

The patients' characteristics are listed in Table 1. Their median age was 66 (range, 48–81) years, 17% of them were women, and 77% had an Eastern Cooperative Oncology Group performance status 0 and 1. Current smokers or exsmokers accounted for 98% of the patients, and emphysematous change was detected in 41% of the patients. Pre-existing PF was detected in 12% of the patients, but none of them had dyspnea. Amrubicin was used as a second-line treatment in 43% of the patients, and 57% had received two or more prior chemotherapy regimens. Amrubicin was diluted in 50 ml of normal saline and administered as a 5-minute daily intravenous injection at a dose of 30 to 45 mg/m^2 on 3 consecutive days, every 3 to 4 weeks.

Incidence and Outcome of ILD

After receiving amrubicin, 7 (7%) of the 100 SCLC patients developed pulmonary infiltrates in the absence of un-

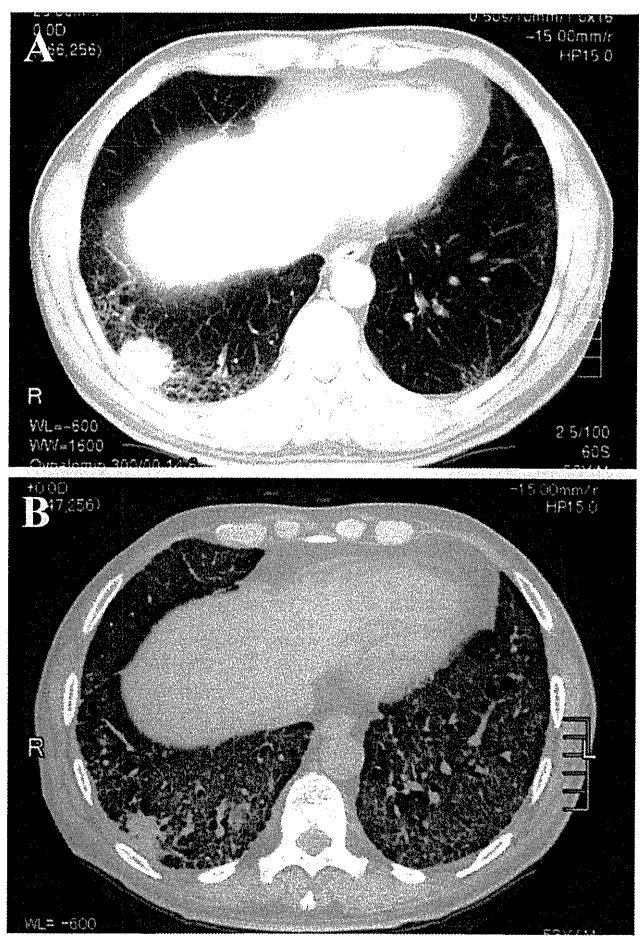

FIGURE 1. Computed tomography (CT) scans of the chest before and after treatment with amrubicin (patient 2 in Table 2). *A*, This CT scan of the chest before treatment with amrubicin shows a bilateral reticular shadow just beneath the pleura and a primary tumor in the right lower lobe. *B*, CT scan of the chest on day 17 of the first course of amrubicin therapy showing bilateral diffuse ground-glass opacities.

TABLE 2. Summary of Patients Who Developed Interstitial Lung Disease Associated with Amrubicin Therapy

No.	Age (yr)	Sex	PS	Smoking History	Prior Chemotherapy	Prior TRT	PF	Time to ILD From First AMR (d)	Initial Manifestations	ILD Status	Time to Death From Last AMR (d)
1	78	M	1	Yes	Carboplatin Etoposide	No	No	15 (day 15 in cycle 1)	Dyspnea, cough, hypoxemia	Died	23
2	53	M	2	Yes	Cisplatin Etoposide Irinotecan	No	Yes	17 (day 17 in cycle 1)	Dyspnea, fever, hypoxemia	Died	30
3	55	M	1	Yes	Cisplatin Etoposide Irinotecan	No	Yes	21 (day 21 in cycle 1)	Dyspnea, hypoxemia	Improved	—
4	70	M	1	Yes	Carboplatin Etoposide	No	Yes	22 (day 22 in cycle 1)	Dyspnea, fever, hypoxemia	Improved	—
5	64	M	1	No	Cisplatin Etoposide Irinotecan	Yes	No	43 (day 15 in cycle 2)	Cough, fever	Improved	—
6	62	M	1	Yes	Cisplatin Etoposide Irinotecan	No	Yes	72 (day 18 in cycle 3)	Dyspnea, hypoxemia	Improved	—
7	63	M	1	Yes	Carboplatin Etoposide	No	No	94 (day 21 in cycle 4)	Dyspnea, fever, hypoxemia	Died	36

PS, performance status; TRT, thoracic radiotherapy; PF, pre-existing pulmonary fibrosis; ILD, interstitial lung disease; AMR, amrubicin.

derlying heart disease, and they were identified as cases of acute ILD associated with amrubicin (Fig. 1). The characteristics of the seven patients with ILD are listed in Table 2. The median time between the start of amrubicin therapy and the diagnosis of ILD was 22 days (range, 15–94 days). All seven patients experienced acute onset or exacerbation of respiratory symptoms, and chest CT scans revealed the new diffuse interstitial changes in both lungs with ground-glass opacity and/or consolidation in all seven patients. Six of the seven patients who developed ILD, the exception being patient 6, received corticosteroid therapy consisting of 500 to 1000 mg methylprednisolone for 3 days, and the ILD improved in four of them. Three patients died of respiratory failure as a result of the ILD, but no autopsy was permitted in any of these three patients.

The results of the univariate analysis of risk factors for ILD associated with amrubicin therapy are shown in Table 3. The incidence of ILD associated with amrubicin was 33% (4/12) in patients with pre-existing PF and 3% (3/88) in patients without PF, and the difference in incidence between the two groups was statistically significant ($P = 0.004$). Based on the results of the univariate analysis, a multivariate analysis was performed using two variables (Pre-existing PF and LDH) and the results showed that pre-existing PF (odds ratio: 10.9, 95% confidence interval: 2.0–66.8) was a significant independent variable correlated with increased risk of ILD associated with amrubicin therapy ($P = 0.006$). LDH was not a significant independent variable (odds ratio: 3.3, 95% confidence interval: 0.44–66.3, $P = 0.30$).

TABLE 3. Relationship Between Clinical Variables and Interstitial Lung Disease Associated with Amrubicin Therapy

Variables	No. of Patients	Incidence of ILD (%)	p
Total	100	7	
Age			
<70 yr	65	7.7	>0.99
≥70 yr	35	5.7	
Sex			
Female	17	0	0.59
Male	83	8.4	
Performance status			
0/1	79	7.6	>0.99
2/3	21	4.8	
Smoking history			
Current/former smoker	98	6.1	0.13
Never smoker	2	50	
No. of prior chemotherapy regimens			
1	43	7	>0.99
2/3	57	7	
Prior thoracic radiotherapy			
Yes	42	2.4	0.23
No	58	10.3	
Pre-existing pulmonary fibrosis			
Yes	12	33.3	0.004
No	88	3.4	
Pulmonary emphysematous change			
Yes	41	9.8	0.69
No	59	5.1	
LDH			
High (more than upper limit of normal)	55	10.9	0.09
Normal	45	2.2	

ILD, interstitial lung disease; LDH, lactate dehydrogenase.

Efficacy of Amrubicin Therapy

The median number of cycles per patient was 2 (range, 1–6). The responses of all 100 patients were assessed, and the results showed a partial response in 32 patients, stable disease in 17 patients, and progressive disease in 51 patients. Thus, the overall response rate was 32% (32/100). The response rate of the chemotherapy-sensitive relapse (defined as relapse at an interval of ≥90 days after the completion of prior chemotherapy) group was 44% (18/41), which is higher than that in the refractory relapse (defined as relapse within 90 days after completion of prior chemotherapy) group (24% [14/59], $P = 0.034$). By contrast, the response rate of the group with pre-existing PF was 25% (3/12), as opposed to 33% (29/88) in the group without PF ($P = 0.74$).

DISCUSSION

Anticancer-agent-associated ILD is an important cause of respiratory failure during cancer chemotherapy.[12] Although the incidence of anticancer-agent-associated ILD seems low, more cases can be expected as increasing numbers of patients receive the new generations of anticancer agents, such as gemcitabine,[13] irinotecan,[14] docetaxel,[15] and gefitinib.[16] To our knowledge, this is the first review on the incidence of ILD in SCLC patients treated with amrubicin.

Amrubicin has already been tested as a treatment for advanced or relapsed SCLC in phase II trials and shown promising activity in Japan and North America. Yana et al.[11] reported finding that 1 (3%) of 33 previously untreated SCLC patients developed interstitial pneumonia after treatment with amrubicin. Inoue et al.[17] reported the results of a randomized phase II trial comparing amrubicin with topotecan in previously treated SCLC patients, and 1 (3.3%) of the 30 patients who received amrubicin had pneumonitis. No amrubicin-associated ILD was reported in two phase II trials of relapsed SCLC patients recently performed in the United States.[9,18] Based on the results of previous clinical trials, the risk of ILD seems to be around 0 to 3% in SCLC patients treated with amrubicin.

In this study, we found a relatively high incidence of ILD (7% of the patients) in SCLC patients treated with amrubicin, and it was higher than in previous clinical trials. The reason for the high incidence is thought to be the possibility of different background between the patients in the present and previous studies. Pre-existing PF has been reported to be the most significant risk factor for the development of anticancer-agent-associated ILD.[19] The patients in our study were treated with amrubicin as clinical practice and the incidence of pre-existing PF was 12%. In previous clinical trials, patients with pre-existing PF were ineligible and the incidence of pre-existing PF was unknown. We attempted to identify the risk factors for the development of amrubicin-associated ILD, and the results showed that pre-existing PF was associated with a significantly higher risk of amrubicin-associated ILD. In our study, six of the seven patients who developed amrubicin-associated ILD received corticosteroid therapy and the ILD improved in four of them. We speculate that patients who developed ILD may benefit partly from corticosteroids.

A major limitation of this study was that none of the patients diagnosed with amrubicin-associated ILD had undergone a lung biopsies during bronchoscopy and no autopsies were performed that would have enabled histologic confirmation of ILD. Therefore, we cannot completely exclude the possibility that the patients had developed lymphangitic carcinomatosis or other diseases and not ILD. However, because the clinical course and radiographic findings of these patients were consistent with drug-induced ILD, we made the diagnosis of amrubicin-associated ILD. In our study, only two patients underwent bronchoalveolar lavage culture. The bronchoalveolar lavage culture obtained from two patients showed no evidence of infection. The exact pathogenetic mechanism of amrubicin-associated ILD is unclear, and further investigation is needed to confirm this finding and evaluate associations between amrubicin-associated ILD and genetic or ethnic factors.

In conclusion, our findings indicated that amrubicin may cause severe ILD and that pre-existing PF was associated with a higher rate of amrubicin-associated ILD. We recommend not administering amrubicin in the treatment of SCLC patients with pre-existing PF. Physicians should have a caution and appropriate management to prevent the development of ILD when using amrubicin to treat patients with pre-existing PF.

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Progress in Cancer Chemotherapy with Special Stress on Molecular-targeted Therapy

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Numerous molecular-targeted drugs have been developed based on the progress in the study of molecular biology. Among them, some of the antibodies and small molecule tyrosine kinase inhibitors have been approved for clinical use. Standard therapies against common cancers have completely been changed. Individualized treatments have been possible in pharmacogenomically specific populations. Unbelievably improved progression-free and/or overall survivals have been achieved and cure rate has also improved in surgically resected patients by using molecular-targeted therapy. Prognostic and/or predictive factors have been identified and biomarker testing has become mandatory for human epidermal growth factor receptor 2 expression/amplification in breast cancer and gastric cancer, Kras mutation in colon cancer and epidermal growth factor receptor mutation in lung cancer. The development of active molecular-targeted therapy and more validated markers could enable the increment of curative populations even in advanced malignancies.

Key words: chemotherapy – molecular-targeted therapy

NEW EVOLUTION OF CANCER CHEMOTHERAPY

With the advances in molecular biological research, strategies for the development of new antineoplastic agents for cancer chemotherapy have changed markedly. Molecular-targeted therapy represents an attempt to achieve antitumor effects by selectively modifying the differences in the biological characteristics between normal and cancer cells or between normal and cancer tissues. An ideal molecular-targeted therapeutic agent should satisfy the following three pre-requisites: the treatment should be directed at the target, the treatment *per se* should have an antitumor effect and the antitumor effect should be explicable in terms of modification of the target. Molecular-targeted therapeutic agents can be classified into (i) compounds selectively modifying the molecular biological characteristics of the tumor cells *per se* and (ii) compounds selectively modifying the molecular biological characteristics of the neoplastic milieu. From the viewpoint of pharmaceutical preparations, they are classified into (i) small molecular substances of defined molecular weight and structure, and (ii) macromolecules such as antibodies, gene therapies, cell therapy and immunotherapy with peptide antigen. Molecular-targeted therapies now account for >70% of all anticancer agents currently under development. Further, the great majority of recent standard therapies for cancers of various organs include molecular-targeted therapies. Drugs capable of producing tumor shrinkage in types of cancer such as carcinoma of the kidney and carcinoma of the liver, for which no effective drugs existed until now, have been developed (1,2). Drugs such as thalidomide and lenalidomide have also been shown to be efficacious for myelomas, although the precise underlying mechanisms of actions are not yet known.

It was reported earlier that unlike conventional cytocidal antineoplastic agents, molecular-targeted therapies merely inhibit tumor growth and have no tumor-shrinkage effect, and adverse reactions are uncommon. This concept has proven totally misleading. Even though the view that therapeutic responses of molecular-targeted therapies should not be evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST) guideline (3) had been drilled into us, responses to anticancer agents are now evaluated using the RECIST guideline, regardless of who the investigator is, and drug approvals by the regulatory authority are based on such evaluation data in the case of accelerated approval. The tumor-shrinking effects of molecular-targeted therapies are actually dramatic. Unlike cytocidal antineoplastic agents,

toxicities such as myelotoxicity and alopecia are rare with molecular-targeted therapies, which exhibit various other organ toxicities, varying in profile.

MOLECULAR-TARGETED DRUGS AND MOLECULAR TARGETS

Of the conventional cytocidal antineoplastic agents, the actions of platinum compounds are directed toward the cellular DNA as the molecular target, those of taxanes and vinca alkaloids toward tubulin, those of camptothecin and etoposide toward topoisomerases I and II, respectively, and those of antimetabolites toward their respective target enzymes or proteins. These agents are usually not classified as molecular-targeted drugs, inasmuch as these targets also occur in normal cells. Recently developed drugs such as aurora kinase inhibitor, nevertheless, are basically thought to be cytocidal antineoplastic agents, although opinions are divided on which category they fall under. Cytocidal antineoplastic agents were identified earlier through random screening; eventually, this confusion seems to have arisen because it has recently become a common practice to select compounds which selectively inhibit pre-determined targets, as is the case with molecular-targeted drugs, through screening.

The molecular targets of molecular-targeted therapeutic agents occur more frequently in tumor cells and in the neoplastic milieu than in normal cells, so that the former become subject to a greater impact of treatment. In other words, molecular-targeted therapeutic agents also exhibit relatively selective toxicity, similar to cytocidal antineoplastic agents, with consequent efficacy (1).

There exist, needless to mention, certain molecular-targeted drugs directed toward tumor-specific targets such as Bcr-abl (4), EMR-4/ALK (5,6), mutant epidermal growth factor receptor (EGFR) (7,8) and mutant c-kit (9). Screening for molecular-targeted therapeutic agents is carried out by selectively modifying the identified targets, through a usually random process. Consequently, the compounds developed unfailingly modified the target, yet the effects of the drugs were not necessarily limited to the target alone. Eventually, this led to the development of a number of 'dirty' (multitargeted) drugs, as described below.

EFFECTS OF MOLECULAR-TARGETED THERAPEUTIC AGENTS

Therapeutic responses to a molecular-targeted drug are determined depending on whether or not there exists a target for the drug; therefore, they would be the all or none type in the case of tumor cell-specific molecular-targeted therapeutic agents. Thus, the antitumor spectrum of such drugs is narrow, whereas the therapeutic responses are pronounced. On the other hand, the responses to cytocidal antineoplastic agents are reverse (Fig. 1) (10). Figure 2 shows a Waterfall plot analysis of the effects. Cytocidal antineoplastic agents

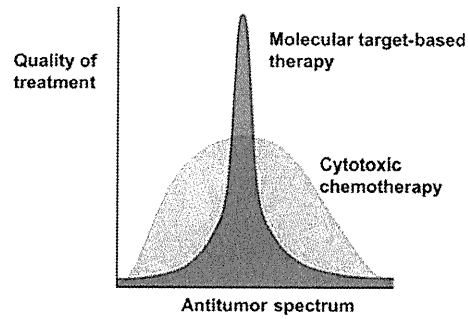

Figure 1. Improvement of treatment quality.

exert antitumor effects in owing to their cytotoxicity affecting the DNA and the cytoskeleton, so that they produce a considerable reduction in the tumor bulk even in cases of stabilized disease other than responders such as complete response + partial response according to RECIST, when compared with untreated cases. Molecular-targeted therapeutic agents, on the other hand, exert no effect at all on cells devoid of the target; therefore, the reduction in tumor bulk achieved following their use is estimated to be smaller even at comparable response rates when compared with that achieved with cytocidal antineoplastic agents. Thus, the points at issue inherent in the comparison of responses to molecular-targeted therapeutic agents, especially those compounds specifically acting upon tumor cells, and those to cytocidal antineoplastic agents on the same scale (Fig. 2) are yet to be adequately discussed.

TARGET CLASSIFICATION OF MOLECULAR-TARGETED THERAPEUTIC AGENTS

Targets for molecular-targeted therapeutic agents have been classified into several categories: (i) cell surface antigens, (ii) growth factors/receptors/signal transduction pathways, (iii) cell cycle, (iv) apoptosis, (v) antigens, (vi) telomere/telomerase, (vii) metastasis and (viii) angiogenesis (Table 1). Most molecular-targeted therapeutic agents that are targeted to cell surface antigens are antibodies. One of the representative agents is Rituxan, which has contributed significantly to the improvement of the therapeutic outcome in patients with lymphomas. Antibodies labeled with radioisotopes for enhancement of the therapeutic effect have been used. Immunotherapy with peptide antigens also comes under this category. Recently, Oncophage cancer vaccine of Antigenics Inc., which has been designed to capture the particular cancer's fingerprint containing unique antigens based on heat shock technology, has received approval for individualized therapy of kidney cancer in Russia and an application has been filled with European Medicines Evaluation Agency (EMEA). Furthermore, it has been reported that administration of a

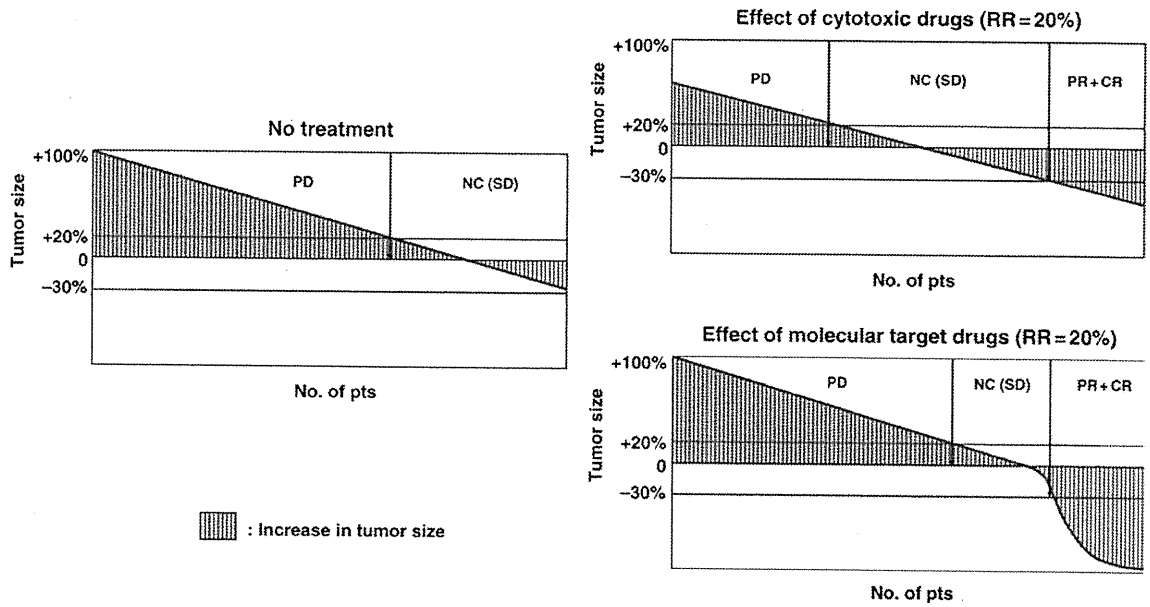

Figure 2. Difference in the effect of cytotoxic drugs and molecular target drugs (Waterfall plots).

Table 1. Classification of molecular targets and molecular-targeted drugs

Surface antigen
Anti-CD20 antibody, peptide antigen
Growth factor, receptor, signal transduction pathways
Anti-EGFR Ab, anti-HER1 Ab, anti-EGFR Ab
EGFR-TKI, c-kitR-TKI, Bcr-abl-TKI, farnesyltransfarase inhibitor, protein kinase inhibitor, m-TOR inhibitor, proteasome inhibitor, PARP inhibitor
Cell cycle
Cyclin kinase inhibitor
Apoptosis
Apoptosis inducer
Angiogenesis, Metastasis
Anti-VEGF Ab: VEGF-TKI
MMP inhibitor: salidomide
Angiostatin: endostatin
Multitarget
Multitarget TKI

Ab, antibody; m-Tor, mammalian target of rapamycin; MMP, matrix metalloprotease.

vaccine called Provenge targeted for prostatic acid phophatase, a product of Dendreon Corporation, prolonged the survival time of patients with prostatic cancer refractory to standard hormone therapy (11).

There are numerous molecular-targeted therapeutic agents related to growth factors/receptors/signal transduction systems. Trastuzumab (9,12–14), c-kit and Bcr-abl tyrosine kinase (4) inhibitors have proven to be remarkably efficacious in the clinical setting, thereby completely changing the conventional standard treatments. NSABP B-31, NCCTGN9831 and HERA trials clearly demonstrated the survival benefit of trastuzumab in HER-2(+) breast cancer compared with chemotherapy alone. EGFR tyrosine kinase inhibitors were shown to yield a dramatically beneficial effect with high response rates in the treatment of lung cancer carrying mutant EGFR (7,8,15–19); however, the treatment yields only low response rates in non-selected patients and proves entirely ineffective in patients carrying non-mutated EGFR (Fig. 3); therefore, it has been difficult to demonstrate a survival-prolonging effect in clinical trials in unselected population.

Attention has been focused in recent studies on drugs such as poly-ADP-ribose polymerase (PARP) inhibitors, which are selectively effective in the treatment of BRCA1- or BRCA2-deficient carcinomas of the ovary (20–22). Drugs such as cell cycle inhibitors and apoptosis inducers have also been investigated in various studies, including gene therapies, but with no noticeable results yet.

In contrast, unexpectedly gratifying results have been obtained with angiogenesis inhibitors. Matrix metalloprotease inhibitors have been evaluated in clinical trials from the outset; however, all of these agents have been found negative for clinical efficacy, suggesting that molecular-targeted therapeutic agents acting on the neoplastic milieu might not prove all that effective. However, bevacizumab, an antibody directed against VEGF *per se*, was demonstrated to significantly prolong the progression-free and overall survivals in patients with carcinoma of the large bowel (23–25), non-small cell cancer of the lung (26,27), breast cancer (28–32) and gastric cancer. It was thought earlier that inhibition of angiogenesis might decrease

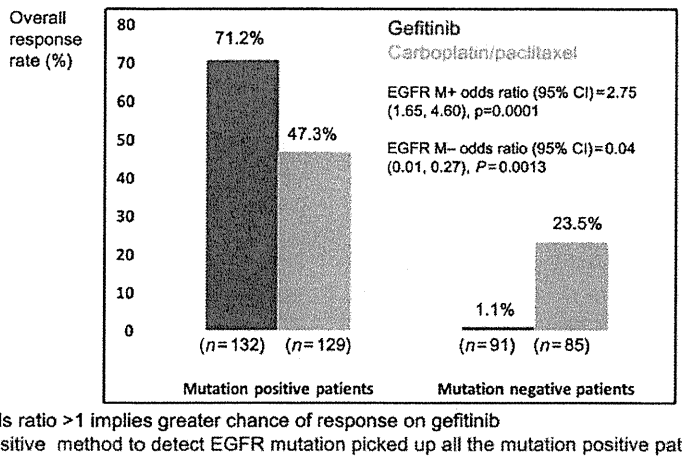

Figure 3. Objective response rate in EGFR mutation-positive and -negative patients. EGFR M, EGFR mutation.

antineoplastic agents from reaching the lesion, diminishing their efficacy. Undoubtedly, concomitant use of bevacizumab with antineoplastic agents has markedly improved the response rate, although it remains unknown to what extent the theory that vascular normalization and reduction in tissue pressure produced by bevacizumab would bring about enhancement of the effect of antineoplastic agents is valid (33–35). A recently reported comparative study of FOLFOX (5FU + leucovorin + oxaliplatin) + bevacizumab as a post-operative adjuvant therapy in colorectal cancer patients failed to demonstrate any additive/synergistic effect with the addition of bevacizumab (36). This might be ascribed to the characteristics of angiogenesis inhibitors. In other words, enhancement of the effects of cytocidal antineoplastic agents and the effect solely upon actively newly generated blood vessels are considered to account for the response.

MULTIMOLECULAR-TARGETED THERAPEUTIC AGENTS

Recently, a number of molecular-targeted therapeutic agents that act upon diverse targets have been developed. When viewed with reference to the process of drug development, these drugs, although termed molecular-targeted agents, do not necessarily act on any particular target alone, even if they selectively modify a certain target. It seems very likely that the development of multimolecular-targeted therapeutic agents were not initially aimed at multitarget modification (1,2). Since signal transduction systems are composed of complex networks, one of the potential targets could be involved in inhibition of tumor growth by simultaneously blocking a plurality of pathways involved. However, the more complex the targets, the more difficult will be to conduct a proof-of-principle (POP) study. It is also difficult to choose between the use of a dirty (multitargeted) drug or concurrent use of molecular-targeted drugs directed at different targets. Investigations on drugs such as sorafenib, sunitinib and vandetanib, which are ongoing, have been confirmed to prolong progression-free or overall survival, yet it is not uncommon that even investigators themselves do not clearly recognize the target of the study drug in the clinical trials they are conducting. The drugs, therefore, deserve the given name of dirty drugs. It appears that much clinical trial data which would only be a source of brain-wracking troubles may be gained if clear POP studies are lacking. Selection of a patient population possessing the target is considered to be necessary for clinical trial of a molecular-targeting therapy directed at a molecular target occurring in cancer cells *per se*, so that at least patient selection for the trial based on pharmacogenomic and/or clinicopathological data is advisable. In the case of cancer milieu-specific molecular-targeted therapeutics, on the other hand, patient selection is not undertaken because the target does not exist in the cancer cells *per se*. It is generally thought that combined effects can be obtained in the case of dirty (multitargeted) drugs because the drugs are endowed with multiple functions. It has proven extremely difficult, nevertheless, to verify how various functions contribute to the antitumor therapeutic responses.

POP STUDY

The trend of antineoplastic drug development has been shifting toward a more theoretical approach targeted at genes causative of malignant changes and directing cancer growth and development of metastases. For the development of cytocidal antineoplastic agents, compounds are screened first for cytocidal activity both *in vitro* and *in vivo*, followed by studies to elucidate the underlying mechanism of actions, whereas for the development of

molecular-targeted therapeutics, a target is to be identified in the first place and then a compound developed that would selectively modify the target, as described above. An important type of study in the process of development of a molecular-targeted therapeutic agent is called a POP study, and this term is used as a surrogate for translational study in the USA. Studies conducted to demonstrate the antitumor activity *in vivo* of a compound developed as an antineoplastic agent and to demonstrate that the antitumor activity is effected via modification of a target molecule are called POP studies and may be said to represent research to evaluate the effect against the target molecule that can be correlated with clinical responses (clinical effect surrogate or clinical benefit surrogate). The often used term 'Molecular Correlate' differs from a POP study. 'Molecular Correlate' does not always correlate with clinical responses, even though findings appearing by chance to be correlated may be obtained. The methods of quantitation applied in POP studies are pharmacogenomics (PGx) and functional imaging (1,2). Techniques for PGx investigation include immunohistochemistry, genetic constitution, gene expression (genomics) (37,38), protein expression (proteomics) and single-nucleotide polymorphism (SNP) analysis (39–42) (Table 2). Studies for comprehensive analysis of gene or protein expressions, i.e. genomics and proteomics, have reportedly been contributory to the identification of gene signature which constitutes a prognostic factor in breast and colon cancers. However, there are little or no data of value from the viewpoint of the relationship with clinical effects. Such hypothesis-free analyses may enable exploration of novel candidates in some instances, but they do not carry adequate investigative potential that can make an immediate contribution, and involve frequent slipping of inexplicable molecules. Gene signatures identified fail to match among studies or even by the assay kit used, and opinions casting doubt were put forth at the symposium held by the American Association for Cancer Research (AACR) and the American Society of Clinical Oncology (ASCO). The genes and proteins which have been selected using biostatistical methods include a number of those of which the biological significance remains unclear. Meanwhile, results of studies on deletions/mutations of specific genes and expressions of SNP and gene products (proteins) are relatively reliable in so far as the samples and techniques are dependable. These studies analyze only what are comprehensible because of their hypothesis-driven nature. Therefore, they are readily explicable on biological bases and have investigative potential that can contribute from the outset. In fact, examples where a POP study proves valid in the clinical setting are uncommon, but a majority of the POP studies are hypothesis-driven. Regarded as representative are Bcr-abl in chronic myelogenous leukemia (4), mutant c-kit in gastrointestinal stromal tumor (9) and CD20 in lymphosarcoma, but, in each of these disorders, there is a 1:1 correspondence of the pathological name with the molecular target, so that a POP study is unnecessary in a certain sense of the term, while it is rather important to search for an accountable gene in the case of emergence of resistance. HER-2 expression with trastuzumab, EGFR expression with cetuximab and effect of EGFR tyrosine kinase inhibitors (EGFR-TKIs) in relation to EGFR mutation (7,8) as well as PARP inhibitors in BRCA1- and 2-deficient tumor and ALK inhibitors in EML-4/ALK translocation may be said to exemplify somewhat successful POP studies (Table 3). It is a well-known fact, nevertheless, that vast amounts of negative data were accumulated in the early stage of investigation until April 2004 when the target in EGFR-TKIs was thought to be EGFR expression.

The author would like to refer a little here to POP study on cytocidal antineoplastic agents, rather than molecular-targeted antineoplastic agents, to avoid confusion. There have been many reports dealing with the relation of platinum resistance with the excision repair cross-complementation 1 (ERCC1) expression in lung cancer. ERCC1 expression constitutes a prognostic factor, its up-regulation occurrence is higher and the prognosis is

Table 2. Techniques for the detection of pharmacogenomic differences

Immunohistochemistry
Gene constitution
Mutation (deletion, point mutation, re-arrangement)
Amplification
Transcription: gene expression (single gene, exhaustive analysis, gene signature)
Proteom: protein expression (single protein, exhaustive analysis, protein signature)
SNP analysis
Functional imaging

SNP, single nucleotide polymorphism.

Table 3. Classification of biomarkers

Known valid biomarkers: test required
Accepted by scientific community at large to predict clinical outcome
Herceptin (Her2), EGFR-TKI (EGFRmt), Erbitux (EGFR, KRASmt), PARP-I (BRCA1&2 mt.def.)
ALK-I (EML4-ALK), HL-A type
Probable valid biomarkers: test recommended
Appears to have predictive value but not yet replicated or widely accepted
UGT1A1*28,*6, Cytidine deaminase*3
Exploratory biomarkers: (valid, non-valid) information only
Supported by initial identification data
Genomic and proteomic predictors (single gene: ERCC1, RRM1, MSH2, TS, exhaustive analysis, gene/protein signatures)

RRM1, ribonucleotide reductase M1; MSH2, mtS homolog 2; TS, thymidylate synthetase; UGT, uridine 5′diphosphate glucuronyl transferase.

favorable, but the tumor sensitivity to platinum drugs is diminished, with a consequently poorer therapeutic response (43–49). Further, numerous study data have been reported concerning gemcitabine in relation to ribonucleotide reductase subunit 1, taxanes in relation to α- or β-tubulin abnormalities, thymidylate synthetase; levels in relation to fluorinated pyrimidines and pemetrexed etc. The meaning of individualization naturally differs between positive selection of effective drugs using biomarkers and negative selection of not using drugs considered to be ineffective, and it is difficult to gain positive data in the latter case. In any event, it is necessary that validation of results obtained through POP studies is carried out in terms of correlation with the response rate and survival time based on the RECIST guideline.

CLINICAL DEVELOPMENT OF MOLECULAR-TARGETED THERAPIES

The efficiency of the current drug development system is poor, in that it entails problems such as (i) increased costs of new drug development, (ii) protracted duration of development, (iii) discontinuation or suspension of development at the late stage and (iv) impracticable estimation or monitoring of clinical responses. The Food and Drug Administration (FDA) put forth a proposal in 2006 for reformation of the drug development system through the Critical Path Initiative, viz. (50), curtailment of research expenses for new drug development, improvement of the development success rate and speeding up of the development. As an effective tool for the embodiment of these objectives, utilization of biomarkers in all processes of drug development is recommended. The FDA published a guideline in the form of FDA exploring the investigational new drug (IND) guideline in concert with the critical path initiative to guide the conduct of exploratory early-phase clinical trials. To make the clinical path, which is the process from non-clinical studies to Phase I–III clinical trials, more consistent with the theory, the guideline recommends researches on biomarkers serving as clinical effect/benefit surrogates and their development. A biomarker is defined as 'a characteristic that can be objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes or pharmacologic/pharmacodynamic responses to a therapeutic intervention (51).' The reason why pharmaceutical manufacturers attach importance to biomarkers rests not only in the improvement of the efficiency with respect to the costs of drug development/duration/size of patient population, but also importantly in the fact that the developmental effort relies on PGx-based biomarker data when it is difficult to make a GO/NO-GO decision on the ground of pharmacokinetic/pharmacodynamic data from Phase I clinical trials. A biomarker used under such circumstances is measured as a clinical effect/benefit surrogate, where it is of importance to observe the following precautions. They include the extent of implication of the target in tumor growth etc., sensitivity of the target detection technique, the specificity, singularity of target expression in each tissue/organ, degree of heterogeneity, utilizability of tissue(s) and validation based on clinical evaluation (52). The following points may account for failures in the evaluation of a surrogate marker: (i) the surrogate does not constitute the cause of the disease; (ii) a therapeutic agent only has impact on pathway(s) to which the surrogate is related, while a disease may arise via various pathways; (iii) the surrogate is non-existent in the pathway subject to modification by therapy, or should it occur in that pathway, it is insensitive to therapy; and (iv) therapy operates through a mechanism of action divergent from the cause of the disease.

It is ideal indeed that as proposed by the FDA, measurement of a surrogate and the development of biomarker(s) be pursued concurrently with the development of a therapeutic agent, but many biomarkers are still in a stage of basic research. Studies on biomarkers, especially POP studies, nevertheless, will lead to reverse-translational studies that can lead to clearer elucidation of the cancer biology and are expected to bring forth discovery of new molecular targets and the development of compounds against those targets.

CONCLUSION

Recent development of molecular-targeted drugs has been summarized. Chemotherapy has become one of the most important strategies for cancer treatment. Cure rate, overall survival and progression-free survival have dramatically improved by individualized therapy.

Identification of valid biomarker will enable the further improvement of molecular-targeted therapy.

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Conflict of interest statement

None declared.

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Original Articles

Lung Cancer Working Group Report

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Asia needs a guideline for non-small-cell lung cancer because of differences in medical care, medical care insurance, ethnic variation and drug approval lag within Asian countries and compared with Western countries. Due to ethnic differences, drug dosages are often higher in the USA than in Japan. EGFR mutation in non-small-cell lung cancer was detected in 32% of Asians but only 6% of non-Asians, while differences in irinotecan metabolism cause higher frequencies of toxicity (leukopenia, diarrhea) in Asians. Pharmacodynamic ethnic differences in relation to paclitaxel/carboplatin resulted in longer median survival and a higher 1-year survival rate for Japanese-advanced non-small-cell lung cancer patients compared with Americans. To solve the problem of drug lag, pharmaceutical companies must perform multinational Asian clinical trials with quick accrual of patients, while regulatory authorities must establish high-quality, efficient approval processes, and achieve regulatory harmonization. The National Comprehensive Cancer Network promotes creation of national clinical practice guidelines, and Korea, China and Thailand adapted the National Comprehensive Cancer Network guidelines. Many Asian countries still lack such guidelines, and there are no pan-Asian guidelines for non-small-cell lung cancer. Japan developed its own non-small-cell lung cancer guidelines and also a gefitinib guidance. The study group members concluded that immediate establishment of an Asian non-small-cell lung cancer guideline will be difficult because of the differences among the countries. Asian collaborative trials on treatment of non-small-cell lung cancer need to be started at an early date to generate Asian data.

Key words: non-small-cell lung cancer – EGFR mutation – ethnic differences

GUIDELINES

Asia needs a guideline for non-small-cell lung cancer (NSCLC) (1,2). One reason is the differences in medical care for lung cancer within Asian countries (3–9), such as performance of systematic lymph node dissection versus sampling only. There are also differences in medical care insurance and the economic situations among Asian countries. Ethnic variation in pharmacogenomics is yet another reason for needing an Asian guideline (10–14). Differences exist in the selection of validated data, such as for histology, that is, non-squamous versus squamous, biomarkers such as ERCC1, RRM1 and MSH2 (15–23). The concept of consolidation/maintenance therapy also differs between Western and Asian countries. Drug lag in some Asian countries is another important factor affecting treatment of NSCLC (Table 1).

With regard to ethnic differences, the ICH-E5 guideline states that, 'Although ethnic differences among populations may cause differences in a medicine's safety, efficacy, dosage or dose regimen, many medicines have comparable characteristics and effects across regions.' However, comparison

Table 1. Why do we need Asian guideline for lung cancer?

Difference in medical care for lung cancer
Systematic LN dissection versus sampling
Difference in Medical Care Insurance and economical situation
Ethnic difference of PGX
Evidence obtained specifically from Asian (Japanese) patients (trials)
UFT adjuvant (Stage 1B)
Gefitinib and erlotinib (advanced)
Irinotecan (small and non-small)
Difference in the selection of validated data
Histology: non-squamous versus squamous
Biomarker: ERCC1, RRM1, MSH2
Consolidation/maintenance therapy
Drug lag

between the US and Japan revealed that the US daily doses were higher than those in Japan for 33% of several cardiovascular and other drugs. In addition, ethnic differences are seen in regard to the molecular target, with the EGFR mutation rate being different, as well as drug metabolism and receptor sites.

Concerning molecular targeting, gefitinib monotherapy data can be compared between geographic regions on the basis of the IDEAL I and II Phase II studies (24,25), which were carried out in Japanese and non-Japanese populations, and in Americans, respectively. The patient characteristics were exactly the same in the three populations, but the response rate was significantly higher in the Japanese population, the median survival duration was also higher and the 1-year survival rate was double that of Americans. EGFR mutation in NSCLC was detected at a higher incidence in Asians than in non-Asians, by 32 to 6%. Moreover, the frequency of EGFR mutations was higher in every clinical subgroup, i.e. smokers, non-smokers, adenocarcinoma, males, females, etc., of East-Asian patients compared with non-East-Asian patients (1,26). Gefitinib is known to induce pulmonary toxicity. In Japanese studies, the frequency of gefitinib-induced interstitial lung disease (ILD) ranged from 3.5 to 5.8%, and the ILD mortality ranged from 1.6 to 3.6% (1). In contrast, the frequency of ILD was very low in the USA and other Asian countries, i.e. 0.36 and 0.34% (Table 2).

Irinotecan is another example of ethnic differences is in drug metabolism. Irinotecan is activated to SN-38 by carboxyesterase and then converted to SN-38G by beta-glucuronidase. UGT1A1 is an enzyme that converts SN-38 to SN-38G by glucuronidation. The UGT1A1 promoter shows polymorphism (4,5). When the UGT1A1 promoter has a genotype of 7/7, SN-38 glucuronidation is greatly decreased, and bilirubin glucuronidation is also somewhat decreased. Thus, patients with the 7/7 genotype show higher frequencies of toxicity, such as grade 4 leukopenia and/or grade 3 or higher diarrhea, compared with other UGT1A1 genotypes. In patients with the 7/7 genotype, the AUC of SN-38 is higher compared with other genotypes, while the SN-38G/SN-38 ratio is significantly lower. The distributions of the UGT1A1*28 promoter genotypes differ among racial groups. The 7/7 genotype was observed in only 3% of Japanese and Asian populations, whereas it was present at significantly higher rates of 17% in Canadians, 12% in Caucasians and 23% in Africans (3).

A common-arm analysis was performed to detect pharmacodynamic ethnic differences in paclitaxel plus carboplatin in the treatment of advanced NSCLC in Japan and the USA (27,28). Three trials were included in the analysis: the FACS, JMTO (LC00-03) and SWOG (S0003). The common arm was paclitaxel/carboplatin. The patient characteristics (age, gender and percentages of Stage IV and non-squamous cell carcinoma) were compared and were almost the same in the three studies. The toxicity of the treatment was analyzed with regard to the frequencies of neutropenia and febrile neutropenia, both of which were significantly higher in the Japanese population compared with the American population. When the same dose and same schedule were employed and the efficacy was analyzed, the response rate was almost the same in each of the studies. However, the median survival was 12 and 14 months in the two Japanese studies compared with 9 months in the American study (Tables 3 and 4). The 1-year survival rate was also higher in the Japanese populations compared with the American

Table 2. ILD by EGFR-TKI

	Number of patients	ILD (%)	ILD mortality (%)	Risk factors
WJTOG	1976	70 (3.5)	31 (1.6)	Male, smoker, pulmonary fibrosis
Prospective study of AZ	3322	193 (5.8)	75 (2.5%)	Poor PS, smoker, pulmonary fibrosis, prior CT
Okayama study group	330	15 (4.5)	8 (2.4)	
NCCH	112	6 (5.4)	4 (3.6)	
USA	~24 000	0.36	0.06	
AZ (Asian patient excluding Japanese)	53 150	0.34	0.11	
Korea	111	0		
China	31	0		

Table 3. Toxicity analysis

	FACS ($N = 145$)	LC00-03 ($N = 197$)	S0003 ($N = 186$)	*P*-value
Neutropenia (group 4), *N* (%)	102 (69)	106 (69)	48 (26)	<0.0001
Febrile neutropenia (groups 3–4), *N* (%)	26 (18)	38 (19)	6 (3%)	<0.0001

Gandara: ASCO 2004; Crowley: ASCO 2006; Gandara JCO 2009 (27).

Table 4. Efficacy

	FACS ($N = 145$)	LC00-03 ($N = 197$)	S0003 ($N = 182$)	*P*-value
Complete + partial response, *N* (%)	47 (32)	71 (36)	61 (34)	0.61
PFS (months)	4.5	6	4	NA
MST (months)	12	14	9	NA
1-year survival rate (%)	51	57	37	0.001

NA, statistical comparison not applicable.
Gandara: ASCO 2004; Crowley: ASCO 2006; Gandara JCO 2009 (27).

Table 5. Solution to drug lag in East Asia

Pharmaceutical companies
Simultaneous clinical development
Multinational clinical trial
Asian clinical trial
Investigations
Quick accrual of patients
Regulatories
Established high quality and speedy approval process
Regulatory harmonization and more collaborations among regulatory agencies

population: 51 and 57% versus 37%. Korean and Chinese trials have shown the same tendency.

Another very important factor is the lag time until drug approval. Comparison of Japan with the EU and the US shows that the average time from the first approval anywhere in the world until approval in each other country was about 500 days in the US and the UK, but over 1400 days in Japan. Looking at drug lag in East Asia shows that Taiwan and Korea were a little bit quicker than Japan and China for approval of some drugs. To solve this problem of drug lag in East Asia, it will be necessary for pharmaceutical companies to perform simultaneous clinical development in multiple countries, multinational clinical trials and Asian clinical trials. Also, investigators need to achieve quick accrual of patients, while the regulatory authorities need to establish high quality and speedy approval processes, and achieve regulatory harmonization and better collaboration among agencies (Table 5).

The National Comprehensive Cancer Network (NCCN) is an alliance of 21 of the world's leading cancer centers that is based in the USA. The NCCN promotes the importance of continuous quality improvement and creation of international and national clinical practice guidelines (10). The NCCN has international initiatives in Asia, including adaptation of NCCN Clinical Practice Guidelines in Oncology to create NCCN approved, translated and/or regionally adapted materials for national use. The process for such adaptation is that the NCCN authorizes selected groups to adapt its Practice Guidelines for national use. The participating countries select disease-specific representatives to review and suggest modifications to specific guidelines. Then the NCCN guidelines are circulated to multidisciplinary physicians in that country to determine where local practice is not concordant with the NCCN version. Regional meetings are held to agree on proposals, supported by data, for adaptation of the guidelines. A consensus for adaptation is approved by the NCCN, and the changes from the NCCN version are identified in the adaptation.

Asian consensus statements are intended as a reference and stepping stone for individual countries in Asia that do not yet have local editions of the NCCN guidelines so that they can develop their own guidelines. There have still been no pan-Asian guidelines developed for NSCLC. In general, the NCCN guidelines or national adaptations, or other recognized guidelines (e.g. ASCO, ACCP), are followed. Asian consensus statements are developed through the NCCN to help individual countries establish their own guidelines. As national NSCLC guidelines, Korea, China and Thailand adapted the NCCN guidelines. In Japan, the Japanese Society of Lung Cancer developed a Lung Cancer Practice Guideline in 2003 (13); this is different from the NCCN guidelines. China also has a Chinese Lung Cancer Management Guideline that is based on Chinese clinical practice and is used by most Chinese doctors. It was issued by the Chinese Society of Lung Cancer and is revised every 2 years. Hong Kong, India, Malaysia, Taiwan and Singapore have no NSCLC guideline (Table 6).

There are several differences between the NCCN version 2/2009 and the Korean NCCN 2008. For Stage IIIB resectable satellite lesions, the Korean NCCN guidelines specify the strategies for pN 0-1 and pN0. The therapy for recurrent and metastatic disease, chemotherapy for progressive disease and adjuvant chemotherapy regimens also differ between these guidelines. Comparison of the Korean NCCN guidelines and the ASCO guidelines shows that key differences exist in relation to Stage I disease and resected Stages I–IIIA. For Stage I, the Korean NCCN guidelines suggest adjuvant chemotherapy as an option, whereas it is not recommended in the ASCO guidelines (29). For resected Stages I–IIIA, the Korean NCCN guidelines suggest adjuvant radiotherapy when margins are positive, but it is not routinely recommended in the ASCO guidelines. The ASCO

Table 6. Current NSCLC guidelines in Asia

Pan-Asian guidelines
There are no pan-Asian guidelines developed for NSCLC
NCCN guidelines (or national adaptations of these) or other recognised guidelines (e.g. ASCO, ACCP) are generally followed
Asia Consensus Statements are developed through NCCN to help countries develop their own guidelines
National guidelines
Korea, Thailand: adaptation of NCCN guidelines
Japan: Japanese Society Lung Cancer developed Lung Cancer Practice guideline (2003)
China: adaptation of NCCN guidelines, Chinese LC Management Guideline
The following countries do not appear to have individual national guidelines
Hong Kong, India, Malaysia, Taiwan, Singapore

guidelines are very conservative and revised every 5 years, whereas the Korean NCCN guidelines are revised very frequently. Major institutions generally apply the Korean KCCN guidelines (11).

Regarding the current guideline for NSCLC in Japan, the background of its preparation includes such factors as that lung cancer is the number-one cause of death in Japan, the death rate due to lung cancer is increasing rapid, the cure rate is low at about 10–15%, there has been development of diverse diagnostic and treatment methods, and there is a need for a guideline that indicates standard medical care for lung cancer. The guideline should be evidence based, with scientific evidence obtained from clinical trials, should take into account the patients' requirements and preferences, and should also take into account physicians' professional experience and knowledge. As the method for development of a guideline, a systematic search of the published literature during the last 10–20 years should encompass PubMed, the Cochrane Review, Japanese medical journals, etc., critical and quantitative/qualitative evaluation of evidence, and scientific recommendations. Various key words are used to search the literature.

With regard to the history of development of a guideline for medical care of lung cancer in Japan, a study group was formed in 2001, with support from the Japanese Ministry of Health, Labour and Welfare (MHLW). The study group consisted of representatives from various Japanese medical societies, including the Japanese Society of Lung Cancer and the Japanese Society of Respiratory Disease. In 2003, the first 'Guideline for Medical Care in Lung Cancer (13),' also supported by grants from the MHLW, was developed. In 2005, the Guideline was revised by the Japanese Society of Lung Cancer. The contents of the guideline consisted of medical care (diagnosis and treatment modalities) and staging. The classification of the evidence level was similar to that for other guidelines. The highest level of evidence was (i) systematic review and meta-analysis of multiple randomized clinical trials. Subsequent levels consisted of (ii) more than one RCT, (iii) a non-RCT such as a Phase II study, (iv) an analytical-epidemiological study such as a cohort study or case-controlled study, (v) case reports and/or case series, and (vi) personal opinions of specialists or committee members. The recommendation levels consisted of (A) strongly recommended, (B) recommended, (C) not enough data for recommendation and (D) recommended not to do. Decision-making regarding the recommendation was based on the (A) evidence level, (B) amount of evidence and consistency, (C) hazard ratio (difference in efficacy), (D) clinical applicability and (E) evidence of toxicity and cost.

In the EBM guideline to chemotherapy for lung cancer, the recommendations regarding the roles of chemotherapy for advanced NSCLC are (i) chemotherapy in unresectable advanced NSCLC patients prolongs survival, improves QOL and is strongly recommended in this group of patients (Grade A recommendation) and (ii) chemotherapy in elderly, unresectable advanced NSCLC patients prolongs survival, improves QOL and is strongly recommended in this group of patients (Grade B recommendation). The recommendations regarding the target population for chemotherapy are (i) chemotherapy is recommended in patients less than 75 years old with a good performance status (PS 0, 1) (Grade A), (ii) chemotherapy is also recommended in patients more than 75 years old with a good PS (0, 1) (Grade B) and (iii) possibility of chemotherapy in PS 2 patients, but there is no evidence (Grade C). (underlining indicates a difference from Western guidelines.) There is the issue of use of gefitinib in patients with EGFR mutation, and the guideline thus needs to be revised.

The recommendations regarding the selection of anti-cancer drugs are (i) cisplatin-containing doublets are strongly recommended in patients less than 75 years old with a good PS (0, 1) (Grade A), (ii) drugs to be combined with cisplatin are irinotecan, vinorelbine, gemcitabine, paclitaxel and docetaxel (Grade A), and (iii) non-platinum doublets are recommended in patients who might be suffering from cisplatin-induced toxicity (Grade A). Questions remain regarding the use of gefitinib in patients with EGFR mutation and whether pemetrexed should be used, and the guideline thus needs to be revised.

The recommendation regarding the duration of chemotherapy is that first-line chemotherapy should consist of three to six courses (Grade B). But recently there has been development of the concepts of consolidation and maintenance therapy, so this recommendation also needs to be revised. For second-line chemotherapy (defined as chemotherapy for refractory or recurrent NSCLC after first-line chemotherapy), it is recommended that docetaxel be administered for refractory or recurrent NSCLC after first-line chemotherapy (Grade B). However, pemetrexed, erlotinib and gefitinib are now available, and this recommendation thus needs to be revised. With regard to molecular-target-based therapy, there is insufficient evidence for recommendation of EGFR/TKI in NSCLC (Grade C). However, positive results have since been obtained in EGFR-mutated NSCLC, and this description in the guideline thus also needs to be revised.

With regard to chemoradiotherapy (CRT) for locally advanced NSCLC, the recommendations are as follows: (i) CRT containing cisplatin is strongly recommended for inoperable, locally advanced NSCLC (Grade A); (ii) CRT is strongly recommended for patients with a good PS (0, 1) (Grade A); (iii) Chemotherapy should be given concurrently (Grade A); (iv) The dose of radiotherapy should be 60 Gy by usual fractionation (1.8–2.0 Gy/day) (Grade A); (v) there is no evidence for an effect of split-course radiotherapy on survival benefit, while there is not enough data for recommending not to split radiotherapy (Grade C); (vi) the chemotherapy regimen for concurrent CRT should be a platinum-containing doublet or triplet (Grade B). There is not enough data from large clinical trials regarding CRT-containing irinotecan, paclitaxel, docetaxel, vinorelbine and gemcitabine, and these drugs should be used only in clinical trials (Grade C). However, positive results have recently been obtained with paclitaxel and vinorelbine, and this description in the guideline thus also needs to be revised.

The recommendation with regard to adjuvant immunotherapy (postoperative) is that there is not enough evidence for an improved prognosis by using an immunostimulant. There is also no clear evidence for recommending use of an immunostimulant after surgery (Grade C). The recommendation with regard to preoperative chemotherapy in Stage I/II NSCLC is that there is not enough data to recommend preoperative chemotherapy (Grade C).

In addition to the guideline, since 2005 Japan has had a guidance for gefitinib prescription. The indication for gefitinib is inoperable or recurrent NSCLC. Gefitinib is not indicated for patients without prior chemotherapy, as adjuvant therapy, as maintenance therapy after CRT or in combination with anti-cancer drugs or radiotherapy. Gefitinib is recommended for the following patients: females, adenocarcinoma, non-smokers, Japanese (Asians) and patients with EGFR mutation.

Thus, Japan has an NSCLC guideline and a gefitinib guidance, but the reality is somewhat different. With regard to the market share of the first-line regimens for NSCLC in Japan, carboplatin/paclitaxel is number one, followed by gefitinib, which is surprising. As the second-line regimen, gefitinib is number one, followed by docetaxel. There is thus a discrepancy between the guidelines and actual clinical practice.

Based on the discussions among the study group members from various Asian countries, it seems difficult to establish a common guideline for NSCLC among Asian countries at the present time because of the differences in medical care in each country as well as the drug lag seen in some countries. Asian collaborative trials on treatment of NSCLC need to be started at an early date to generate Asian data.

EARLY-STAGE LUNG CANCER

Some differences are seen between Asia and Europe and the USA in regard to early-stage lung cancer. Based on clinical practice, it is found that the results of surgery for early-stage lung cancer are better in Asia than in the West. There are also differences with regard to the value of adjuvant chemotherapy. For example, for Stage I, adjuvant chemotherapy is not used in China, whereas in the US and Europe adjuvant chemotherapy is recommended for Stage IB lung cancer. One problem is how to treat patients with early-stage lung cancer with EGFR mutation, which occurs at a much higher incidence of about 30% in Asian populations. Asian clinical trials are needed to answer this.

LOCALLY ADVANCED NSCLC

In regard to locally advanced NSCLC, it is accepted that concurrent chemoradiation therapy (CRT) should be accepted as standard treatment. However, there are several questions regarding the drug to be used in Asian populations: the type of drug, dosage and schedule that will be suitable. As reported, chemotherapy toxicity is higher in Asian populations, but the response and survival are better than in the West. The radiation technique used in CRT has mostly been 3D conformal irradiation. However, this may not be possible in all Asian countries, so further investigation is needed regarding the radiation technique to be used concurrently with chemotherapy. Induction chemotherapy or CRT prior to surgery also needs to be studied in Asia, as does surgery for locally advanced NSCLC. A third point regarding locally advanced NSCLC is maintenance therapy, especially tyrosine kinase inhibitors (TKIs). Detrimental effects were reported in an American population administered maintenance TKI. However, because of the high incidence of EGFR mutation in Asians, it is not known whether maintenance therapy with TKIs will benefit the patient or not. In the West most population studies were based on PET CT, whereas in most Asian countries, especially Southeast Asia, the method is usually only CT scan. Thus, there are various problems remaining in Asian populations with regard to locally advanced NSCLC.

ADVANCED NSCLC

Three aspects of management of advanced NSCLC in the Asian region need to be addressed. First, there are some epidemiological differences, especially the incidence of NSCLC mortality. Second, there seem to be some differences in the etiological factors implicated in lung cancer in the East compared with the West. In the East, there are more cases that are not directly associated with smoking, meaning that lung cancer non-smokers are more prevalent, especially in East Asian women. Third, there is increasing evidence in support of major differences in treatment of advanced NSCLC in terms of the efficacy and toxicity, especially with TKIs. Asian patients derive much greater benefit from TKIs compared with Caucasian people. In fact, some of the Korean consensus guidelines suggest broader recommendation of TKIs even to patients with a poor performance status.

Cytotoxic agents are usually relatively or absolutely contraindicated for poor PS patients, but TKIs are much more convenient to administer and much less toxic than cytotoxic agents. Thus, TKIs can be recommended to a broader range of patients with a poor performance status. There are also recent data that indicate possible benefit from TKIs even in the first-line setting, without any prior chemotherapy.

In summary, there is mounting evidence of differences between Asian and Caucasian lung cancer patients in many aspects, including epidemiology, etiology and treatment outcomes and toxicities. Asia truly needs its own region-specific clinical trials to address each of these issues in regard to NSCLC.

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