

ADVANCES IN DRUG DEVELOPMENT

Current Developments in Oncology Drug Research

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Population Differences in the Use of EGFR-targeted Agents

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H&O What do we currently know about epidermal growth factor receptor (EGFR)-targeted therapies and population differences?

NS EGFR-targeted therapies can largely be divided into 2 categories: EGFR small molecule tyrosine kinase inhibitors (TKIs) and antibodies.

First of all, we know that the response rates for EGFR TKIs such as gefitinib (Iressa, Astrazeneca) and erlotinib (Tarceva, Osi Pharmaceuticals) are significantly higher in Asians, females, adenocarcinomas, and non-smokers. Survival rates are also better than in the total population. As for the toxicity profiles, incidences of pulmonary toxicities are higher in males, smokers, and squamous cell carcinomas. Within the Asian population, we currently know that the frequency of interstitial pneumonia is significantly higher in Japanese patients than in the Chinese and Korean population.

Secondly, there are the antibodies such as cetuximab (Erbix, Imclone). This year at the American Society of Clinical Oncology meeting, the results from an interesting FLEX study—a randomized, multicenter, phase III investigation that compared cetuximab in combination with cisplatin/vinorelbine versus cisplatin/vinorelbine alone in advanced non-small cell lung cancer patients—were presented. There were very few data pertaining to the Asian population, but when the researchers divided the data of Caucasians and Asians, the results seemed to be better in Caucasians. In the Asian population, there was no difference in survival rates; I think this is because the majority of Asian people receive small-molecule

EGFR TKIs after antibody treatment, a factor that may confuse the survival results.

H&O How are these differences explained by EGFR and K-Ras mutation rates in certain populations?

NS About 30–40% of Asians are said to have an EGFR mutation. In Caucasians, the reported mutation rate is less than 10%. This corresponds with study results that show the same type of difference—a higher response and survival rates in the Asian population to EGFR inhibitor therapy—between the 2 populations. We currently do not know much about the mutation rates in other populations such as blacks, hispanics, etc., although it is said that in the hispanic population, the mutation rate seems to be very low.

In the 2008 European Society of Medical Oncology (ESMO) meeting this September, Professor Tony Mok from the Chinese University of Hong Kong presented results from the IRESSA Pan-Asia Study (IPASS), which clearly showed that EGFR mutation is related to response and survival.

The IPASS study, of which I was one of the co-workers, was an open label, randomized, parallel-group trial that tested gefitinib versus carboplatin/paclitaxel (carbo/paclitaxel) as first line treatment in a selected population of patients from Asia. It included 1,217 Asian people whose tumors were of adenocarcinoma histology, who had not received prior chemotherapy, and who were non smokers or light smokers. Japanese people were about

20% of the participants; Chinese people were about 30%; the rest were from other Asian countries. The aim of the trial was to demonstrate that gefitinib was non inferior to carbo/paclitaxel doublet chemotherapy.

Subjects were randomized (about 600 subjects in each arm) to gefitinib or carbo/paclitaxel (ie, standard chemotherapy). The primary endpoint was progression-free survival (PFS).

Results showed that the gefitinib group had superior PFS and higher tumor response compared with intravenous carbo/paclitaxel chemotherapy in the overall population. However, although the PFS in the gefitinib group was significantly better, we noticed that the 2 curves for gefitinib and carbo/paclitaxel crossed at 5–6 months. Interestingly, during the first 5–6 months, the carbo/paclitaxel group was doing better, but after that point, the gefitinib group showed better PFS. These were 2 very strange curves. Statistically, when we analyzed the differences using the Cox proportional hazard model, there was a significant difference between the 2 groups, overall favoring gefitinib. However, there is really no consensus as to whether crossed curves can be analyzed by the Cox proportional hazard model.

Also noteworthy was that among the 1,217 patients, about one-third were analyzed by biomarkers such as EGFR mutation, EGFR amplification, and EGFR expression. We found that in patients with EGFR mutation, gefitinib did significantly better than carbo/paclitaxel. However, in patients with the wild-type EGFR, the PFS of the carbo/paclitaxel group was significantly better than that of the gefitinib group. This was a very interesting observation.

As you know, patients who have an EGFR mutation do not have a K-Ras mutation, and vice versa. One might therefore speculate that, in a sense, K-Ras mutation is inversely associated with the efficacy of EGFR-targeted therapy, but the truth is that there is not enough data in lung cancer. In colon cancer, if the EGFR is mutated, anti-EGFR antibodies such as cetuximab are not effective. In lung cancer, we do not have much data mainly because K-Ras mutation rate is not very high.

H&O Have there been studies investigating the differences within the Asian population (ie, Japanese, Korean, Chinese, etc.)?

NS This is a difficult question because we have very few data. We do know that the mutation rates of the Japanese and Koreans are nearly the same—around 30–40%. At present, we do not have sufficient data on the mutation rates of the Chinese and other Asian countries, so we have not been able to make a complete comparison yet.

H&O What technology is there to detect EGFR mutation, and how reasonable is it to use it to predict EGFR TKI efficacy?

NS Some claim that other biomarkers such as EGFR amplification and fluorescence in situ hybridization (FISH) could also be indicators; but in my mind, they are not very reliable. I believe that EGFR mutation is the most reliable predictor we currently know. And reliability here depends on the number of samples; we need to get enough samples to analyze. How we detect mutation is a separate issue—a technical problem. I think that if we use copy numbers of the EGFR for amplification parameters, it would be reasonably reliable because it is very quantitative.

The problem with FISH results is that they contain 2 elements. FISH positive includes EGFR amplification and high polysomy. However, EGFR amplification is closely correlated to mutation whereas high polysomy does not show any correlation.

When studies include both, the end analysis may be very complicated. This is the case with the majority of the data from the University of Colorado Cancer Center or from Dr. Federico Cappuzzo at the Istituto Clinico Humanitas IRCCS in Italy, who sees FISH technology to be the best method for patient selection when the main endpoint is survival. But I think the mix of 2 different kinds of FISH data is very difficult for us to interpret. Even in the IPASS trial, analysis of survival based on FISH positivity showed a similar tendency but the analysis based on EGFR mutation was much more clear.

I also think that clinical factors such as nonsmoking, females, adenocarcinomas, etc. are related to these EGFR mutations. So at this point, I believe that EGFR mutation is most highly predictive. If patients have the mutation, nearly 80% of them will respond.

H&O Should EGFR TKIs be included in the initial therapy for patients with EGFR mutation?

NS This is a crucial question. And as was evident from my results at the ESMO meeting this year, we can conclude that for patients with EGFR mutation, the first choice of therapy could be gefitinib. For patients without EGFR mutation, chemotherapy should be chosen as the first choice of therapy. But, the IPASS data are for PFS and not overall survival (OS). We still need to wait for OS data, and it will take some time.

But I think the important thing is to focus on the primary endpoint of a clinical trial. If the primary endpoint is OS, it is rather easy for us to interpret the results. If the primary endpoint is PFS or time to treatment failure (TTF), it is rather difficult to make hard conclusions. PFS

and TTF are not that accurate, making them softer endpoints, which do not directly relate to patient benefit.

H&O What sort of studies do you think are necessary to investigate this topic further? Are there any ongoing that are noteworthy?

NS Right now, there are talks of 2 randomized Japanese trials: one by researchers at Tohoku University and the other by the West Japan Oncology Group (WJOG). The study designs are very similar; both are testing gefitinib

versus platinum doublet in EGFR-mutated patients. The Tohoku group is testing carbo/paclitaxel, whereas the WJOG group is testing cisplatin plus docetaxel, for their chemotherapy arm. The primary endpoint is PFS. Both trials are currently accruing patients.

However, the IPASS data has heavily influenced these clinical trials because they have already shown that PFS in EGFR-mutated patients is significantly better in the gefitinib group than in the chemotherapy group. So the question whether to continue these 2 randomized trials has become an ethical one, and still remains unanswered.