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...
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>
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<tr>
<th>Table 1. Why do we need Asian guideline for lung cancer?</th>
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<td>Difference in medical care for lung cancer</td>
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<td>Systematic LN dissection versus sampling</td>
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<td>Difference in Medical Care Insurance and economical situation</td>
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<td>Ethnic difference of PGX</td>
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<td>Evidence obtained specifically from Asian (Japanese) patients (trials)</td>
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<td>Gefitinib and erlotinib (advanced)</td>
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<td>Irinotecan (small and non-small)</td>
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<td>Histology: non-squamous versus squamous</td>
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<td>Consolidation/maintenance therapy</td>
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<td>Drug lag</td>
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Table 2. ILD by EGFR-TKI

<table>
<thead>
<tr>
<th>Number of patients</th>
<th>ILD (%)</th>
<th>ILD mortality (%)</th>
<th>Risk factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>WJTOG</td>
<td>1976</td>
<td>70 (3.5)</td>
<td>31 (1.6)</td>
</tr>
<tr>
<td>Prospective study of AZ</td>
<td>3322</td>
<td>193 (5.8)</td>
<td>75 (2.5%)</td>
</tr>
<tr>
<td>Okayama study group</td>
<td>330</td>
<td>15 (4.5)</td>
<td>8 (2.4)</td>
</tr>
<tr>
<td>NCCH</td>
<td>112</td>
<td>6 (5.4)</td>
<td>4 (3.6)</td>
</tr>
<tr>
<td>USA</td>
<td>~24 000</td>
<td>0.36</td>
<td>0.06</td>
</tr>
<tr>
<td>AZ (Asian patient excluding Japanese)</td>
<td>53 150</td>
<td>0.34</td>
<td>0.11</td>
</tr>
<tr>
<td>Korea</td>
<td>111</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>China</td>
<td>31</td>
<td>0</td>
<td></td>
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</table>
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 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.

There are several differences between the NCCN version 2/2009 and the Korean NCCN 2008. For Stage IIIIB resectable satellite lesions, the Korean NCCN guidelines specify the strategies for pN0-1 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–III. 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–III, 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
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

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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Conflict of interest statement

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References