Editorial

Ten lessons from EGFR

The first epidermal growth factor receptor tyrosine kinase inhibitor (EGFR TKI), gefitinib, was put on the market in 2002, followed by erlotinib and afatinib. In the past 12 years, both pros and cons of these drugs have emerged.

1. Super responders to EGFR TKI and their clinical backgrounds

In early-phase clinical trials, EGFR TKI showed dramatic anti-tumor effects in certain patients with advanced lung cancer refractory to standard cytotoxic agents. The success was so impressive that health-care professionals as well as patients and their families had great expectations of the drug. Some early trials have indicated that gefitinib is more effective in nonsmoking female patients with well-differentiated adenocarcinoma.

2. Efficacy of EGFR TKI and EGFR gene status

Lynch et al.[1] reported groundbreaking results that revealed that most lung cancer patients with EGFR gene mutation responded to EGFR TKI, but those without the mutation did not. The finding led to recognition of driver oncogenes and their clinical implications.

3. Ethnic differences and Asian studies

It was previously considered that nonsmoker patients with lung cancer were relatively common in Asian countries, and that the prognosis in these patients was relatively good. However, the details were not clear, and this matter was not investigated in Western countries. The discovery of EGFR gene mutations and their relationship with the effect of EGFR TKI focused attention on the fact that ethnic differences do exist in terms of gene abnormalities. Thereafter, many clinical trials aimed at proving the efficacy of EGFR TKI were conducted in Asian countries where this gene mutation is common, and Asia has become the leader in mutation-based clinical trials for lung cancer.

4. Asian trials save Western patients

Studies of ethnic differences have been criticized because of their racism-related implications, but this criticism misses the point. Several clinical trials [2–4] conducted in Asian countries showed that EGFR TKI is superior to standard chemotherapy in patients with EGFR gene mutation, and these results led to the approval of gefitinib in Western countries, where gene-mutated patients represent the minority of the population.

5. Individualized medicine/BBM

Results from assorted basic and clinical research have found applications in daily practice. The clinical practice guideline for lung cancer by the Japan Lung Cancer Society (JLCS) recommends determining EGFR gene status in adenocarcinoma before initiating drug therapy. The era of individualized medicine or biomarker-based medicine for lung cancer has arrived.

6. OS or PFS?

It is known that EGFR TKI prolongs progression-free survival (PFS) but not overall survival (OS) if patients receive both chemotherapy and EGFR TKI. Current opinions differ as to whether the primary endpoint of clinical trials to evaluate the effect of drug therapy for lung cancer should be PFS or OS.

7. Asian trial groups and publication

Since the development of EGFR TKI, the importance of Asian studies has been globally recognized, and the achievements of Asian investigators have been gaining acclaim. In Japan, many clinical trial groups such as JCOG, WJOG, and NEJ are conducting clinical trials to accumulate evidence.

8. Complicated resistance mechanism

However, the EGFR story is not all positive. It has been shown that the effects of EGFR TKI have certain limitations, i.e., effects depend on gene mutation status, de novo resistance is seen in nearly 30% of patients with sensitive gene mutations, and drug resistance is induced within one year in patients initially sensitive to the drug. Recent studies [5–7] have uncovered various resistance mechanisms such as T790M mutation, C-Met gene amplification, and hepatic growth factor (HGF) overexpression. Elucidation of resistance...
mechanisms is expected to lead to measures to overcome drug resistance.

9. ILD and drug safety

Another negative factor is drug-induced interstitial lung disease (ILD). In Japan, three large-scale surveillance studies [8–10] have shown that serious ILD occurs in 4–5% of patients receiving EGFR TKI. In most patients, the ILD occurred within two weeks after the start of administration, and 40–50% of these patients died of rapidly progressive diffuse lung damage. The risk factors for ILD are reported to be smoking, squamous cell lung cancer, predisposing interstitial pneumonia, and poor performance status. Regarding ILD, Japanese patients appear to be more susceptible to ILD induced by EGFR TKI than Western patients.

10. Guidelines and COI

Considering the high incidence of severe ILD, the Japanese Ministry of Health, Labour and Welfare requested the JLCS to publish guidelines on proper use of gefitinib. Despite their firm belief that the guidelines were prepared fairly and appropriately, the JLCS faced criticism that some members had serious conflicts of interest (COI), of which most members had not been aware. This was a most unexpected and unpleasant experience for the members concerned. Consequently, the JLCS now strictly adheres to a COI policy, including situations where decisions regarding guidelines are involved.

Nevertheless, EGFR TKI has shifted our paradigm, and we have learned much from the drug. It is important not to neglect the negatives and to continue to develop standards for optimized drug use.

REFERENCES


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