Drug-induced Disaster Due to IRESSA

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1. What is IRESSA?

IRESSA is an anticancer drug indicated for unresectable or recurrent non-small cell lung cancer. Developed as a molecularly targeted drug with a mechanism of action that differs from conventional cytotoxic anticancer agents, IRESSA was rapidly approved on July 5, 2002 after an extraordinarily short period of only about 6 months after the submission of the approval application. This approval, complying with the guideline at that time, was granted based on the data up to Phase II clinical trials obtained at the time of application, with the condition that Phase III clinical trials should be executed to confirm the survival benefit after its approval.

2. Occurrence of suffering due to adverse reactions

Starting immediately after the approval of IRESSA, there were multiple cases of adverse reactions of serious interstitial pneumonia and acute lung disorder, and an Urgent Safety Information Report was issued on Oct. 15, 2002, a mere 3 months after approval. Cases of the lung disorder continued to occur thereafter; as of September 2009, there had been 799 deaths reported due to adverse reactions. This number of deaths is unbelievably high compared to the past anticancer drugs.

3. Error in evaluation at the examination stage

This issue of suffering due to adverse reactions to IRESSA was not unpredictable. Even at the time of the approval examination process, there had been 20 cases recognized by the government. Moreover, 9 of those events were deaths, representing a high mortality rate. The Ministry of Health, Labour and Welfare was also aware of the occurrence of interstitial pneumonia. However, they focused on that disease name and failed to look into the symptom of the cases, thus ended up overlooking many other events that had been reported under different disease names. They also neglected events that occurred outside of clinical trials, and thus ended up underestimating the risk associated with IRESSA.

4. Efficacy

The many cases of adverse reactions were not the only problem surrounding IRESSA. After the approval of the drug, four overseas clinical trials failed one after another to prove the survival benefit of IRESSA. On the basis of these results, the US FDA prohibited, in principle, the administration of IRESSA to new patients, while in the EU, AstraZeneca itself withdrew its approval application. In contrast, in Japan, although a domestic Phase III clinical trial (V1532) carried out as a condition for approval failed to prove the survival benefit of IRESSA, no review of the contents of the approval of IRESSA was performed. This shows the problems associated with accelerated approval with certain approval conditions.

5. Promotional Advertising

Behind the ballooning problems surrounding IRESSA lies AstraZeneca's clever marketing strategy. AstraZeneca-sponsored articles were published in medical journals, and specialists heaped praise on IRESSA. Press releases from AstraZeneca emphasized the efficacy and safety of IRESSA, and numerous articles appeared in newspapers and other mass media, introducing IRESSA as a novel anticancer drug with few adverse reactions. None of these articles touched upon the fact that there had been cases of fatal interstitial pneumonia as an adverse reaction prior to approval of the drug. This sort of reporting began even before IRESSA had been approved—AstraZeneca was able to circumvent the strict regulations regarding advertising for ethical drugs, and the company succeeded in creating an image of IRESSA as an innovative drug with few adverse reactions.

6. Inadequate warning statements

The initial version of the package insert for IRESSA did not include a "Warnings" column. Moreover, although there was a statement regarding interstitial pneumonia in the "Clinically Significant Adverse Reactions" column, it was not clearly stated that this adverse reaction could be life-threatening, or that deaths had actually occurred. This type of statement was completely insufficient as a warning of fatal risk, and the

image of IRESSA as a “safe drug” that had been created by AstraZeneca’s marketing strategy clearly prevailed in the minds of physicians and patients.

7. Conflict of interest

Specialists who recommended IRESSA in various media played a large role in the creation of the image of IRESSA as an “innovative drug.” Many of these specialists had economic ties with AstraZeneca, receiving speaking fees, donations, or honoraria for participating in the IRESSA clinical trials or cooperating in research.

8. Lawsuits regarding drug-induced suffering due to IRESSA

Lawsuits regarding drug-induced disaster due to IRESSA were initiated in 2004 in the Osaka District Court and the Tokyo District Court, and they will be concluded on July 30 in the Osaka District Court and on August 25 in the Tokyo District Court. Prior to that, the plaintiffs formed a unified plaintiffs’ group in March and have strengthened the movement and presented demands for an overall settlement including the following 5 elements: (1) an apology, (2) compensation, (3) review of the approval of IRESSA, (4) establishment of a relief system for deaths and injury due to adverse reactions to anticancer drugs, and (5) verification and prevention of recurrence.