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.

ACKNOWLEDGEMENTS

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THE ASCO® POST

News and views from the world of clinical oncology and hematology

Neoadjuvant Endocrine Treatment Makes Sense for Estrogen Receptor–rich Breast Tumors

But early failure to suppress proliferation may signal need for chemotherapy

By Caroline Helwick

Although chemotherapy is the standard neoadjuvant treatment in postmenopausal women with large breast tumors, an endocrine approach may be more suitable and may, in fact, help further optimize systemic treatment as well.

"Estrogen receptor (ER)-positive disease is highly heterogeneous, and this heterogeneity can be studied and treatment personalized by taking advantage of the neoadjuvant setting," said **Matthew J. Ellis, PhD, MB, BChir**, of Washington University, St. Louis.

Matthew J. Ellis, PhD, MB, BChir

Dr. Ellis, who has been studying the characteristics of ER-rich tumors for years, is leading the multicenter phase II American College of Surgeons Oncology Group (ACOSOG)

Z1031 study, which is evaluating the benefit of an endocrine neoadjuvant approach in postmenopausal patients with ER-rich tumors. Preliminary analyses, reported at the 2010 ASCO Annual Meeting by Dr. Ellis, showed clinical response rates to exceed 60%, and the breast-conservation rate to be 51% for patients slated for mastectomy at presentation.[1]

'Dramatic Effect'

"For the 150 or so women in this study who were clearly headed for mastectomy this is really a dramatic effect, achieved with very low toxicity, and arguably

Expert Panel Highlights Need to Intensify Cancer Care in Poorer Countries

By Caroline Helwick

A panel of experts in global health made news recently by emphasizing the disparity in cancer care between countries of low and middle income and those with more resources, such as the United States. The report, which was published online August 16th in *The Lancet*,[1] called for more recognition of the global burden of cancer and outlined strategies that might answer the specific needs of poorer countries.

The report was authored by Paul Farmer, MD, of Harvard School of Public Health, and an international consortium of 22 participants ranging from ASCO President Douglas Blayney on cancer survivor and cyclist Lance Armstrong.

Julie Gralow, MD, Professor of Oncology at the University of Washington, Seattle, noted the "uniqueness" of the collaboration. "Very few cancer-specific specialties are actually represented among the authors. We have infectious disease experts, health economists, and

Julie Gralow, MD

public health specialists," she pointed out. "We felt there are people out there who have made tremendous advances in global health outside of oncology, and we should learn from and partner with them. We are trying to be inclusive and learn from each other."

Closing the Gap in Survival Rates

The consortium called for an end to the assumption that cancer is a "disease of the rich" and one that warrants a back seat to infectious diseases, such as malaria and AIDS, in the developing world. Almost two-thirds of the 7.6 million cancer deaths per year occur in low-

Multinational Trials Reveal Striking Regional Differences

Nagahiro Saijo, MD, PhD

Many multinational clinical trials have recently been conducted to enable the rapid accrual of patients and the use of registration data in multiple countries. Such trials often include multiple ethnicities, and regional differences sometimes affect the treatment results. Many factors can cause regional differences, including medical care, medical insurance, and clinicopathologic features, as well as pharmacogenomics. When discrepant data are observed between Asian and Caucasian populations, new clinical trials should be scheduled in specific populations. This commentary discusses three examples of such trials.

EGFR Tyrosine Kinase Inhibitors

During phase II trials of the epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor gefitinib (Iressa), such as the Iressa Dose Evaluation in Advanced Lung Cancer (IDEAL) 1 and 2 studies,[1,2] the response rate appeared to be higher among Japanese patients than among Caucasians.

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Multinational Trials Reveal Striking Regional Differences

However, a subsequent placebo-controlled randomized phase III trial named the Iressa Survival Evaluation in Lung Cancer—or ISEL study—did not stratify patient populations according to Asian vs non-Asian. With an enrollment of 1,692 advanced or metastatic non–small cell lung cancer (NSCLC) patients who had undergone prior chemotherapy, the ISEL study was designed to investigate the effect on survival of gefitinib as a second- or third-line therapy. Overall survival was not statistically significantly different among the entire population (HR = 0.89, P = .087) or among patients with adenocarcinoma (HR = 0.84, P = .089).

Among the 342 patients of Asian origin, however, the median survival was significantly different from that of non-Asian patients (HR = 0.66, P = .01). On the other hand, the survival curves of EGFR tyrosine kinase inhibitor and placebo groups were completely superimposable in Cauca-

sians.[3] Although the analysis was pre-planned, these data represent a post-study stratification. Thus, the data were regarded as preliminary in many countries with regard to the approval of regulatory affairs.

The reason the response rate to gefitinib is higher among Asian populations has been explained pharmacogenomically as the presence of a higher EGFR mutation rate in this population.

The Iressa Pan-Asia Study (IPASS), comparing gefitinib vs standard chemotherapy, including carboplatin and paclitaxel, was conducted only in Asian patients with adenocarcinoma who had not received prior chemotherapy. These patients were either never-smokers or light smokers. The progression-free survival (PFS) period was significantly longer in the gefitinib arm, although the PFS crossed over at 6 months. (PFS before 6 months was better in the standard chemotherapy

arm.) A clear advantage was observed in the gefitinib group among EGFR mutation–positive patients.[4] In two other Japanese randomized controlled trials comparing gefitinib vs standard chemotherapy in EGFR mutation-positive patients, gefitinib produced a significantly better PFS than chemotherapy.[5,6]

Based on these data, new algorithms for the treatment of NSCLC have been established. The frequency of EGFR mutation is 35% to 40% among East Asian populations vs less than 10% among Caucasian populations. Therefore, the strategy for treating NSCLC differs considerably between East Asians and 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 ad-

vanced 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; how-

ever, 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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NEWS & VIEWS

Tyrosine-kinase inhibitors—new standard for NSCLC therapy

Nagahiro Saijo

> **Practice point**
>
> A new step has been introduced in the treatment algorithm for advanced NSCLC. For patients with EGFR-mutated NSCLC, EGFR-TKIs should be considered to be the standard first-line therapy.

A clinical trial of patients with pharmacogenomically-selected non-small-cell lung cancer clearly demonstrated an improvement in progression-free survival after gefitinib treatment compared with standard chemotherapy. This report is the first to suggest that personalized therapy based on pharmacogenomics could be standardized in the treatment of lung cancer.

Although platinum-based cytotoxic chemotherapy has been established as a useful treatment for advanced non-small-cell lung cancer (NSCLC), the effect has reached a plateau. The development of molecular-targeted drugs is essential if we are to see further improvement in the treatment results of patients with NSCLC. In recent years, the understanding of cancer at the molecular level has progressed, and numerous genes and proteins have been identified to be a driving force of tumor growth. By establishing these genes and proteins as clinical targets, small-molecule signal transduction inhibitors (for example, tyrosine kinase inhibitors [TKIs]) and monoclonal antibodies have been developed for the treatment of cancer. Among these novel therapies, EGFR-TKIs, such as gefitinib and erlotinib, and anti-VEGF antibodies, such as bevacizumab, have been approved for the treatment of NSCLC.

> **❝ The objective response rate was significantly higher in the gefitinib group than in the chemotherapy group... ❞**

Gefitinib and erlotinib are orally administered EGFR-TKIs that have exhibited dramatic antitumor activity against NSCLC. Although many clinical trials of EGFR-TKIs have been conducted in the first-line and second-line setting in patients with NSCLC, contradictory data have been obtained.[1,2] Empirically, EGFR-TKIs have been shown to be most effective in female never smokers, patients with adenocarcinoma, and patients of East Asian origin.[3] In May 2004, two pivotal studies demonstrated that tumors

were highly responsive to gefitinib if they had base-pair deletions at exon 19 of *EGFR* (base pairs 746–750 deleted) or a point mutation at exon 21 of *EGFR* that causes the L858R mutation in EGFR.[4,5] These two mutations can be described as gefitinib-sensitive mutations. Despite this discovery, the majority of clinical trials have been conducted in unselected populations of patients with NSCLC and therefore definite conclusions about the efficacy of EGFR-TKIs in different genetic populations have been difficult to make.[1,2] In addition, each technique to detect *EGFR* mutation differs in its sensitivity and specificity, which can cause some confusion regarding the prognostic and predictive value of *EGFR* mutations. For example, the sensitivity of the direct sequencing method, which has been used to detect *EGFR* mutations in many clinical trials, is not sufficiently high; 10–15% of *EGFR* mutations are missed using this method.

Phase II studies and their meta-analyses have suggested that EGFR-TKIs are highly active and treatment can produce a 70–80% response rate against NSCLC tumors with mutated *EGFR*.[6,7] The IPASS trial, which was an open-label, randomized and controlled trial in East Asian patients with advanced pulmonary adenocarcinoma who were nonsmokers or low smokers, demonstrated that treatment with gefitinib provided a significantly better progression-free survival (PFS) period than standard chemotherapy using carboplatin and paclitaxel.[8] In a subgroup of patients who were positive for both of the *EGFR* gene mutations, detected using the Scorpions™ ARMS (Amplification Refractory Mutation System) method, the PFS was significantly

longer among the patients receiving gefitinib therapy, compared with the chemotherapy group (P <0.0001). On the other hand, the PFS was significantly better in the chemotherapy group among *EGFR* wild-type patients (P <0.0001).[8] However, the percentage of patients taking part in clinical trials who had their *EGFR* status analyzed was only 30–36% (36% in the IPASS trial), and selection bias cannot be excluded in the IPASS trial. Therefore, conclusions based on the results of subset analyses of patients with *EGFR* mutations might be misleading.

The North East Japan Study Group (NEJSG) conducted an open-label, randomized and controlled trial with an enrollment of 230 chemotherapy-naive, *EGFR*-mutation-positive patients with NSCLC.[9] The patients received either gefitinib (250 mg per day) or a standard 3-weekly chemotherapy regimen of carboplatin (area under the concentration–time curve 6) and paclitaxel (200 mg/m²). The primary end point of the study was PFS, and secondary end points included overall survival, response rate and toxic effects. All the patients had sensitive *EGFR* mutations and did not have a secondary T790M mutation, which is one of the causes of EGFR-TKI resistance. The *EGFR* mutation was examined using the peptide nucleic acid–locked nucleic acid (PNA–LNA) PCR clamp method, which has a sensitivity and specificity of 97% and 100%, respectively.

Interim analysis of the first 200 patients showed that the median PFS was significantly longer in the gefitinib group than in the chemotherapy group (10.4 months versus 5.5 months; hazard ratio for death or disease progression with gefitinib 0.36; P <0.001), resulting in early termination of the study.[9] Significant difference was again observed in the final analysis of a total of 230 patients (median PFS 10.8 months with gefitinib versus 5.4 months with chemotherapy; hazard ratio 0.30; P <0.001). The objective

"...the efficacy of first-line gefitinib was superior to that of standard chemotherapy... "

response rate was significantly higher in the gefitinib group than in the chemotherapy group (73.7% versus 30.7%; P <0.001). The overall survival did not differ significantly (30.5 months in the gefitinib group and 23.6 months in the chemotherapy group; P <0.31) because 94.6% of the patients in the chemotherapy group received gefitinib after the completion of chemotherapy, and the response rate to second-line gefitinib was 58.4%. The median PFS and the response rate did not differ significantly between patients with an $EGFR$ mutation consisting of an exon 19 deletion and those with the L858R point mutation. The most common adverse events in the gefitinib group were rash (grades 1 and 2 66%; grade 3 or greater 5.3%) and elevated levels of aspartate aminotransferase or alanine aminotransferase (grades 1 and 2 28.9%; grade 3 26.3%). Interstitial lung disease was reported in six patients (5.3%) in the gefitinib group; three of these cases were severe, and one was fatal. However, the incidence of severe toxic effects (grade 2 and 3) such as neuropathy (P <0.001) arthralgia

(P <0.001), neutropenia (P <0.001) and anemia (P <0.001) was significantly higher in the chemotherapy group.[9]

The NEJSG study clearly demonstrated that the efficacy of first-line gefitinib was superior to that of standard chemotherapy, with an acceptable level of toxic effects in patients with advanced NSCLC harboring sensitive $EGFR$ mutations. The West Japan Thoracic Oncology Group recently presented a similar result for gefitinib, although the techniques used to detect $EGFR$ mutations and the patient populations were heterogeneous when comparing the two trials.[10] In addition, at ESMO 2010, a Chinese group presented a comparison of erlotinib and cytotoxic chemotherapy in $EGFR$-mutated NSCLC.

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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 sur-vival rate for Japanese-advanced non-small-cell lung cancer patients compared with Americans. To solve the problem of drug lag, pharmaceutical companies must perform multi-national 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, bio-markers 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 treat-ment 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 character-istics 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 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, and 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 for 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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Pooled Analysis of S-1 Trials in Non-Small Cell Lung Cancer According to Histological Type

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Abstract. *Background: The antimetabolic agent S-1 inhibits thymidylate synthase similar to pemetrexed, but through a different mechanism of action. Whether the antitumour activity of S-1 depends on histological type remains unclear. We analysed pooled data from 2 phase II clinical studies of cisplatin and S-1 in patients with previously untreated advanced non-small cell lung cancer. Patients and Methods: We comprised 110 patients with stage IIIB or IV non–small cell lung cancer. Univariate and multivariate analyses were performed to determine the effects of histological type on progression-free survival and response rates. Results: On pooled analysis of the data, according to histological type, median progression-free survival was 3.8 months in patients with squamous cell carcinoma and 4.4 months in those with non-squamous cell carcinoma. Both analyses showed that progression-free survival and response rate did not differ significantly. Conclusion: Unlike molecular targeted agents and pemetrexed, a combination of cisplatin and S-1 may be no difference in response according to histological type.*

Lung cancer continues to affect more than 100 million people worldwide. About 80% of all cases are non-small cell

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Key Words: Cisplatin, S-1, pooled analysis, histological type.

lung cancer (1). Stage IV advanced lung cancer is usually treated by chemotherapy with anticancer drugs; however, outcomes remain far from satisfactory. Various treatment regimens have been developed to improve survival.

The anticancer drug pemetrexed, classified as an antimetabolic agent, has recently become standard treatment for malignant pleural mesothelioma. Pemetrexed acts by inhibiting the activity of several enzymes, including thymidylate synthase (TS), which is involved in the *de novo* synthesis of thymidine triphosphate, dihydrofolate reductase, which reduces folic acid to its active form required for DNA synthesis, and glycinamide ribonucleotide formyl transferase, which participates in purine synthesis (2). A randomised clinical trial comparing pemetrexed with docetaxel as second-line treatment in patients with non-small cell lung cancer was conducted outside of Japan (3). The trial failed to establish that pemetrexed was superior to docetaxel in terms of efficacy, but it had lower toxicity. Pemetrexed was therefore approved by the Food and Drug Administration and is now used as a standard treatment in the United States. Subsequently, a retrospective analysis was performed to examine the effectiveness of pemetrexed according to histological type (squamous cell carcinoma *vs.* non-squamous cell carcinoma). Pemetrexed was found to improve survival in patients with non-squamous cell carcinoma, but was less effective than docetaxel for squamous cell carcinoma (4). Scagliotti *et al.* demonstrated that cisplatin plus pemetrexed is not inferior to cisplatin plus gemcitabine in terms of overall survival in patients with advanced non-small cell lung cancer who received first-line chemotherapy (5). That study included an analysis of response according to histological type.

Cisplatin plus pemetrexed was shown to be associated with significantly better survival in patients with non-squamous cell carcinoma, although this was not a primary endpoint of the investigation. On the basis of these results, cisplatin plus pemetrexed was approved for the first-line treatment of non-small cell lung cancer in the United States and Europe; however, squamous cell carcinoma was excluded from the approved indication. A phase III study assessing the benefits of maintenance therapy with pemetrexed after platinum-doublet chemotherapy showed that pemetrexed significantly improves progression-free survival and overall survival as compared with placebo in patients with non-squamous cell carcinoma. In squamous cell carcinoma, however, pemetrexed was associated with slightly shorter progression-free survival and overall survival than placebo (6).

The following molecular rationale has been proposed to explain the differences in the response to pemetrexed according to histological type. Pemetrexed inhibits TS, as described above. However, the baseline expression of the TS gene is significantly higher in squamous cell carcinoma than in adenocarcinoma. Preclinical data suggest that high expression of TS is associated with reduced activity of pemetrexed (7).

S-1 is an oral anticancer drug that combines tegafur, a prodrug of 5-fluorouracil, with gimeracil and oteracil potassium. Gimeracil reversibly inhibits the rate controlling enzyme system responsible for the metabolism of 5-fluorouracil, thereby increasing concentrations of 5-fluorouracil in blood and enhancing its antitumour activity. Oteracil potassium reversibly inhibits the phosphorylation of 5-fluorouracil, thereby reducing its gastrointestinal toxicity (8, 9). A phase II study of S-1 monotherapy reported a response rate of 22% in patients with non-small cell lung cancer (10). Subsequently, 2 other phase II studies were performed in Japan to evaluate the efficacy and safety of combined chemotherapy with cisplatin and S-1 in patients with previously untreated, advanced non-small cell lung cancer. In the first study, cisplatin (60 mg/m^2) was given on day 8 ('day 8 study') (11). The response rate was 47.2%, and the median survival was 11.1 months. In the second study, cisplatin (60 mg/m^2) was given on day 1 ('day 1 study') (12). The response rate was 32.7%, and the median survival was 18.1 months. Two phase III studies of S-1 combined with platinum preparations are now in progress; the results are awaited.

S-1 acts primarily by inhibiting TS. Therefore, the antitumour activity of S-1 may depend on histological type, similar to pemetrexed. To explore whether the response to combined chemotherapy with cisplatin and S-1 depends on histological type, similar to pemetrexed, this study jointly analysed the results of two phase II studies of cisplatin plus S-1 in patients with previously untreated, advanced non-small cell lung cancer and compared treatment outcomes according to histological type (squamous cell carcinoma vs. non-squamous cell carcinoma).

Patients and Methods

Study design and subjects. This study analysed pooled data from 2 phase II clinical studies in which patients were enrolled from September 2000 through December 2005. The primary endpoints were progression-free survival and response rate; the secondary endpoint was overall survival. The numbers of patients who were enrolled or included in the full analysis set were 56 and 55 (respectively) in the day 8 study and 55 and 55 (respectively) in the day 1 study, the protocols of which are briefly described in the following section. The difference in the two studies is the administration schedule of CDDP and S-1. One patient in the day 8 study was ineligible and excluded. A total of 110 patients were thus included in the analysis. In both studies, eligible patients had to have a histopathologically confirmed diagnosis of stage IIIB or IV non-small cell lung cancer, measurable lesions, an age of 20 to 74 years, a performance status of 0 to 2 on the Eastern Cooperative Oncology Group scale, an expected survival of at least 3 months and adequately maintained organ function. Written informed consent was obtained from all patients before enrollment and the study protocol was approved by Institutional Review Boards at the participating centres. Both studies were conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice.

Treatment regimens. S-1 was supplied by Taiho Pharmaceutical Co., Ltd. (Tokyo, Japan) as 20- and 25-mg capsules. In the day 8 study, S-1 was given after meals on days 1 to 21, and cisplatin was given on day 8, followed by 2 weeks of rest. This 5-week cycle was repeated. In the day 1 study, cisplatin was given on day 1, and S-1 was given after meals on days 1 to 14, followed by 1 week of rest. This 3-week cycle was repeated. Cisplatin was administered according to the recommendations of the package insert. In both studies, the dose of cisplatin was 60 mg/m^2. The dose of S-1 was based on the patient body surface area (BSA) as follows: BSA<1.25 m^2, 80 mg/day; 1.25≤BSA<1.5 m^2, 100 mg/day; and BSA≥1.5 m^2, 120 mg/day.

Evaluation methods. Progression-free survival was defined as the period from the date of enrollment to the date on which disease progression was first confirmed (the date of evaluation). For patients who died before disease progression, death was attributed to disease progression. If there was no evidence of disease progression, the final day of evaluation was used to calculate progression-free survival. Response rates were evaluated according to the World Health Organisation criteria (13) in the day 8 study. In the day 1 study, response rates were assessed according to new guidelines for evaluating the treatment response of solid tumours (Response Evaluation Criteria in Solid Tumours guidelines) (14). Response rates were based on the combined total of complete responses (CR) and partial responses (PR). Overall survival was defined as the period from the date of enrollment to the date of death from any cause. Data on patients who were alive were censored on the last date on which the patient was confirmed to be alive. Data on patients who were lost to follow-up were censored on the date on which the patient was last confirmed to be alive, before being lost to follow-up. The incidences of adverse events were calculated according to version 2 of the National Cancer Institute Common Toxicity Criteria (NCI-CTC) (15).
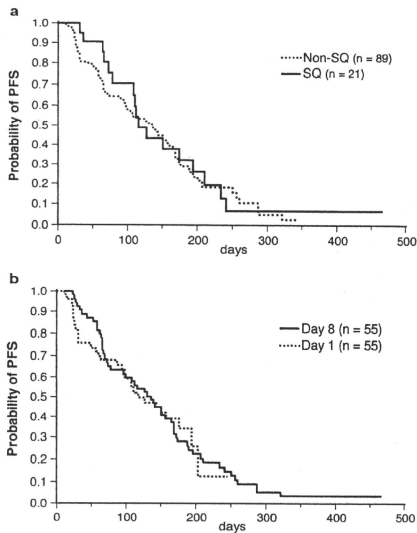
Figure 1. *a: Progression-free survival (PFS) according to histological type. b: Progression-free survival according to study. SQ: Squamous cell carcinoma.*
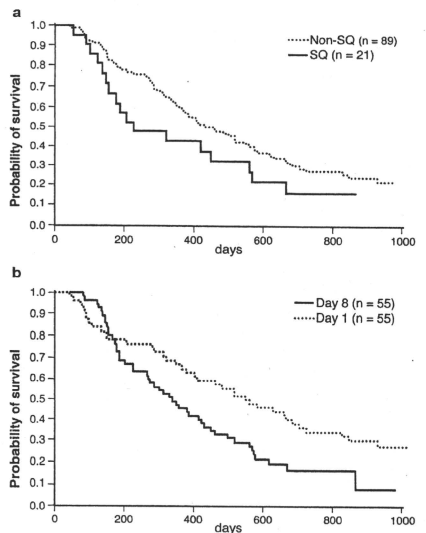
Figure 2. *a: Overall survival according to histological type. b: Overall survival according to study. SQ: Squamous cell carcinoma.*

Statistical analysis. Progression-free survival and overall survival curves were estimated by the method of Kaplan-Meier. Survival curves were compared between groups by the log-rank test. Response rates were compared by the Chi-squared test. Trial-stratified tests were also conducted after checking the assumption of common effect size across studies. A multiple Cox or logistic regression model including age, sex, performance score and clinical stage as well as histological type was applied according to whether a response variable was time-to-event or binary. All hazard ratios and odd ratios are reported with reference to patients who had a histological diagnosis of non-squamous cell carcinoma. Thus a hazard ratio >1 implies that patients with non-squamous cell carcinoma have better survival than those with squamous cell carcinoma, while an odds ratio >1 implies that patients with squamous cell carcinoma have a higher response rate than those with non-squamous cell carcinoma. All reported *p*-values are two-tailed. *P*-values <0.05 were considered to indicate statistical significance. All analyses were performed using SAS software ver. 9.1.3 (SAS Institute, Cary, NC, USA).

Results

Demographic characteristics of patients. Of the 111 patients who were enrolled from September 2000 through December 2005, 110 received the protocol treatment, excluding 1 ineligible patient. Table I shows the demographic characteristics of the treated patients. Most patients (66.4%) were male, 80.9% had non-squamous cell carcinoma, 78.2% had stage IV disease, and 45.5% had a performance status of 0. Their median age was 61 years (range, 36 to 74 years). The median number of treatment courses was 4 in the day 1 study (range, 1 to 9) and 3 in the day 8 study (range, 1 to 12).

Progression-free survival and overall survival. Median progression-free survival according to histological type, on the basis of pooled data from both studies, was 3.8 months in patients with squamous cell carcinoma and 4.4 months in those with non-squamous cell carcinoma (hazard ratio, 0.91; 95% confidence interval [CI], 0.53 to 1.54; *p*=0.71) (Figure 1a). Median progression-free survival did not differ between the studies (Figure 1b) and trial-stratified analysis did not change the results (hazard ratio, 0.92; 95% CI, 0.54 to 1.57; *p*=0.75). Multivariate analysis also showed that there was no difference according to histological type (hazard ratio, 1.04; 95% CI, 0.59 to 1.86; *p*=0.86). The response rate according to histological type in the pooled data set was 47.6% (10 of 21 patients) in patients with squamous cell carcinoma and 38.2% (34 of 89

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Table I. *Demographic characteristics of patients according to study.*

Characteristics	Day 8 study (n=55)	Day 1 study (n=55)	Total (n=110)
Gender			
Male (%)	41 (74.5)	32 (58.2)	73 (66.4)
Female (%)	14 (25.5)	23 (41.8)	37 (33.6)
Histological type			
Squamous (%)	14 (25.5)	7 (12.7)	21 (19.1)
Non-squamous (%)	41 (74.5)	48 (87.3)	89 (80.9)
Stage			
IIIB (%)	10 (18.2)	14 (25.5)	24 (21.8)
IV (%)	45 (81.8)	41 (74.5)	86 (78.2)
Age (years)			
<70 (%)	42 (76.4)	47 (85.5)	89 (80.9)
≥70 (%)	13 (23.6)	8 (14.5)	21 (19.1)
Performance status (ECOG)			
0 (%)	30 (54.5)	20 (36.4)	50 (45.5)
1 (%)	23 (41.8)	35 (63.6)	58 (52.7)
2 (%)	2 (3.6)	NA	2 (1.8)

NA: not applicable; ECOG: Eastern Cooperative Oncology Group scale.

Table II. *Overall response rates according to histological type in the two studies analysed*.*

	Overall (%)	Squamous cell carcinoma (%)	Non-squamous cell carcinoma (%)
Day 8 study	18/55 (32.7)	8/14 (57.1)	18/41 (43.9)
Day 1 study	26/55 (47.3)	2/7 (28.6)	16/48 (33.3)
Total	44/110 (40.0)	10/21 (47.6)	34/89 (38.2)

*No. of patients who responded/No. of patients treated.

patients) in those with non-squamous cell carcinoma (odds ratio, 1.47; 95% CI, 0.56 to 3.83; *p*=0.43) (Table II). Similar results were obtained in trial-stratified analysis (odds ratio, 1.32; 95% CI, 0.49 to 3.52; *p*=0.59). Multivariate analysis also showed no apparent effect of histological type (odds ratio, 1.25; 95% CI, 0.45 to 3.47; *p*=0.67).

Median overall survival according to histological type in the pooled data set was 7.4 months in patients with squamous cell carcinoma and 14.1 months in those with non-squamous cell carcinoma (Figure 2a). However, the median overall survival was 18.1 months in the day 1 study as compared with only 11.1 months in the day 8 study (Figure 2b). The discrepancy in Figure 2a was caused by this between-trial difference in overall survival. The adjusted hazard ratio on trial-stratified analysis was 1.40 (95% CI, 0.82 to 2.40; *p*=0.22). The difference in survival between trials in Figure 2b may have been largely due to the post-protocol use of epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKI); EGFR-TKI was widely used in clinical practice in Japan at the time of the day 1 study, while no patient in the day 8 study received EGFR-TKI since it was not available at that time. However, due to the lack of detailed data, it was not possible to evaluate the difference.

Discussion

Many clinical studies have recently reported interactions between clinical characteristics and treatment outcomes in patients with non-small cell lung cancer. For example, a secondary analysis of data from the Iressa Survival

Evaluation in Lung Cancer (ISEL) study, which compared gefitinib with placebo in previously treated patients, suggested that gefitinib is effective for subsets of patients with specific characteristics, such as adenocarcinoma, female sex, and nonsmoker status (16). In the Iressa Pan Asian Study (IPASS), which was recently performed in previously untreated patients, treatment outcomes differed according to the presence or absence of EGFR mutations (17). The Evaluation of Sorafenib, Carboplatin and Paclitaxel Efficacy in Non-small Cell Lung Cancer (ESCAPE) study, in which sorafenib was combined with carboplatin/paclitaxel in previously untreated patients, suggested that this regimen is less effective for squamous cell carcinoma (18).

Clinical trials have provided evidence that pemetrexed is more effective against adenocarcinoma than against non-adenocarcinoma, similar to molecular targeted agents. This difference in response may be attributed to the inhibition of TS, one of the mechanisms of action of pemetrexed. The lower expression rate of TS in adenocarcinoma in comparison to squamous cell carcinoma (19) provides a theoretical basis for the difference in treatment response.

Factors related to the response to such newly developed drugs for the treatment of non-small cell lung cancer have increasingly become clear. As described above, the response to several drugs has been shown to depend on histological type. Outcomes are gradually improving in patients with adenocarcinoma, but remain poor in patients with squamous cell carcinoma. The present pooled analysis indicated that the antitumour response to cisplatin plus S-1 does not depend on histological type. In contrast, overall survival differed according to histological type. This difference may be attributed to the following factors. In the day 1 study, many patients received EGFR-TKI after completion of the protocol treatment, whereas the day 8 study was performed before EGFR-TKI was approved. Overall survival was thus considerably better in the day 1 study than in the day 8 study. Another factor was that most patients in the day 1 study had non-squamous cell carcinoma. The prolongation of overall survival in the day 1 study may thus reflect the high proportion of patients with non-squamous cell

carcinoma. However, this conclusion remains speculative because adequate follow-up data on the response to EGFR-TKI as subsequent treatment were not obtained.

The present analysis showed that progression-free survival does not differ according to histological type (squamous cell carcinoma *vs.* non-squamous cell carcinoma), in contrast to the results reported for pemetrexed. Although S-1 also inhibits TS, the mechanism involved differs from that of pemetrexed. 5-Fluorouracil derived from tegafur undergoes nucleic acid metabolism and is phosphorylated to 5-fluoro-2'-deoxyuridine 5'-monophosphate (FdUMP). FdUMP then reacts with reduced folate cofactors to form a ternary complex with TS, thereby inhibiting DNA synthesis. Apart from the metabolism of 5-fluorouracil by nucleic acids, resulting in cytocidal activity, most 5-fluorouracil is metabolised by dihydropyrimidine dehydrogenase (DPD), producing inactive molecules. S-1 contains gimeracil, which strongly and reversibly inhibits DPD, and has been experimentally shown to be less affected by DPD than conventional 5-fluorouracil derivatives (20). Orotate phosphoribosyl transferase (OPRT), a key enzyme that catalyses the first step in the phosphorylation of 5-fluorouracil by nucleic acids, has been suggested to have an important role in the antitumour activity of 5-fluorouracil. Ichikawa *et al*. reported that low TS expression and high OPRT expression are predictors of the response to S-1 (21). Nakano *et al*. immunohistologically evaluated the expression levels of TS and OPRT according to histological type, using surgically resected specimens of non-small cell lung cancer (22). They found that adenocarcinoma is associated with low TS expression/low OPRT expression, whereas squamous cell carcinoma is associated with high TS expression/high OPRT expression. Low expression of the target enzyme TS in adenocarcinoma is thus consistent with the theory that pemetrexed is effective against adenocarcinoma. With regard to the relation between the expression of these enzymes and the response to S-1, adenocarcinoma may respond well to S-1 because of the low expression of these target enzymes, similar to pemetrexed. Although squamous cell carcinoma shows high expression of the target enzyme TS, the expression of OPRT, which catalyses the first step in phosphorylation of 5-fluorouracil, is also high. This high OPRT expression may account for the good response of squamous cell carcinoma to S-1. These mechanisms of action may explain the lack of a difference in the responses to S-1 between adenocarcinoma and squamous cell carcinoma.

Cisplatin and pemetrexed can be administered concurrently with thoracic radiotherapy. Clinical studies have reported a good response to this treatment regimen, and further clinical development is awaited. However, squamous cell carcinoma accounts for a high proportion of all locally advanced, stage III, non-small cell lung cancer cases for which a combination of chemotherapy and radiotherapy remains the standard treatment. The number of such patients who receive pemetrexed is limited because of its low efficacy for this type of lung cancer. Because S-1 acts as a radiosensitiser, a phase II study evaluated the combination of cisplatin plus S-1 and thoracic radiotherapy. This regimen was found to be safe and very effective for unresectable stage III non-small cell lung cancer (response rate, 87.5%; median progression-free survival, 13.4 months; median survival time, not reached) (23). Therefore, cisplatin plus S-1 is a new candidate for the standard treatment of advanced non-small cell lung cancer that can be combined with thoracic radiotherapy. An important advantage of this regimen is that response does not differ according to histological type and can therefore also be used to treat squamous cell carcinoma.

In conclusion, the results from the present study suggest that S-1 is well tolerated and effective regardless of histological type. However, at the present time there are insufficient data to evaluate this exploratory analysis. Further two phase III studies will help evaluate the histological efficacy of S-1. S-1 is therefore expected to be effective against non-squamous cell carcinoma as well as squamous cell carcinoma.

Acknowledgements

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Original Article

Common Arm Comparative Outcomes Analysis of Phase 3 Trials of Cisplatin + Irinotecan Versus Cisplatin + Etoposide in Extensive Stage Small Cell Lung Cancer

Final Patient-Level Results From Japan Clinical Oncology Group 9511 and Southwest Oncology Group 0124

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BACKGROUND: Southwest Oncology Group 0124 was a large North American phase 3 trial that failed to confirm a survival benefit for cisplatin/irinotecan over cisplatin/etoposide in patients with extensive stage small cell lung cancer (SCLC). These results were contrary to Japan Clinical Oncology Group 9511, a phase 3 trial exclusively in Japanese patients. Because 0124 and 9511 used identical treatment regimens and similar eligibility criteria, patient-level data were pooled from both trials, and a common arm analysis was performed to explore potential reasons for the divergent results. **METHODS:** Patients with documented extensive stage SCLC and adequate end-organ function were randomized to intravenously receive either cisplatin 60 mg/m^{2} Day 1 + irinotecan 60 mg/m^{2} Days 1, 8, and 15 every 4 weeks or cisplatin 80 mg/m^{2} Day 1 + etoposide 100 mg/m^{2} Days 1-3 every 3 weeks. Demographic and outcome data were compared among 805 patients enrolled in 9511 and 0124 receiving identical treatment using a logistic model adjusted for age, sex, and performance status (PS). **RESULTS:** Of 671 patients in 0124, 651 eligible patients were included, as were all 154 patients from 9511. Significant differences in sex and PS distribution as well as toxicity were seen between trials. There were also significant differences in response rates (87% vs 60%, P<.001) and median overall survival (12.8 vs 9.8 months, P<.001) when the cisplatin/irinotecan arms from both trials were compared. **CONCLUSIONS:** Significant differences in patient demographics, toxicity, and efficacy were identified in the 9511 and 0124 populations. These results, relevant in the current era of clinical trials globalization, warrant: 1) consideration of differential patient characteristics and outcomes among populations receiving identical therapy; 2) utilization of the common arm model in prospective trials; and 3) inclusion of pharmacogenomic correlates in cancer trials where ethnic/racial differences in drug disposition are expected. *Cancer* 2010;116:5710–5. © *2010 American Cancer Society.*

KEYWORDS: small cell lung cancer, chemotherapy, extensive stage, cisplatin, irinotecan.

Lung cancer represents the most common cause of malignant disease globally. Almost 1.4 million new cases of lung cancer are diagnosed annually worldwide, with nearly 1.2 million deaths.[1] Small cell lung cancer (SCLC) is a unique subtype of lung cancer that accounts for approximately 15% of all new cases.[2] Unfortunately, most SCLC patients die from the disease, due commonly to systemic metastasis (defined as "extensive stage").[3,4] Over the past 20 years, standard therapy for most patients with extensive stage SCLC has been either carboplatin or cisplatin in combination with etoposide.[5]

This paradigm was challenged in 2002, when the results of the Japanese phase 3 study Japan Clinical Oncology Group 9511, comparing etoposide/cisplatin with cisplatin/irinotecan in 174 patients, demonstrated that tumor response, progression-free survival (PFS), and overall survival (OS) rates were significantly higher in the cisplatin/irinotecan group.[6] It must be noted that 9511 was stopped early at interim analysis by its data safety monitoring board when prospectively prespecified efficacy parameters were met.

Subsequently, the Southwest Oncology Group conducted a large phase 3 trial (0124) involving 671 patients that used virtually the same eligibility criteria and treatment regimens as the Japanese trial to confirm the results of 9511 in North American patients.[7] As reported previously, 0124 found no statistical differences in tumor response, PFS, and OS between the 2 arms, contrary to the results of 9511.

To explore potential reasons for the divergent results of these identically designed phase 3 trials, a pooled comparative outcomes analysis inclusive of patient-level data from both trials was conducted.

MATERIALS AND METHODS

Patients in both trials had cytologically or histologically confirmed SCLC and clinical evidence of extensive stage disease (defined by distant metastasis, contralateral hilar-node metastasis, or malignant pleural effusion). Eligibility criteria for both trials were similar and have been previously reported. Patients were randomly assigned to receive either etoposide/cisplatin or cisplatin/irinotecan. The cisplatin/irinotecan regimen consisted of 4 cycles of 60 mg of irinotecan per square meter of body surface area on Days 1, 8, and 15 and 60 mg of cisplatin per square meter on Day 1. Cycle length for this arm was 4 weeks. The etoposide/cisplatin regimen consisted of 4 cycles of 100 mg of etoposide per square meter on Days 1, 2, and 3 and 80 mg of cisplatin per square meter on Day 1. Cycle length for this arm was 3 weeks.

All patients underwent evaluations every cycle that included an assessment of symptoms, a physical examination, a complete blood count, and blood chemistry studies. Tumor response was assessed after every 2 cycles. In the 0124 trial, tumor response was evaluated according to the Response Evaluation Criteria in Solid Tumors, whereas in the 9511 trial, the World Health Organization criteria were used.[8] OS was calculated as the time between trial registration and death or date of last contact. PFS was

calculated as the time between trial registration and death or progression, with censoring if alive without progression at last contact.

Study Design and Statistical Analysis

The primary objective of both studies was to compare the survival in patients with extensive SCLC treated with etoposide/cisplatin (standard arm) with that in comparable patients treated with the cisplatin/irinotecan (experimental) on an intent-to-treat basis. As 0124 and 9511 protocols used identical treatment regimens and similar eligibility criteria, patient-level data from both trials were pooled to explore potential reasons for the divergent results. Final results of both trials have previously been reported. Of 671 patients in 0124, 651 were eligible and included in this analysis, as were all 154 patients from 9511. Patient demographics, toxicity, and outcomes were compared among 805 patients receiving identical treatment using a common arm analysis. OS and PFS as compared between the Japan and US trials for both treatment arms in the combined sample were analyzed using Cox proportional hazards regression, adjusted for age, sex, and performance status. A logistic model adjusted for age, sex, and performance status was used to compare response to treatment between the 2 trials for the 2 treatment arms. The existence of possible interactions between trial (Japan Clinical Oncology Group vs Southwest Oncology Group) and treatment arm was evaluated for all endpoints, using data pooled over both arms. Significance was set at $P < .05$.

RESULTS

Patient Demographics

Median age in 9511 and 0124 was 61 and 62 years, respectively. There were proportionally more men in 9511 (86%, n = 132) compared with 0124 (57%, n = 370). There were more patients with Zubrod performance status 0 in 0124 (211, 32%) compared with 9511 (19, 12%). Demographics are summarized in Table 1.

Toxicity

Common arm comparisons of select attributable hematologic toxicities are summarized in Table 2. Regardless of treatment arm, patients in 9511 experienced significantly more hematologic toxicity consisting of neutropenia, leucopenia, and anemia than 0124. Other than a difference in infection rates in the cisplatin/etoposide arm, no

Table 1. Patient Demographics

Characteristic	JCOG-9511			SWOG-0124		
	Cisplatin + Etoposide	Cisplatin + Irinotecan	Total	Cisplatin + Etoposide	Cisplatin + Irinotecan	Total
Age, y						
Median	63	63	63	63	62	63
Minimum	41	30	30	35	22	22
Maximum	70	70	70	86	86	86
Male sex	90%	82%	86%	56%	58%	57%
PS						
0	12%	13%	12%	33%	32%	32%
1	75%	79%	77%	66%	67%	66%
2	13%	8%	10%	0%	0%	0%

JCOG-9511 indicates Japan Clinical Oncology Group 9511 trial; SWOG-0124, Southwest Oncology Group 0124 trial; PS, performance status.
Comparisons of the JCOG and SWOG populations with respect to differences in sex and PS were significant by chi-square test (P <.0001 for both comparisons).

Table 2. Common Arm Comparative Toxicity Analysis

≥Grade 3 Toxicity	Cisplatin + Etoposide			Cisplatin + Irinotecan		
	JCOG-9511	SWOG-0124	P	JCOG-9511	SWOG-0124	P
Infection	3 (4%)	52 (16%)	.01	4 (5%)	36 (11%)	.23
Neutropenia	71 (92%)	220 (68%)	<.001	49 (65%)	107 (34%)	<.001
Leukopenia	41 (53%)	109 (34%)	.006	20 (27%)	57 (18%)	.04
Anemia	25 (32%)	39 (12%)	<.001	21 (28%)	18 (6%)	<.001

JCOG-9511 indicates Japan Clinical Oncology Group 9511 trial; SWOG-0124, Southwest Oncology Group 0124 trial.

differences in nonhematologic toxicities between the 2 trials were seen.

Treatment Delivery and Dose Intensity

In the original 9511 and 0124 papers, there were no significant differences reported between the 2 arms in terms of treatment delivery. A preliminary common arm comparison of treatment delivery and dose intensity (DI) was performed in the current analysis. These results are summarized in Table 3. There are no clear differences in the proportion of patients completing all 4 cycles of therapy. However, a higher proportion of patients completed all 4 cycles of etoposide/cisplatin in 9511 versus 0124 (38% vs 29%). A more modest difference was seen in the cisplatin/irinotecan arm (29% vs 23%). When comparing the published DI data (9511 vs 0124), there was a numerical difference in the proportion of irinotecan (80.4% vs 66%) and cisplatin (95.3% vs 78%) DI.

Efficacy

Common arm comparisons of efficacy endpoints including response rate, PFS, OS are summarized in Table 4 and Figure 1. Ten patients (2 from Japan Clinical Oncology Group and 8 from Southwest Oncology Group) were excluded from the analysis of treatment response because they did not receive treatment. Significant differences in response rates were seen in the common arm comparisons when evaluated in multivariate logistic regression models, which enabled adjustment for age, sex, and performance status. Specifically, for the etoposide/cisplatin arm, response rates were 68% in 9511 and 57% in 0124 (P = .02). For the cisplatin/irinotecan arm, response rates were 87% for the 9511 and 60% in 0124 (P<.001). In an expanded logistic regression model that pooled the data for both treatment arms, there was a significant arm by trial interaction, indicating that the difference in response between the Japanese and US patients is significantly greater in the cisplatin/irinotecan arm patients. (P value for interaction = .03)

There were no differences in PFS and OS for the etoposide/cisplatin arm across trials. However, significant differences were seen for OS for the cisplatin/irinotecan arm. Specifically, median OS was 12.8 months for 9511 and 9.9 months for 0124 ($P<.001$, adjusted for age, sex, and performance status via Cox proportional hazards regression). Similarly, 1-year survival rates were 58% and 41%, respectively. The 1-month numerical difference in PFS in the cisplatin/irinotecan arm was not statistically significant. Kaplan-Meier survival curves of OS common arm comparisons in the cisplatin/irinotecan arm are shown in Figure 1. In a multivariate proportional hazards regression model including trial (Japan vs United States) treatment arm, age, sex, and performance status, the interaction between trial and treatment arm is significant, confirming that the survival difference by site (Japan vs United States) depends on treatment arm (P value for interaction term $= .01$). A performance status of 0 (vs 1 or 2) was also independently prognostic for increased survival in multivariate modeling ($P<.001$). Age and sex were not.

Table 3. Common Arm Analysis of Treatment Delivery and Dose Intensity

Treatment Arm   **P + E**   **P + I**

Completed all 4 cycles

JCOG-9511	55/77 (71.4%)	53/77 (68.8%)
SWOG-0124	218/327 (66.6%)	213/324 (65.8%)

Completed 4 cycles without dose modification

JCOG-9511	29/77 (38%)	22/77 (29%)
SWOG-0124	94/327 (29%)	76/324 (23%)

Reported average dose intensity[a]

JCOG-9511	E: 83.9%; P: 84.6%	I: 80.4%; P: 95.3%
SWOG-0124	E: 78%; P: 81%	I: 66%; P: 78%

P indicates cisplatin; E, etoposide; I, irinotecan; JCOG-9511, Japan Clinical Oncology Group 9511 trial; SWOG-0124, Southwest Oncology Group 0124 trial.
[a] Percentage of total planned dose.

Table 4. Common Arm Analysis of Efficacy

Efficacy Measure	Cisplatin + Etoposide			Cisplatin + Irinotecan		
	JCOG-9511	SWOG-0124	P	JCOG-9511	SWOG-0124	P
Response rate	68%	57%	.01	87%	60%	<.001
Median PFS, mo	4.7	5.2	.18	6.8	5.8	.6
Median OS, mo	9.4	9.1	.5	12.8	9.9	<.001
One-year survival rate	38%	34%		58%	41%	

JCOG-9511 indicates Japan Clinical Oncology Group 9511 trial; SWOG-0124, Southwest Oncology Group 0124 trial; PFS, progression-free survival; OS, overall survival.

DISCUSSION

This common arm comparison of 9511 and 0124 using pooled patient-level data provides unique insights into potential reasons for the divergent results of these trials. In addition, this analysis highlights the issue of whether in the current era of clinical trials globalization, the results of randomized oncology studies conducted outside the Unites States are directly translatable to North American populations.[9] These issues obviously have regulatory implications.

This analysis is unparalleled because 0124 was designed a priori as a confirmatory trial for 9511, albeit accruing from a different ethnic patient pool. The design of the 0124 protocol was modeled directly on 9511, including similar eligibility criteria and identical treatment dose schedules. The observed differences in demographics, toxicity, and efficacy outcomes between these trials can be attributed to many factors, some of which were previously discussed in the 0124 paper. With the pooled multivariate analysis, we were able to investigate (and rule out) the possibility that the different outcomes between trials in the cisplatin/irinotecan arms were attributable to clear differences in patient populations with respect to sex and performance status. Our analysis of both survival and response showed that although performance status was prognostic for survival, the differences between trials in the cisplatin/irinotecan arm persisted even after adjusting for this imbalance.

Other potential factors included the smaller sample size and/or the early stopping of 9511, which may have overestimated the treatment effect.[10]

This common arm analysis demonstrates that the principal difference in OS was seen only in the cisplatin/irinotecan arms. The control etoposide/cisplatin arms in both 0124 and 9511 had identical OS results. In the context of irinotecan-based therapy, 1 hypothesis that has been posited is that there are inherent genetic differences related to genes involved in irinotecan drug disposition