Minireview

Emerging ethnic differences in lung cancer therapy

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Although global clinical trials for lung cancer can enable the development of new agents efficiently, whether the results of clinical trials performed in one population can be fully extrapolated to another population remains questionable. A comparison of phase III trials for the same drug combinations against lung cancer in different countries shows a great diversity in haematological toxicity. One possible reason for this diversity may be that different ethnic populations may have different physiological capacities for white blood cell production and maturation. In addition, polymorphisms in the promoter and coding regions of drug-metabolising enzymes (e.g., CYP3A4 and UGT1A1) or in transporters (e.g., ABCB1) may vary among different ethnic populations. For example, epidermal growth factor receptor (EGFR) inhibitors are more effective in Asian patients than in patients of other ethnicities, a characteristic that parallels the incidence of EGFR-activating mutations. Interstitial lung disease associated with the administration of gefitinib is also more common among Japanese patients than among patients of other ethnicities. Although research into these differences has just begun, these studies suggest that possible pharmacogenomic and tumour genetic differences associated with individual responses to anticancer agents should be carefully considered when conducting global clinical trials.

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Lung cancer is the most common malignancy worldwide. Approximately 1.2 million people are diagnosed with lung cancer annually (accounting for 12.3% of all cancers); the second most common malignancy is breast cancer (10.4%), followed by colorectal cancer (9.4%). As lung cancer almost invariably has a poor prognosis, it is the largest single cause of death from cancer in the world, with a mortality of 1.1 million annually (Stewart and Kleihues, 2003). Only 15% of lung cancer patients have a disease that is confined to the lung and are candidates for surgical resection; most patients with this disease have distant metastases or pleural effusion at the time of their initial diagnosis. These patients can be treated with systemic chemotherapy, but the efficacy of currently available anticancer agents is limited and patients with advanced diseases rarely live long.

As the development of new anticancer agents and chemotherapeutic regimens is both time and money consuming, clinical trials need to be as efficient as possible. One effort in this direction has been the adoption of global clinical trials for new agents that involve trial centres on more than one continent; this strategy enables adequate sample sizes to be obtained in a relatively short-time period and eliminates the need for redundant clinical trials with similar objectives conducted in different countries. However, whether the results of clinical trials performed in one population can be fully extrapolated to other populations remains questionable because of potential differences in trial designs, study-specific criteria, patient demographics, frequency of monitoring, and population-related pharmacokinetics, pharmacodynamics and pharmacogenomics. Recently, these genetic and physiologic factors influencing cancer chemotherapy have been increasingly examined and reported.

CLINICAL OBSERVATIONS OF TOXICITY DURING CYTOTOXIC CHEMOTHERAPY

A comparison of phase III trials for the same drug combinations against non-small cell lung cancer conducted in different countries shows a great diversity in toxicity (Sekine et al, 2006). Among trials studying the combination of carboplatin and paclitaxel, the dose of carboplatin was fixed in all the trials, but the dose of paclitaxel was 200 mg m⁻² in Japanese and European trials and 225 mg m⁻² in American trials. Grades 3–4 neutropenia was noted in 88% of the patients in the Japanese trial, 15–51% of the patients in the European trials, and 6–65% of the patients in the American trials. Meanwhile, grades 3–4 febrile neutropenia was encountered in 16% of the patients in the Japanese trial, 0–9% of the patients in the European trials, and 2–4% of the patients in the American trials (Table 1). For combinations of cisplatin and docetaxel (Table 1) and cisplatin and vinorelbine (Table 2), the incidences of grades 3–4 neutropenia and febrile neutropenia were almost the same between phase III trials performed in different areas, but the doses of docetaxel and vinorelbine in the Japanese trials were lower than those in the European and American trials. Thus, neutropenia in patients receiving a combination of platinum and antimitotubule agents may be more severe in Japanese than in Europeans and Americans. A higher frequency of grades 3–4 neutropenia in Japanese patients than in American patients was associated with combinations of cisplatin and irinotecan (65 vs...
ETHNIC DIFFERENCES IN DRUG METABOLISING ENZYMES

An explanation for the ethnic differences in haematological toxicity may be the varying activities of drug-metabolising enzymes and transporters that are mainly associated with polymorphisms in the promoter and coding regions of these enzymes (Fujita and Sasaki, 2007). The haematological toxicity of docetaxel monotherapy was associated with the clearance of this agent in Asian patients, a phenomenon that can be largely explained by CYP3A4 activity (Yamamoto et al., 2000). A study conducted in the Netherlands showed that docetaxel clearance was associated with the homozygous C1236T polymorphism in the ABCB1 (p-glycoprotein) gene (ABCB1*8) but was not associated with any CYP3A4 gene polymorphisms (Bosch et al., 2006). In contrast, docetaxel pharmacokinetics were not associated with the percent decrease in neutrophil counts nor with any polymorphisms in the CYP3A4 and ABCB1 genes in American patients (Lewis et al., 2007). Another example of ethnic differences in drug-metabolising enzymes is the association between polymorphisms in genes involved in irinotecan metabolism and irinotecan-induced neutropenia. Among the patients who received irinotecan with or without another anticancer agent, grade 4 neutropenia was noted in 40–57% of the patients with UDP-glucuronosyltransferase (UGT) 1A1*28 (a polymorphism in the promoter region of the UGT1A1 gene) homozygosity, whereas neutropenia was only observed in 15% or less of the patients with wild-type alleles. This association was consistent in both Asian and Caucasian patients, although the frequency of homozygosity was about 10% in Caucasians and much lower in Asians. The UGT1A1*6 allele is another polymorphism at exon 1 that is associated with defective glucuronidation function and is found almost exclusively in Asian individuals with a frequency as high as 20% (Fujita and Sasaki, 2007). A haplotype including UGT1A1*6 and UGT1A17*3, noted in as many as 15% of Japanese patients, and UGT1A1*6 homozygosity, noted in 7% of Korean patients, were significantly associated with decreased glucuronosyltransferase activity for SN-38 and severe neutropenia (Han et al., 2006; Fujita et al., 2005).
Emerging ethnic differences in lung cancer therapy
I Sekine et al

A similar association between objective responses and ethnicity was observed in studies on erlotinib monotherapy for previously treated advanced NSCLC. In an American phase II trial of this agent in 57 advanced NSCLC patients with disease progression or relapse after platinum-based chemotherapy, the response rate was 12% and the MST was 8.4 months (Perez-Soler et al., 2004). In contrast, the combined data of two Japanese phase II trials of erlotinib in similar patient populations showed objective responses in 30 of 106 (28%) patients and an MST of 13.8 months. Among the responders, significantly higher proportions of females (50%) than males (17%) (P = 0.0009) and of never smokers (51%) than smokers (14%) were observed (P < 0.0001) (Tamura et al., 2007). A phase III trial of erlotinib or a placebo in 731 NSCLC patients previously treated with one or two chemotherapy regimens showed that the response rate in Asian patients was higher than that in patients of other ethnicities (28 vs 10%, P = 0.02) (Shepherd et al., 2005).

These results of phases II and III trials consistently suggest that EGFR tyrosine kinase inhibitors may be more effective in Asian patients than in patients of other ethnicities.

In April 2004, the activating mutations of the EGFR gene were identified in NSCLC specimens, and cancers with these mutations were reported to be highly sensitive to gefitinib. The populations with higher responses to gefitinib (females, non-smokers and patients with an adenocarcinoma histology) also have higher incidences of EGFR mutations (Kosaka et al., 2004; Pao et al., 2004; Shigematsu et al., 2005). The incidence of EGFR mutations in surgically resected tissue samples is summarised in Table 3 (Kosaka et al., 2004; Pao et al., 2004; Marchetti et al., 2005; Qin et al., 2005; Shigematsu et al., 2005; Sasaki et al., 2005; Yang et al., 2005; Sasaki et al., 2006). The incidence varies from one report to another, but EGFR mutations tend to be more common among patients with an adenocarcinoma histology and among non-smokers. Among Asian patients, the average incidences of EGFR mutations were 31% overall, 47% among patients with adenocarcinoma, and 56% among non-smokers; among other ethnic populations, however, the average incidences were 7–8% overall, 13–15% among patients with adenocarcinoma, and 34–35% among non-smokers (Table 3). Thus, the percentage of responders to gefitinib or erlotinib almost paralleled the percentage of patients with EGFR mutations.

In NSCLC, mutations in EGFR are common among patients with an adenocarcinoma histology and among non-smokers. Among Asian patients, the average incidences of EGFR mutations were 31% overall, 47% among patients with adenocarcinoma, and 56% among non-smokers; among other ethnic populations, however, the average incidences were 7–8% overall, 13–15% among patients with adenocarcinoma, and 34–35% among non-smokers (Table 3). Thus, the percentage of responders to gefitinib or erlotinib almost paralleled the percentage of patients with EGFR mutations.

EGFR is composed of an extracellular domain, a single transmembrane domain, and a cytoplasmic domain. The extracellular domain contains the ligand binding site for EGF and related molecules, and the cytoplasmic domain contains a tyrosine kinase domain that is responsible for activating downstream signalling pathways. EGFR mutations in NSCLC have important clinical implications, as they are associated with responsiveness to EGFR tyrosine kinase inhibitors and with improved survival. In an analysis of 1120 patients with NSCLC and EGFR mutations, 28% of patients with wild-type EGFR and 51% of patients with EGFR mutations received treatment with gefitinib or erlotinib, and the response rate was 46% for patients with EGFR mutations compared with 12% for patients with wild-type EGFR (P < 0.0001). In addition, the MST was 12.2 months for patients with EGFR mutations compared with 7.2 months for patients with wild-type EGFR (P = 0.0077). These results suggest that EGFR mutations are predictive of sensitivity to EGFR tyrosine kinase inhibitors in NSCLC patients.

In summary, EGFR mutations are common among Asian patients with NSCLC and are associated with improved survival and responsiveness to EGFR tyrosine kinase inhibitors. These findings highlight the importance of considering ethnicity and genetic factors in the selection of patients for EGFR tyrosine kinase inhibitors.
INTERSTITIAL LUNG DISEASE ASSOCIATED WITH GEFITINIB AND ERLOTINIB

The frequencies of grades 3–4 common toxicities after the administration of gefitinib, including diarrhoea, skin rash, and elevated liver transaminase levels, have been similar among study populations, but the incidence of severe interstitial lung disease (ILD) associated with the administration of gefitinib differs between patients in Japan and those in other countries. In the IDEAL studies, two Japanese patients developed grades 3–4 ILD (2%), whereas no patients outside of Japan experienced ILD (Fukuoka et al., 2003; Kris et al., 2003). A retrospective study of 1976 consecutive patients treated with gefitinib at 84 institutions showed that the incidence of ILD was 3.5% and the mortality rate was 1.6%. Several risk factors for the development of gefitinib-induced ILD were identified in the Japanese population: a history of pulmonary fibrosis, a history of smoking, a poor performance status, and a male sex (Ando et al., 2006). A similar incidence of ILD (4.6%) was also noted in association with erlotinib chemotherapy in Japanese phase II trials (Tamura et al., 2007).

The association between ILD and anticancer treatment is a major topic in Japan because (1) the diagnosis of ILD can be difficult and a consensus among physicians is sometimes not reached, (2) the risk factors for ILD have not been fully established, 3) an effective treatment for ILD has not been established and the condition is often fatal, and (4) the low frequency of this complication makes it difficult to conduct pertinent clinical trials. Gefitinib-induced ILD seems to be more common among Japanese patients than among other patients, but the reasons for this ethnic difference are totally unknown.

CONCLUSION

The findings discussed here suggest that considerable variations in the toxicity and efficacy of anticancer agents may exist among patients of different ethnicities. Although research into these differences has just begun, these studies suggest that possible pharmacogenomic and tumour genetic differences associated with individual responses to anticancer agents should be carefully considered when conducting global clinical trials.

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Table 3  Incidence of EGFR mutations in surgically resected specimens

| Author     | Country | Total N | Mutation N (%) | Adenocarcinoma Total N | Mutation N (%) | Non-smokers Total N | Mutation N (%) |
|------------|---------|---------|----------------|-------------------------|---------------|---------------------|---------------|
| **Western areas** |         |         |                |                         |               |                     |               |
| Shigematsu | USA     | 80      | 11 (14)        | 44                      | 11 (25)       | 26                  | 7 (27)        |
| Pao        | USA     | 96      | 11 (11)        | 72                      | 11 (15)       | 15                  | 7 (47)        |
| Yang       | USA     | 219     | 26 (12)        | 164                     | 25 (15)       | 34                  | 12 (35)       |
| Marchetti   | Italy   | 860     | 39 (5)         | 375                     | 39 (10)       | 103*                | 23 (22)       |
| **Total**  |         | 1255    | 87 (7)         | 655                     | 86 (13)       | 75                  | 26 (35)       |
| **Asian areas** |       |         |                |                         |               |                     |               |
| Shigematsu | Japan   | 263     | 71 (27)        | 154                     | 67 (44)       | 78                  | 47 (60)       |
| Kosaka     | Japan   | 277     | 111 (40)       | 224                     | 110 (49)      | 112*                | 76 (68)       |
| Tokumo     | Japan   | 120     | 38 (32)        | 82                      | 37 (45)       | 36                  | 25 (69)       |
| Sasaki     | Japan   | 95      | 35 (37)        | 71                      | 32 (45)       | 36                  | 25 (69)       |
| Shigematsu | Taiwan  | 93      | 32 (34)        | 55                      | 31 (56)       | 55                  | 27 (49)       |
| Qin        | China   | 41      | 10 (24)        | 17                      | 7 (41)        | 21                  | 6 (29)        |
| Soung      | Korea   | 153     | 30 (20)        | 69                      | 26 (38)       | 54                  | 25 (46)       |
| Shigematsu | Others  | 361     | 107 (30)       | 214                     | 102 (48)      | 135                 | 76 (56)       |
| **Total**  |         | 1403    | 434 (31)       | 886                     | 412 (47)      | 415                 | 231 (56)      |
| **Other areas** |       |         |                |                         |               |                     |               |
| Shigematsu | Australia | 83     | 6 (7)          | 36                      | 5 (14)        | 7                   | 4 (57)        |
| Shigematsu | Others   | 158     | 13 (8)         | 75                      | 12 (16)       | 31                  | 9 (29)        |
| **Total**  |         | 241     | 19 (8)         | 111                     | 17 (15)       | 38                  | 13 (34)       |
| **Total**  |         | 2899    | 540 (19)       | 1652                    | 515 (31)      | 528                 | 270 (51)      |

*Including only patients with adenocarcinoma histology.
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Emerging ethnic differences in lung cancer therapy

I Sekine et al.